TJ | Tumori Journal

Scientific Report **2014**

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Istituto Nazionale dei Tumori
Comprehensive Cancer Center

CONTENTS

FROM THE SCIENTIFIC DIRECTOR

UGO PASTORINO

This report provides an overview of the large spectrum of research activities, and multidisciplinary programs performed by INT in 2014, and outlines the strategic directions for future institutional projects.

Our researchers obtained excellent results in 2014, as shown by the growth of our total Impact Factor, which reached 3,518.06 with 639 publications: the IF increased by 756.08 and the number of published papers by 89 compared to 2013. We submitted 239 research projects to various funding bodies. Of the 29 projects submitted within Horizon 2020, 14 were successful at the first stage, and one has already been funded.

An independent international assessment of INT's scientific output was provided by the SCImago ranking system (www.scimagojr.com/), which placed INT at top positions among Italian IRCCSs, as well as in the group of major European research institutions, for the quality of its output, international collaboration, publications in internationally accredited scientific journals, and patent citations.

Clinical research has also been growing steadily: the active clinical trials (i.e. with at least one enrolled patient) were 534 (468 in 2013), 334 of which were non-profit, with 16,551 enrolled patients overall. The quality of active clinical

trials was remarkable, with a 53% rate of randomized studies, corresponding to 193 trials. Among the observational studies, 90% were non-profit, while among drug experimentations the non-profit studies were 48%; these rates show that most of INT's clinical studies are investigator driven.

The high rate of non-profit studies was clearly facilitated by the activity of the institutional **Clinical Trials Center** (CTC). Created in 2011 as a project of the Scientific Directorate and aimed at supporting investigator-driven, early-phase clinical trials and at helping researchers manage spontaneous projects, the CTC has become a fully operational office that, since its beginnings, has coordinated 283 clinical studies, 125 of which are investigator-driven. In 2014, 44 new clinical studies were activated, 29 of which non-profit.

In 2014, Dr Marco A Pierotti, a biologist and experimental researcher, left the charge of Scientific Director after 8 years of tenure, and Dr Ugo Pastorino, head of the Thoracic Surgery Department, took over the interim position.
The appointment of a clinician with long-term experience in large scale clinical trials as Scientific Director was instrumental to the expansion of innovative research fields, and future focus on the improvement of clinical outcome.

In the new research plan, that was agreed with all Department Directors of INT, translational research has been strengthened in order to 1) validate the personalized approach to cancer treatment; 2) offer to the greatest possible number of patients the most innovative therapies, by increasing the rate of patients enrolled in prospective clinical trials; 3) expand randomized trials on early detection and screening, as well as active surveillance programs for indolent disease; 4) identify cases with poor prognosis by characterizing genetic and epigenetic profiles from tissue and liquid biopsies; 5) launch innovative programs of medical and surgical treatment, such as minimally-invasive approach with 3D technology, surgical treatment of metastatic disease, transplant and immunotherapy; 6) implement strategies for primary prevention, including dietary and pharmacological reduction of individual risk.

In order to attain these goals, we had to improve and **potentiate the preclinical lines of research** dealing with unsolved clinical issues, and seeking experimental confirmation or proof of concept in support of innovative clinical decision-making processes. Research projects in line with this vision have already been developed. Validated panels of specific, tumor- or stroma-derived biomarkers (microRNAs, exosomes, proteins) for the main organ-related cancers (such as prostate, lung, breast and colorectal cancer and asymptomatic myeloma) are being consolidated and we are now aiming at the identification of target genes with targeted and next generation sequencing (NGS) techniques. The coordination and integration of the genomic and proteomic platforms that are available at INT and the development of our bio-informatic

infrastructure have made some important discoveries possible, but further support for these areas is indispensable in view of their growing role in cancer research.

Essential support to translational research has been provided by the **institutional tissue bank**, a facility that is constantly expanding and that in future will include tissues from patients with metastatic disease at diagnosis or with tumor recurrence (tumor samples, blood, urine and samples of the specific microenvironment). Finally, murine models still play an irreplaceable role in cancer research, and at INT a new methodology for xenotransplant called PDX, or "human patient-derived xenograft", has been implemented. With PDX we can use patients' surgical samples to recreate their tumors in immune-deficient mice, on which to try out new drugs and fine-tune therapeutic strategies.

As a fundamental tool for the development of translational and clinical research, at the end of 2014 we launched the **institutional tumor registry** (INTR). This project will collect the diagnostic, treatment and follow-up data from over 300,000 consecutive patients, treated at INT during the last 40 years, to evaluate the time-trends in long-term survival, and compare them with the results of randomized clinical trials, with the addition of new genomic analysis.

The INT vision on the value of an integrated and multidisciplinary research effort is exemplified in a special program granted by AIRC 5x1000, which is aimed at the study of the cross-talk between the tumor and its microenvironment to generate a new class of microenvironment-related biomarkers for early detection and assessment of high-risk disease. The project concluded in 2014 its first three years, and was renewed for two additional years after an external site-visit where international examiners recognized the impressive pre-clinical and clinical efforts and the amount of results achieved. In the next two years we aim at turning the experimental findings into patients' cure by exploiting large prospective trials for major tumor types such as colon, prostate, lung and breast.

The importance of micronvironmental changes for generation of novel biomarkers and therapies has been recently proven by the revolutionary results obtained by immunotherapy trials using immune checkpoint inhibitors, where the INT has played a leading role for rapid clinical testing, with a substantial contribution to patients enrolment in major International studies.

Finally, we pursued with determination the objective of offering to the majority of our patients the benefit of **multidisciplinary teams, working on organ-related diseases**. This has already guaranteed the most suitable diagnostic, therapeutic and healthcare approaches, based on state-of-the-art scientific evidence, within a framework of integrated knowledge, integrated resource management, and therapeutic appropriateness.

INT received some important accreditations in 2014: the acknowledgment of ENET Center of Excellence by the European NeuroEndocrine Tumor Society (ENETS) for the quality of care in gastroenteropancreatic tumors, the status of "Comprehensive Cancer Centre" from the Organization of European Cancer Institutes (OECI), and the international award of "ESMO Host Institution" by the European Society of Medical Oncology.

Among the other international events organized at INT in 2014, the "Consensus Conference on Supportive Care for Patients with Head and Neck Cancer", the World Cancer Day 2014 on "Nanomedicine against Cancer", with the participation of Istituto Besta, Fondazione Don Gnocchi, Fondazione San Raffaele, and the Milano-Bicocca University, the partnership of Worldwide Innovative Network Consortium (WIN), CANCON (Cancer Control) Joint Action, TRANSCAN meetings to finalize the next ERA-NET call, and the publication in Lancet Oncology of the EUROCARE-5 study on survival rates for hematological cancer in Europe.

Finally, the cover of this Scientific Report reproduces the new layout of INT's institutional scientific magazine: Tumori Journal. The new Scientific Editor promoted the complete reshape of the magazine, which is now a web-based paperless journal, with a new editorial board including 28 young section editors (all researchers with a median H-index above 18), a new publishing house and layout, and a title that combines its innovative approach with a reference to the magazine's glorious past.

Ugo Pastorino
Scientific Director

THE ESSENTIAL ABOUT INT IN 2014

SCIENTIFIC ACTIVITY

638
PUBLICATIONS

3513.49
IMPACT FACTOR

EDUCATION

181
EVENTS

4,086
PARTICIPANTS

43,069
FORMATIVE HOURS

29,858
FORMATIVE CREDITS

RESEARCH

534
CLINICAL STUDIES

177 OBSERVATIONAL
357 EXPERIMENTAL

16,551
PATIENTS INCLUDED IN CLINICAL STUDIES

13,599 pts enrolled OBSERVATIONAL
2,952 pts enrolled EXPERIMENTAL

CLINICAL DATA

19,597
TOTAL INPATIENTS

5,948
OUTPATIENTS

1,201,563
CONSULTATIONS

RESEARCH FUNDING

23,314,619
TOTAL

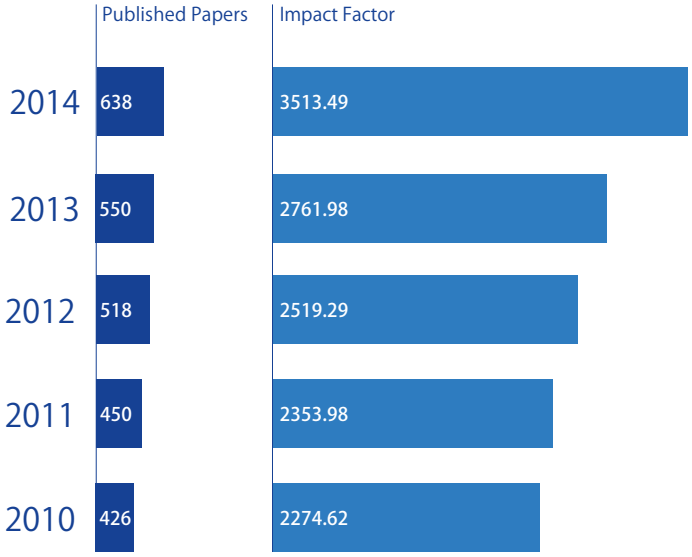
MINISTRY OF HEALTH
€ 7,638,385

FUNDING AGENCIES
€ 11,526,824

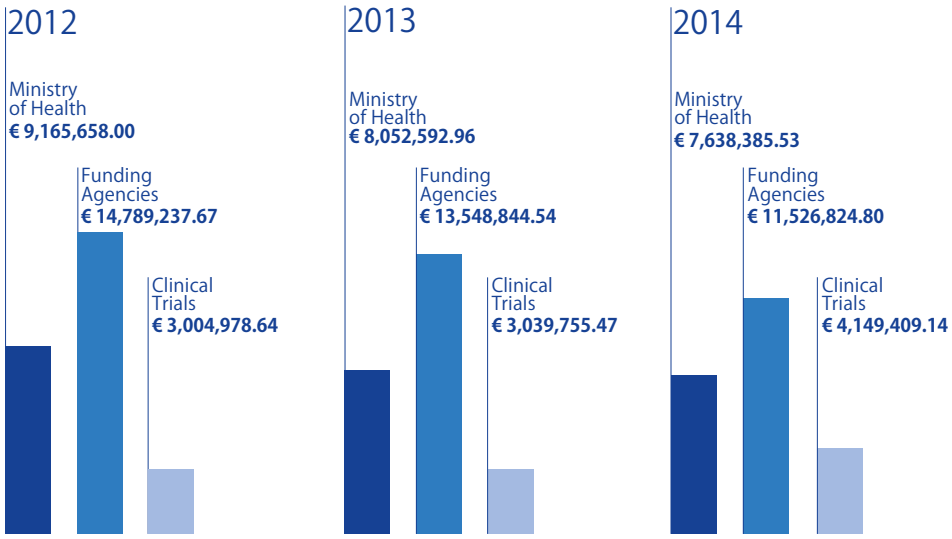
CLINICAL TRIALS
€ 4,149,409

FACTS AND FIGURES

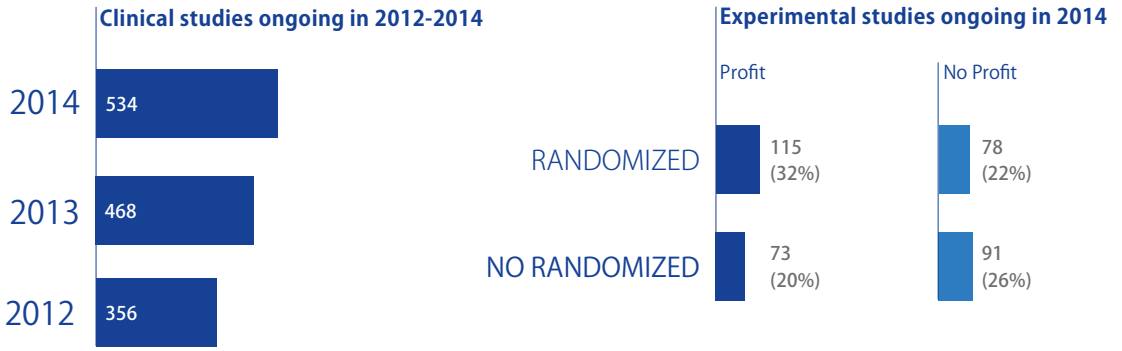
IMPACT FACTOR AND PUBLISHED PAPERS



RESEARCH FUNDING

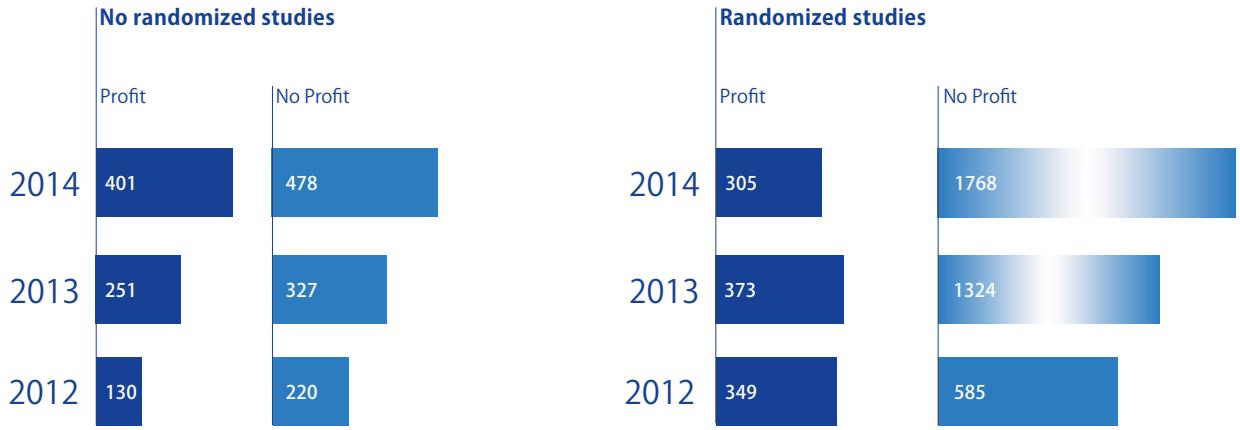


CLINICAL STUDIES



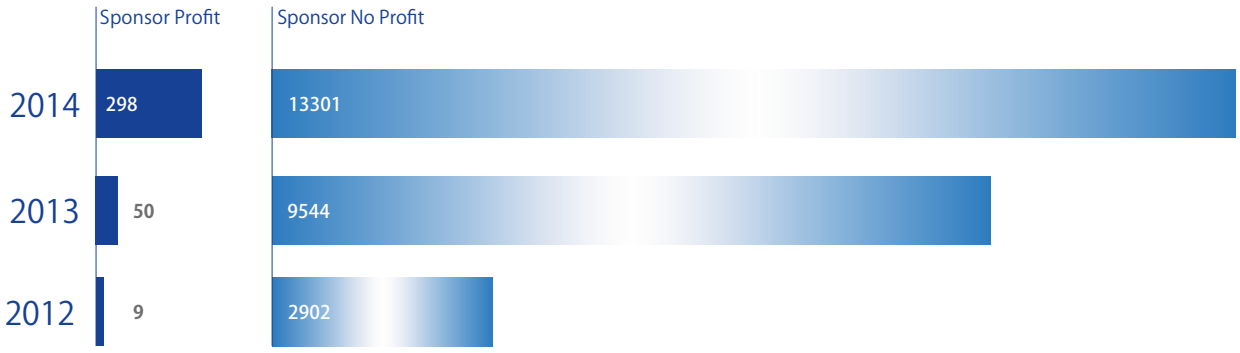
EXPERIMENTAL STUDIES ONGOING IN 2014

N. pts / years



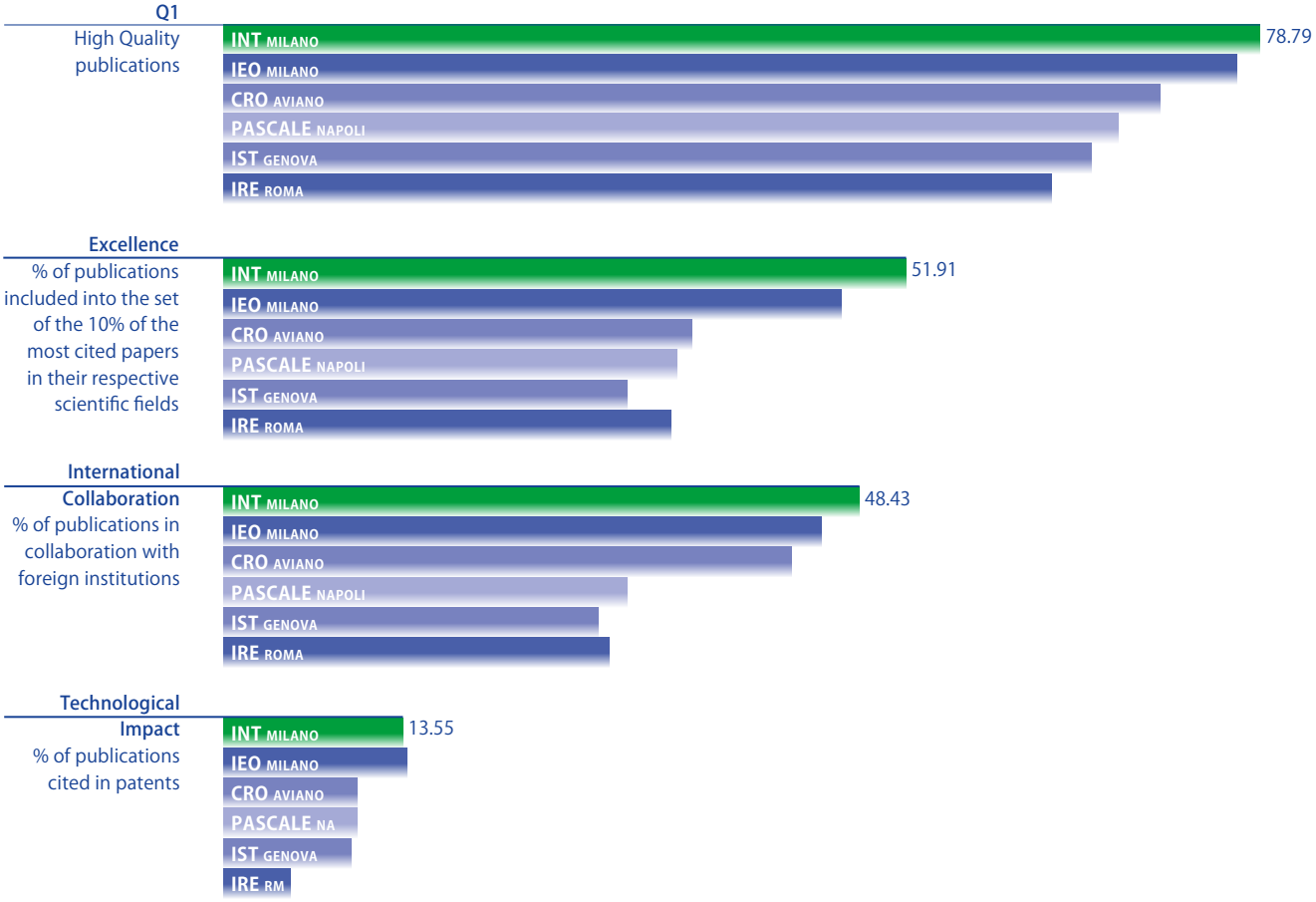
OBSERVATIONAL STUDIES ONGOING IN 2014

N. pts / years



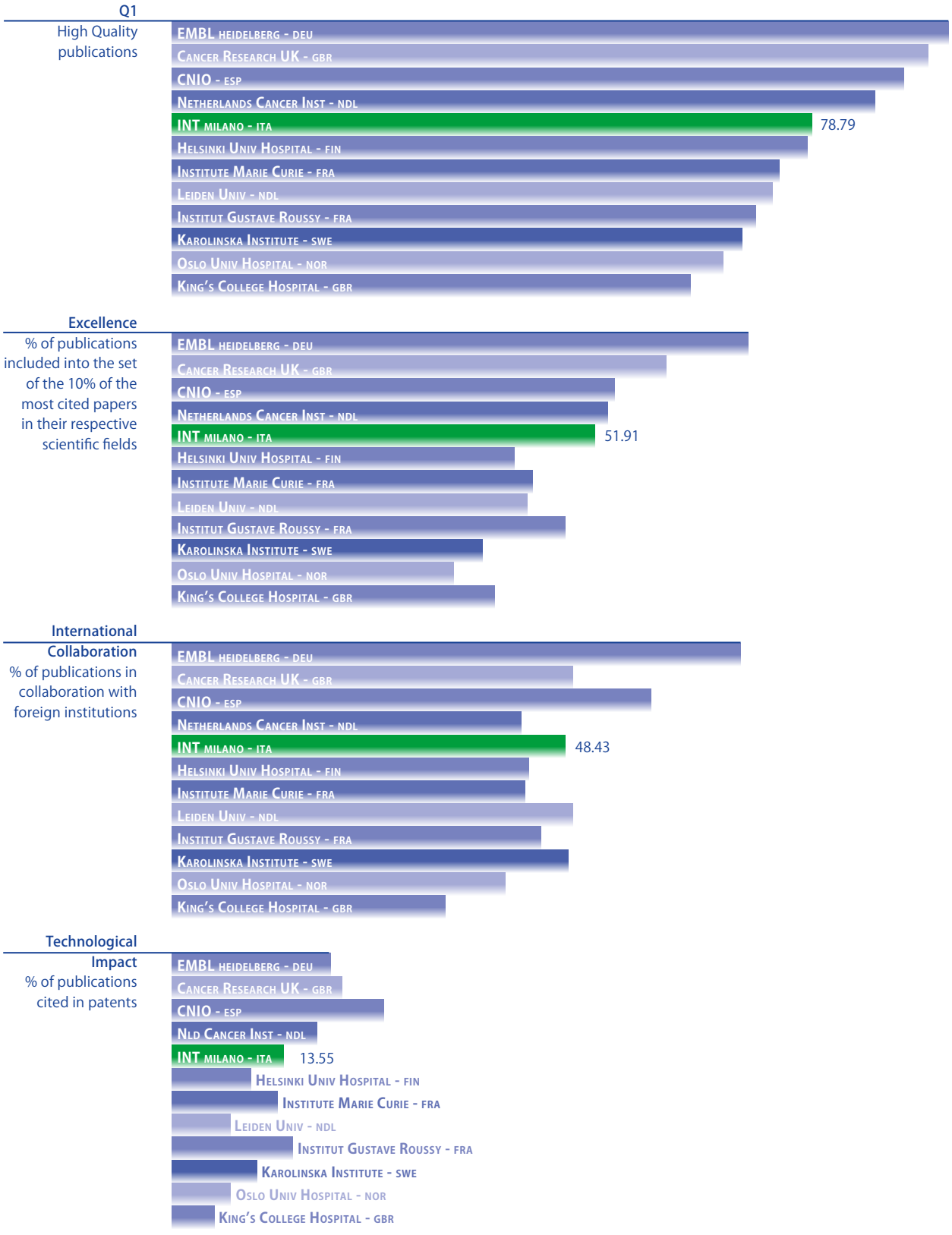
SCIMAGO INDICATORS - ITALY

Source: SIR World Report 2014



SCIMAGO INDICATORS - EUROPE

Source: SIR World Report 2014



AN INTERNATIONAL NETWORK

INTERNATIONAL RESEARCH NETWORKS

BCAC	Breast Cancer Association Consortium
CIMBA	Consortium of Investigators of Modifiers of BRCA1/2
CONTICABASE	European sarcoma database and tumour bank
CRYO-ONCO NETWORK	Includes oncologists, hematologists, pediatricians, surgeons, andrologists and gynecologists, who are all experts in assisted reproductive medicine
ENCR	European Network of Cancer Registries
ENETS	European Neuroendocrine Tumor Society
ENIGMA	Evidence-based Network for the Interpretation of Germline Mutant Alleles
ITCC	The Innovative Therapies for Children with Cancer Consortium
PANCARE	Pan European Network for Care of Survivors after Childhood and Adolescent Cancer
NICSO	Network italiano cure di supporto in oncologia
NATIONAL NETWORK OF RARE TUMORS	Composed of several oncological centers in Italy which have the overall goal of assistance, care, and research on rare tumors
WORLD SARCOMA NETWORK	Cooperative group gathering the main reference centres for sarcomas around the World dedicated to the development and the support of innovative and collaborative clinical trials and to the drug development in Sarcomas

INTERNATIONAL CANCER ORGANIZATIONS

EBMT	European Group for Blood and Marrow Transplantation
ECCO	European CanCer Organisation
EHA	European Hematology Association
EHNS	European Head and Neck Society
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EUROPADONNA	The European Breast Cancer
EUROPAUOMO	The European Prostate Cancer Coalition
OECI	Organization of European Cancer Institutes
WIN	Worldwide Innovative Networking in Personalized Cancer Medicine
UICC	Union for International Cancer Control

EUROPEAN RESEARCH PROGRAMS

EUROCAN PLATFORM	A European Platform for Translational Cancer Research
EPIC	European Prospective Investigation into Cancer and Nutrition
EUROCARE	European Cancer Registry based Study on Survival and Care of Cancer Patients
EUROSARC	European Clinical trials in Rare Sarcomas within an integrated translational trial network
IMMUNOCAN	Toward enhancing activities of European institutions in the FDUSCC-IM cancer research joint institute in China
I.FAMILY	Investigating the determinants of food choice, lifestyle and health in European children, adolescents and their parents
MEMEME	Randomized controlled trial of metformin and dietary restriction to prevent age-related morbid events in people with metabolic syndrome
REQUITE	Validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors

INT AND WEB

Institutional website	www.istitutotumori.mi.it
Art in the Ward Project	www.arteinreparto.com
Early Detection and Risk Assessment Project	www.ederaproject.it
Health Educational website	www.lascuoladellasalute.it
Italian Epidemiological Database on Cancer	www.tumori.net
Italian Society for Adolescents with Onco-Hematological Diseases	www.progettosiamo.it
Lombardy Oncology Network	www.progettorol.it
Multicentric Italian Lung Detection - Clinical Trial	www.biomild.org
Pediatric Oncology - Youth Project	www.ilprogettogiovani.it
SIURO - PRIAS - ITA (Prostate Cancer Research International: Active Surveillance)	www.siuro.it
"When Art meets Medicine" Project	www.artemedicina.com
Tumori Journal website	www.tumorijournal.com

VOLUNTARY ASSOCIATIONS

ADSINT - Associazione Donatori di Sangue Istituto Tumori di Milano	www.adsint.mi.it
AIG - Associazione Italiana GIST Onlus	www.gistonline.it
AILAR - Associazione Italiana Laringectomizzati Onlus	www.ailar.it
ALSI - Associazione Lombarda Stomizzati Incontinenti	www.alsilombardia.it
Amici per la pelle	www.amicixlapelle.it
Associazione Bianca Garavaglia – Onlus	www.abianca.org
Associazione Marta Nurizzo	www.martalive.org
Associazione PaliNUro	www.associazionepalinuro.com
Attive come prima – Onlus	www.attive.org
Casa Amica Onlus	www.casamica.it
F.A.V.O. - Federazione italiana delle associazioni di Volontariato in Oncologia	www.favo.it/associazioni-federate
Fondazione Theodora – onlus	www.theodora.it
Lega Italiana per la Lotta contro i Tumori – LILT	www.legatumori.it
Officine Buone	www.officinebuone.it
Onlus PROMETEO - IRCCS, Istituto Nazionale dei Tumori	www.onlusprometeo.org
Salute Donna – Onlus	www.salutedonnaweb.it

SCIENTIFIC DIRECTORATE

The Scientific Directorate coordinates research and education activities, planning scientific policy and evaluating research projects and clinical trial proposals through the internal review board (Committee of the Scientific Directorate). It keeps the institutional relationships with key health authorities at regional and national level, supports researchers seeking public and private funding through the Grant Office (GO), provides access to information resources with the Biomedical Library services, sustains scientific communication and promotes dissemination of information about health and science to the larger public, in collaboration with the institutional press office.

In 2014, the GO supported INT researchers in preparing and submitting 239 grant applications for public as well as private, national and international funding agencies (Ministero della Salute, Regione Lombardia, MIUR; AIRC-FIRC, Fondazione Berlucchi, Fondazione Cariplo; European Commission, World Cancer Research Fund (WCRF-UK), American Institute for Cancer Research, NIH, Swiss Bridge, Sarcoma Foundation, etc.) and promoted collaborations among the researchers working at INT and outside, helping them to collaborate on research projects.
Through the Clinical Trial Center (CTC) the Scientific Directorate supports investigator driven clinical studies, especially Phase I and II, with the aim of bringing research results and new treatments to the bedside in the shortest time. In 2014 the CTC activated 83 new clinical studies and managed a total of 125 not-for-profit clinical trials.
INT received important national and international accreditations during 2014. In January, upon a site visit audit, the ENETS organization further confirmed for 3 years INT certification as center of excellence for GEP-NET tumors. In September, after a demanding process of accreditation and a severe audit, involving all the Clinical and Experimental Departments, the Organisation of European Cancer Institutes (OECI) granted INT the designation of Comprehensive Cancer Center. Finally, ISO9001:2008 certification has been confirmed at the end of 2014.
The international position of INT has been confirmed in 2014: the Scientific Directorate contributed to the planning and organization of OECI projects (Dr Pierotti has been appointed OECI Executive Secretary), of the CANCON (Cancer Control) Joint Action, and of Transcan meetings to finalize the next ERANET call. The Worldwide Innovative Network (WIN) appointed the chairmanship of the WIN Consortium 2015 to Dr Pierotti who contributed to define the contents and to identify the speakers for this international conference.

In November 2014 Dr Marco Pierotti left the Scientific Director position to Dr Ugo Pastorino. During the last few months of the year Dr Pastorino renewed completely the institutional magazine, Tumori, establishing a new editorial board, creating a new graphic design, restoring the publisher, and replacing the old title in Tumori Journal (TJ).

AWARDS AND RECOGNITIONS

The **Comitato Ospedaledonna of the Osservatorio Nazionale sulla Salute della Donna (O.N.Da)** awarded the Fondazione IRCCS INT with three "Bollino Rosa" prizes for its care in the research and treatment of female diseases and its attention to the specific needs of admitted women.

Dr. Giulia Bertolini of theTumor Genomics Unit was awarded with: Royal Society fellowship; Accademia Nazionale dei Lincei and Progetto Professionalità fellowship; Fondazione Banca del Monte della Lombardia, that supported her scientific visit at the Clinical and Experimental Pharmacology (CEP) group (direct by Prof Caroline Dive) at the Cancer Research UK Manchester Institute.

Dr. Giulia Bertolini and **Dr. Mattia Boeri** of the Tumor Genomics Unit won the AACR-SIC Scholar-in-Training Award for AACR Annual Meeting.

Dr. Augusto Caraceni, Head of the Palliative Care, Pain Therapy, and Rehabilitation Unit, was given the Vittorio Ventafridda Award lecture at the 8th World research congress of the European Association for Palliative Care "Opioid in palliative care: how can research lead to a better clinical practice" (Lleida, Spain. June 5-7, 2014).

Dr. Mario P. Colombo, Head of the Molecular Immunology Unit, was given the: 1st Winner "Premio Fondazione Carlo Chianello 2014".

Dr. Serena Di Cosimo of the Medical Oncology 1 Unit was conferred the "Giovani Ricercatori" award of the Fondazione IRCCS INT.

Dr. Patrizia Gianatempo of the Medical Oncology 1 Unit was conferred the "Giovani Ricercatori" award of the Fondazione IRCCS INT.

Dr. Elena Jachetti of the Molecular Immunology Unit received the COST ACTION Travel Grant, "International Mast Cells and Basophils Meeting 2014".

Dr. Daniele Lecis of the Molecular Mechanisms of Cell Cycle Control Unit was conferred the "Giovani Ricercatori" award of the Fondazione IRCCS INT.

Dr. Valentina Perotti of the Immunology of Human Tumors Unit has been awarded the 1st Prize for the best poster at the XX IMI Congress (Monastier di Treviso, Italy. October 5-7, 2014).

Dr. Sabina Sangaletti of the Molecular Immunology Unit received the EMBL/EMBO Travel Grant, "Symposium Tumor Macroenvironment and Signaling".

Dr. Gabriella Sozzi, Head of the Tumor Genomics Unit, was invited to present the results on the Clinical Utility of a Plasma-based microRNA Signature Classifier within Computed Tomography Lung Cancer Screening at Third AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer (San Diego, California, January 6-9, 2014) and ATS annual meeting (San Diego, California, May 16-21, 2014).

Dr. Tiziana Triulzi of the Molecular Targeting Unit was awarded the fellowship "Fondazione Pezcoller – Ferruccio ed Elena Bernardi 2014".

Dr. Elisabetta Vergani of the Immunotherapy of Human Tumors Unit was selected to participate to the "Novartis Biotechnology Leadership Camp 2014".

The JCO (2014;32:768-73) paper "Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study" by **G. Sozzi, et al**. was cited and commented in Clinical Cancer Advances 2015: ASCO's Annual Report on Progress Against Cancer, JCO, January 20, 2015.

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EDITORIAL

Tumori Journal, 2015 and beyond: the right time for a change

More than a century has passed since the first issue of *Tumori* was published in 1911. The journal quickly established itself as a reference within the oncological community, publishing articles in Italian at first, and then adopting English as the reference language. *Tumori* was indeed amongst the first journals to be indexed in major databases including the National Library of Medicine's Medline and ISI Current Contents, now available under the umbrella of Thomson Reuters Web of Science.

Whilst continuing to attract contributions from all over the world, the visibility of *Tumori* within the scientific community has been somewhat hampered by a publication model prioritizing print distribution over online availability.

2015 will see significant changes in the journal, starting from its title, to stress its nature of an international journal read by scientists and clinicians worldwide, with rapid online publication and Open Access capability upon request.

First of all, *Tumori Journal* will maintain its original nature, covering all branches of cancer science and clinical practice with a strong focus on prevention, translational medicine, and clinically relevant reports.

Most importantly, we want *Tumori Journal* to become a key reference for young investigators who are in the midst of their academic and/or clinical careers and wish to submit "as first authors" solid, methodologically sound investigations, not yet suitable for the most established and impacted journals. We are also inviting them to submit state-of-the-art reviews that will be able to summarize and critically analyze current evidence in all branches of oncology.

In addition, we want to stimulate and attract reports on large series of consecutive patients, that investigate the real impact of new techniques and treatments on day-to-day clinical practice. Our scope will be to implement the evidence from randomized clinical trials, with unselected evaluation of drugs and devices, and health technology assessments on the clinical, economic, and social consequences of cancer.

Last but not least, we welcome submissions of clinical trials protocols.

What we can promise to authors is a fair, rapid, and thorough peer-review process and, in case of acceptance, an ever increasing visibility of their contribution within the oncological community. To readers, we promise the publication of meaningful contributions that may improve basic and clinical oncology; to scientific societies, the affiliation to a 100+ years old journal, now fully equipped for 21st century, state-of-the-art publishing.

I welcome your comments, considerations, and suggestions and I look forward to meeting you as authors, reviewers, and readers of *Tumori Journal*.

Ugo Pastorino
Editor-in-Chief

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WICHTIG

TJ

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Editor-in-Chief

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Carlotta Galeone
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Immunology and Microenviroment

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Pathology

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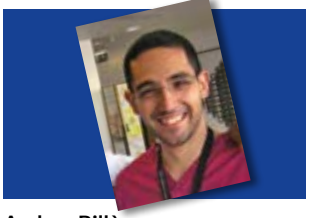
Paola Collini
Pathology



Andrea Billè
Thoracic Oncology

Federico Piccioni
Anesthesia and Intensive Care

Serena Di Cosimo
Breast Oncology

Tumorijournal.com

- International reviewers panel: 63% from Europe, 27% from USA/Canada, 10% from ROW
- Published 6 times a year with advance online publication after acceptance
- 2014 IF 1.09
- Altmetrics data availaible for all articles
- Wide visibility in international libraries/data aggregators/document delivery services
- Indexed in all major databases

Section Editors median age = 42

Section Editors H-Index = 18.5

Annalisa Trama
Epidemiology and Prevention

Filippo Pietrantonio
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Genito-urinary Oncology

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Thoracic Oncology

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Pediatric Oncology

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Radiotherapy/Head and Neck

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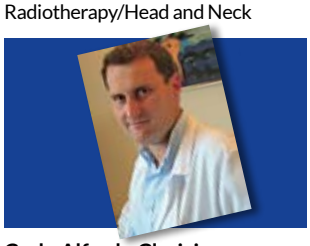

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Nicola Sverzellati
Diagnostic Imaging

Benedetto Mangiavillano
Endoscopy

Alessandro Gronchi
Melanoma and Sarcoma

Niccolò Bolli
Hematology-Oncology

Editorial objectives

- To attract relevant papers in experimental and clinical oncology
- To become a reference journal for young and upcoming oncologists.

Online submission system with fast peer review process (first decision within 3 weeks) at www.editorialmanager.com/tj

MEDICAL STATISTICS, BIOMETRY, AND BIOINFORMATICS (MSBB)

Director: Adriano Decarli, PhD

The MSBB provides quantitative support to research activity across various Departments at INT, and maintains collaborative relationships with other national or international research groups. The activity of the INT group is governed by a convention with the University of Milan.

Biostatistics for Oriented Basic Research and Quality Control (Paolo Verderio, Biol Sci D, PhD; Sara Pizzamiglio, Msc). The team applies statistical methods to different phases of the biomarker development process in oncology. It provides *a*) implementation and statistical analysis of quality control studies for tumor biomarkers and in vitro diagnostic tools, *b*) evaluation of inherited diseases in oncology, *c*) establishment and validation of biological assays, *d*) preclinical pharmacology and testing new molecular detection strategies based on innovative technologies. As partner of the FP7 EU Project SPIDIA, the team is involved in the planning, implementation, and statistical analysis of ring trials, and contributes to the setup and validation of biological assays and testing of new molecular detection strategies based on innovative technologies.

Biostatistics for Bioinformatics and Translational Research (Elia M. Biganzoli, PhD; Giuseppe Marano , PhD). In the context of analytical molecular epidemiology, the team supports the transfer of basic preclinical research to clinics using quantitative approaches to assess the impact of new technologies in oncology according to cost-benefit principles and sustainability perspectives. Within the framework of collaborative projects, the team is involved in research concerning the assessment of high-throughput and next generation sequencing (NGS) platforms for DNA and RNA analysis, qRT-PCR, and highthroughput assays in cancer. Statistical bioinformatics research supports the design and analysis of NGS experiments. Studies on follow-up data with reference to the analysis of risk patterns related to metastatic dormancy are conducted in cooperation with clinical Units.

CLINICAL EPIDEMIOLOGY AND TRIAL ORGANIZATION

Director: Luigi Mariani, MD PhD
Research Staff: Rosalba Miceli, PhD; Elena Landoni, PhD

The Unit provides statistical support relating to the design, conduct, and analysis of clinical trials, observational and population-based studies, mainly in the areas of surgical, medical or hematological oncology.

CLINICAL TRIALS CENTER

Coordinators: Valentina Sinno, Biol Sci D and Luigi Mariani, MD PhD

The operative Clinical Trial Center (CTC) has been re-established in January 2012 by the Scientific Director to support clinical studies, especially investigator driven and Phase I and II studies, with the aim of bringing research results and new treatments to the bedside in the shortest time. The CTC supports Clinical Researchers in managing many aspects of investigational clinical studies, such as study design and statistical validation, submission to the Ethics Committee and regulatory authorities (AIFA for Phase I studies), budget and contract related issues, as well as data management and statistical analysis, thanks to 16 data managers, two medical statisticians, and an administrative and legal specialist. The CTC also provides pharmacovigilance through an “ad hoc” trained pharmacist, employs six qualified Research Nurses to improve patient care in the various steps of the study (scheduling of treatments, blood sampling,

exams, controls, etc.), and two laboratory biologists to handle tissue and blood samples for pharmacokinetics and molecular studies.
CTC works through validated and updated SOP and electronic CRF customized for each specific study; personnel education and training is coordinated by the Scientific Directorate.
The CTC is also improving the organization of sponsored clinical trials, speeding up administrative processes, budget definition, patient recruitment and data management, organizing a centralized record of all radio-diagnostic exams, and assisting Clinical Monitors in their visits.
Since its inception the CTC managed 283 clinical studies, 125 of which investigator-driven; in 2014, 83 clinical studies were activated, 35 of which non-profit.

RESEARCH PROGRAMS

MICROENVIRONMENT AND INFLAMMATION

PROGRAM/PROJECT MEMBERSHIP

M.P. COLOMBO (COORDINATOR)
L. ROZ, D. DELIA, M. GARIBOLDI,
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A core project grouping several Units of INT aims at the identification of new molecules detectable in blood circulation that may have diagnostic and prognostic value at cancer onset or recurrence.

We foresee an approach in which stroma cell components, through the interaction with nascent or recurrent tumor, can be the source of such an early marker. It is strengthening the concept that stroma cell components coevolve with tumors to form a functional unit that gives rise to misinterpretation of a wound-like signal and tumor remodeling and progression.
Many stroma cell components are recruited at the tumor site and the signals leading to cell transformation may represent potential biomarkers. Thus, detection of circulating miRNAs predictive of incipient lung cancer earlier than spiral CT, or linked to existing precancerous lesions in subjects with increased risk of colorectal cancer, plus the possibility that fibroblast or other stromal cells produce some of these factors, indicate that the approach is realistic. Therefore, since 2013, the group of Mario Colombo together with that of Claudio Tripodo (University of Palermo) has investigated the morphologic, phenotypic, and molecular variations occurring in primary and secondary lymphoid organs in relation to transforming mammary glands of transgenic mice selectively expressing an oncogene in the breast. Differentially expressed genes in such organs and circulating miRNAs have been identified and some of the latter were also found in the context of human carcinomas. This correlation will be tested retrospectively in cohorts of patients with known diagnoses and in a prospective study. Investigation of cross-communication between distinct environments (tumor and lymphoid organs) performed in mice is not possible in humans. Consequently, several groups have tried to dissect the tumor environment to identify the relevant cellular and extracellular players, while other groups have combined tumor cells and fibroblasts to identify molecules governing their communication.
Maria Grazia Daidone and Collaborators have found that, in vitro, cancer-associated fibroblasts (CAFs) can promote an autocrine loop sustained by IL-6 and IL-8 in luminal and HER-2 positive cancer cells, whereas basal cells do not seem to depend on fibroblast instigation. On the other hand, supernatants from breast cancer cells induce the expression of TGM2, encoding for tissue transglutaminase 2, a multifunctional protein also involved in modulation and deposition of extracellular matrix (ECM) and up-regulated in inflammation and wound repair.
An ECM gene signature helps to identify the class of risk of breast carcinoma. In particular, type ECM3 in grade III tumors identifies patients with worse survival. This finding from EldaTagliabue's Group has been extended and, in collaboration with the University of Pisa, they found the highest stiffness in ECM3 grade III tumors. Proteomic analysis of soluble extracts from these tumors analyzed for the elastic modulus by two-dimensional difference gel electrophoresis coupled with MALDI mass spectrometry revealed several characteristic spots that identified ECM3 grade III tumors.

In mice, differentially expressed genes in primary and secondary lymphoid organs and circulating miRNAs have been identified and some of the latter were also found in the context of human carcinomas

The main cell type studied in tumor microenvironment is the fibroblast, which can be variably activated and not necessarily depending on the distance from tumor cells. Primary fibroblast cultures have been established by the Group of Luca Roz in Gabriella Sozzi's Unit from surgical specimens either adjacent or distant from the cancer area, and functionally tested for supporting lung tumor xenografts growth in immunodeficient mice, an effect often associated with activation of the Epithelial to Mesenchymal Transition (EMT) program. Pro-tumorigenic properties were also observed by culturing normal lung fibroblasts, suggestive of their ability to generate markers for risk assessment after sensing variations in the lung microenvironment. Stromal markers with potential prognostic significance have been identified in a large IHC study using univariate analyses and more complex risk models developed by the Clinical Epidemiology and Trial Organization Unit (Elena Landoni and Luigi Mariani) and will be validated in a large retrospective clinical series selected by Giuseppe Pelosi and Ugo Pastorino. In vitro, tumor fibroblast co-cultures established that physical contact between cells or their produced ECM induced the most aggressive behavior.

The main cell type studied in the tumor microenvironment is the fibroblast, which can be variably activated and not-necessarily depending on the distance from tumor cells

Nevertheless, cross-talk of tumor-fibroblasts-associated can occur through information passed by miRNAs as shown by Paolo Gandellini in the Nadia Zaffaroni's Unit. Normal epithelium releases miR-205 which neutralizes the pro-oxidant, pro-inflammatory, and pro-tumorigenic vicious circle between cancer and the associated fibroblasts. Another miRNA, namely miR-210, if up-regulated in fibroblasts, further promotes tumor aggressiveness thereby fuelling the tumor with energy-rich metabolites, recruiting endothelial precursor cells, and stimulating HUVEC capillary morphogenesis.

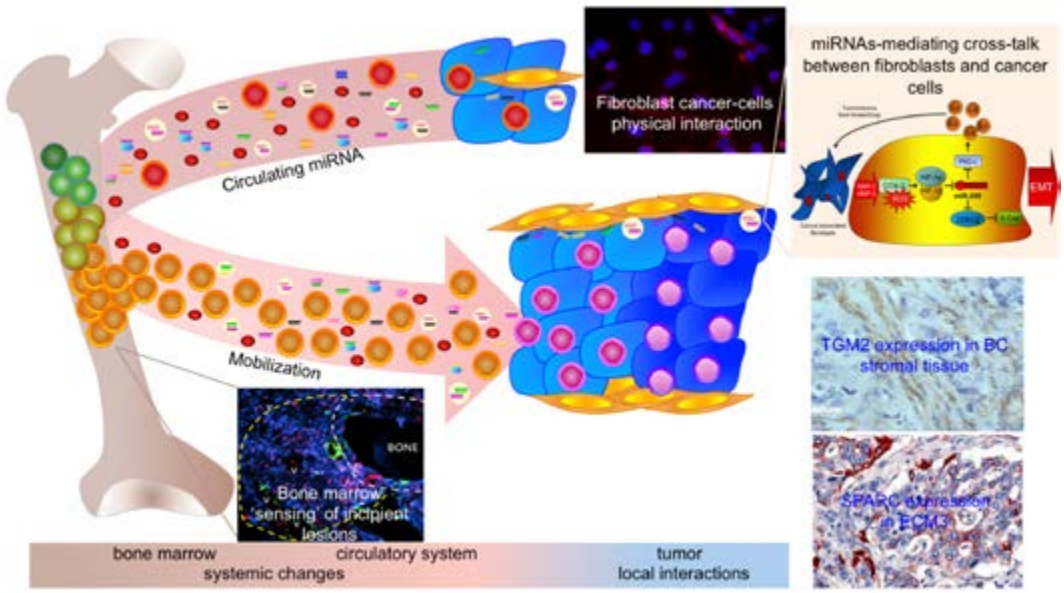
Moreover, Licia Rivoltini and Collaborators have shown that the myeloid cell component of the tumor microenvironment contributes to melanoma progression. The tumor releases exosomes, which are able to convert monocytes into myeloid-derived suppressor cells (MDSC). This conversion is mediated by specific proteins (e.g. CCL2 and TGF β) and selected miRNAs (mir155, 125 and 146) coexisting within the melanoma exosomes passed into monocytes upon contact. Signs of this exosome-mediated MDSC conversion can be found in the peripheral blood of melanoma patients in clear association with a more aggressive disease, suggesting that the pathway is active in vivo and that it can be exploited for prognostic or therapeutic purposes.

The tumor releases exosomes, which are able to convert monocytes into myeloid-derived suppressor cells

Taken together, these studies delineate a plethora of microenvironmental variations among which suitable prognostic markers or markers for early diagnosis can be expected to be identified.

FIGURE

Local and systemic interactions between tumor, stroma, and bone marrow, involving miRNA, and proteins trough exosomes.



IMMUNITY

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Understanding the reasons why the immune system fails to control tumor growth is an essential step in the identification of novel prognostic markers and therapeutic avenues.

Licia Rivoltini and Collaborators (Immunotherapy of Human Tumors Unit) have been focusing on the study of microvesicles and exosomes as conveyors of immunomodulation, and novel immune checkpoints associated with immunological dysfunction. Melanoma exosomes have been found to affect myeloid differentiation and promote the generation of myeloid-derived suppressor cells (MDSC) both in vitro and in mice. MDSC conversion is driven by the multiple co-expression of CCL2, TGF β and selected miRNA (mir120, 146, 150) that are embedded into exosomes and transferred to target cells. The evidence that plasma exosomes and circulating monocytes from melanoma patients express a MDSC cytokine/miRNA signature, demonstrates that exosome-mediated myeloid conditioning does occur in vivo. Through multiple phenotypic analysis of blood cells and mathematical modeling of the immune profile, a Myeloid Index Score (MIS) significantly associated with poor survival has been identified. Including both monocytic and granulocytic MDSC, MIS predicts overall survival in metastatic melanoma patients and represents a potential tool for guiding therapeutic choices. Drugs for the correction of myeloid dysfunction and associated immunosuppression are also under investigation. MDSC-miRNA antagomir and proton pump inhibitors appear to significantly counteract exosome-mediated myeloid conditioning in vitro. A phase II clinical trial (Adesom2) investigating the immunomodulating properties of esomeprazole is presently ongoing in early melanoma patients in collaboration with the Melanoma Unit (Mario Santinami). The myeloid compartment of hepatocellular carcinoma (HCC) is also being studied for prognostic and therapeutic purposes in collaboration with the Gastrointestinal, Hepato-Pancreatobiliary Surgery and Liver Transplantation Unit (Vincenzo Mazzaferro).

A Myeloid Index Score (MIS) significantly associated with poor survival has been identified. MIS predicts overall survival in metastatic melanoma patients and represents a potential tool for guiding therapeutic choices

The evaluation of sentinel and draining lymph nodes (LN) provides pivotal information about the outcome of tumor immunity. Through gene-expression profiling, CD30 has been found to be upregulated in sentinel node of melanoma patients undergoing disease progression. CD30 defines a subset of anergic and immunosuppressive lymphocytes, and possibly represents a novel immune checkpoint involved in tumor immune evasion. The evidence that CD30 inhibition results in reduced melanoma growth in mice is in line with this hypothesis and supports further studies on the potential prognostic and therapeutic role of this marker. Melanoma-invaded LN are also enriched in a specific subset of plasmacytoid dendritic cells (pDCs) expressing LAG-3 and exerting immunosuppressive activity and myeloid cell recruitment. pDCs are thus a crucial component of the tumor microenvironment that should be counteracted to restore effective immunity.

Gene expression profiles of neoplastic cells can provide evidence for immune-related gene signatures that contribute to the biological behavior

of human cancers. Using a case series of stage I breast cancer, Maria Grazia Daidone and Colleagues (Biomarkers Unit) have identified and validated in large series of publicly available datasets a signature of a differentially expressed (DE) metagene, rather than single DE genes, associated with distant metastases beyond classical risk factors. Such a signature, including interferon-induced genes (IFN metagene), proved to be predictive of distant metastasis in patients with luminal/ERBB2$^-$ tumor, and was associated with a low risk of metastasis in patients with ERBB2$^+$ tumor while did not significantly affect prognosis in those with basal tumors. This study confirms the importance of analyzing prognostic variables separately within breast cancer subtypes, highlights the advantages of using metagenes rather than genes, and finally identifies in node-negative luminal/ERBB2$^-$ cancers the unfavorable role of high IFN metagene expression (M. Callari et al. Mol Oncol, 2014). Recruitment of MDSC as possible 'effectors' of the negative prognostic role of the IFN-metagene is currently under investigation.

A differentially expressed metagene signature proved to be predictive of distant metastasis in patients with luminal/ERBB2$^-$ tumor

Emerging evidence in melanoma, NSCLC, and other solid tumors indicates that response to cancer immunotherapy, by targeting of CTLA-4 and PD-1 immune checkpoints, depends on pre-existing tumor immunity that, unfortunately, develops only in some patients. Andrea Anichini and Colleagues (Human Tumors Immunobiology Unit) have focused on understanding how the innate and adaptive arms of the immune system contribute to naturally occurring tumor immunity. They also investigated mechanisms that prevent activation of anti-tumor immunity or response to immune checkpoint therapy. In melanoma, a new subset of NK cells was identified. This subset expressed strong cytotoxicity against autologous melanoma cells and was selectively enriched in tumor-invaded lymph nodes. These findings suggest that even the innate arm of the immune system may be exploited in immune checkpoint blockade approaches, since NK cell activity can be regulated by inhibitory receptors.

In melanoma, a new subset of NK cells was identified

In neoplastic tissues from NSCLC patients, selective enrichment for recently activated and tumor-reactive CD8$^+$ T cells was found compared to adjacent normal lung tissue. These lymphocytes were identified as CD8$^+$ FOXP3$^+$ "early effector cells" (EECs) and were shown to upregulate different inhibitory receptors. These results provide further rationale for the treatment of NSCLC patients with anti-PD-1 monoclonal antibodies to promote the anti-tumor effector functions of these recently activated T cells.

Analysis of processes that prevent activation of adaptive anti-tumor immune responses pointed to the relevance of immune escape mechanisms, such as loss of expression of tumor associated antigens (TAAs) and of HLA molecules by neoplastic cells. In melanoma it was found that the transcription factor NFATc2 is a major intrinsic regulator of melanoma dedifferentiation and immune escape. NFATc2, when constitutively expressed in melanoma cells, suppressed MITF, the master regulator of melanocyte differentiation antigen (MDA) expression. This in turn leads to loss of expression of MDA epitopes recognized as TAAs by T cells. Targeting of NFATc2, by gene silencing or pharmacological inhibition, leads to re-expression of MDAs and to rescue of T cell recognition of melanoma cells. Failure of melanoma patients to respond to anti-CTLA-4 therapy was associated with strong immune escape mechanisms. Pre- and post-therapy lesions from non-responding patients showed loss of expression of HLA Class I molecules, and these lesions lacked infiltrating CD8+ T cells. Instead, HLA molecules were retained in lesions from responding patients. Further investigation on the phenotypic features of tumor-infiltrating lymphocytes and the relationship of immune escape mechanism with resistance to immunotherapy is underway. These studies may lead to better understanding of which patients may be most likely to respond to immune checkpoint blockade.

Failure of melanoma patients to respond to anti-CTLA-4 therapy was associated with strong immune-escape mechanisms

Co-stimulatory molecules are complementary to checkpoint inhibitors for tuning the immune response. Mario P. Colombo (Molecular Immunology

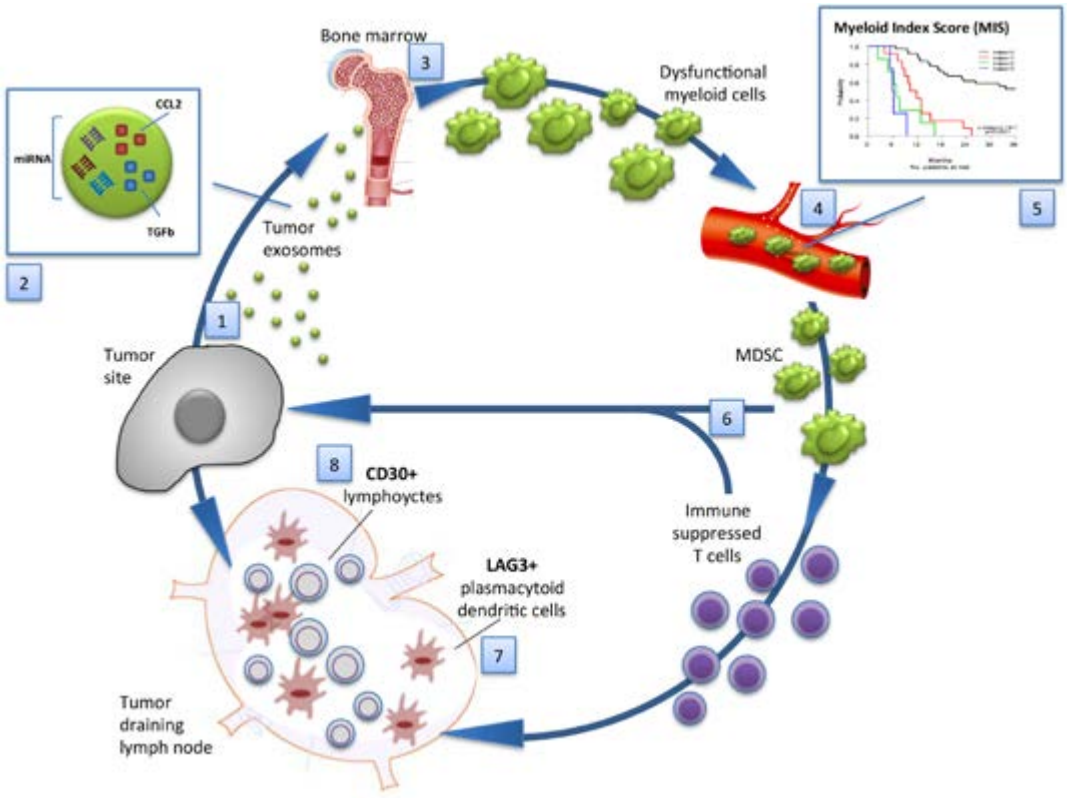
Unit), Massimo Di Nicola (Immunotherapy and Anticancer Innovative Therapeutics Unit) and Collaborators are studying the role of OX40 co-stimulation in regulatory T cells (Treg) infiltrating ovarian carcinomas. Either high or low expression of OX40 in such tumors seems to subdivide patients with different disease-free survival and foresee the possibility of validating OX40 as prognostic marker for ovarian cancer.

Cancer immunotherapy by antibodies to T cell inhibitory receptors (such as CTLA-4 and PD-1) has markedly improved treatment of different advanced tumors, as shown initially by clinical studies targeting CTLA-4 in melanoma and NSCLC. Many cancers co-opt the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway to evade immune-mediated tumor rejection. Encouraging clinical activity against several tumor types has been seen for anti-PD-1 and anti PD-L1 monoclonal antibodies. Traditionally, these drugs were used in malignant melanoma, but now they are under investigation at INT in several clinical trials by Filippo de Braud, Maria Di Bartolomeo, Andrea Necchi, Giuseppe Procopio and Colleagues (Medical Oncology Department, MOD) in other tumor types, such as NSCLC, neuroendocrine tumors, renal cell carcinoma, urogenital tumors and gastric cancer. So far, the majority of trials have been conducted in melanoma by Michele Del Vecchio (MOD) and in NSCLC by Marina Garassino and Colleagues where a large number of patients have been included in several studies and in all treatment lines. In particular, the Thoracic Oncology Unit had an important role in the Checkmate-017 study, which led to the FDA approval of nivolumab (anti-PD-1) in squamous cell carcinoma. Additionally, a basket phase I/2 trial is ongoing with nivolumab or with the combination of nivolumab and ipilimumab (anti-CTLA-4) in patients with advanced disease. In particular, interesting results have been observed in patients with NSCLC where second and further lines are poorly active.

Encouraging clinical activity against several tumor types has been seen for anti-PD-1 and anti PD-L1 monoclonal antibodies

FIGURE

Multiple mechanisms mediating the Tumor Immune-escape.



ORGAN REPLACEMENT & RECONSTRUCTION: LIVER TRANSPLANTATION

PARTICIPATING/PROGRAM MEMBERSHIP

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Indications for liver transplantation (LT) are multifold and can be classified into end-stage liver disease, acute liver failure, and certain benign and malignant liver tumors.

LT should be considered for any patient in whom anticipated overall survival (OS) exceeds life expectancy of the underlying disease or where significant increase in quality of life can be achieved. These criteria may also be valid for many patients with primary liver tumors or hepatic metastases. However, LT for malignant disease is a medical and ethical challenge with regard to long-term oncologic outcomes under immunosuppressive therapy and with regard to allocation due to organ shortage. In the future, ongoing improvements in multimodality cancer therapy may widen the indications for LT in malignant disease.
LT is the only solid organ transplant performed for cure of malignancy. At INT, a median of 35 LTs are performed each year. LT is a part of the process of cure for some specific tumors (hepatocellular carcinoma, metastatic neuroendocrine tumors, and some rare malignancies): both the process of cure associated with LT and subsequent follow-up are managed by a multidisciplinary taskforce that involves surgeons, hepatologists, radiologists, anesthesiologists, oncologists, and a dedicated nursing staff.

Liver transplantation for hepatocellular carcinoma

LT is the only curative treatment option for patients with irreversible acute or chronic liver failure and, in the last four decades, has developed from an experimental approach with very high mortality to an almost routine procedure with excellent short- and long-term survival rates. From the time of its initial development, LT appeared as the ideal cure for primary liver tumors, in particular hepatocellular carcinoma (HCC) arising from established liver cirrhosis, because it had the ability of curing at the same time both the tumor and the underlying liver disease. Early unsatisfactory results emphasized that only a highly selected patient population would benefit from transplantation, as survival of patients is directly related to the stage of HCC at the time of LT (1). This was a field for the development of the prospective study by Vincenzo Mazzaferro and Coworkers conducted at INT, which in 1996 showed that applying a priori restrictive criteria for selection of HCC candidates for LT (namely a single nodule ≤5 cm or 2-3 nodules ≤3 cm, each with no macrovascular invasion at pre-transplant imaging), it was possible to obtain long-term results that were better than any other therapy applied for HCC (2). These so-called Milan Criteria (MC) were subsequently validated by many other groups reporting 5-year survival rates of 70% or better, and were used worldwide as selection guidelines (3).
On January 2015, the National Transplant Center (CNT) published the report on the outcomes of LT in Italy performed in the period from 2000 to 2012. During this period, 12,471 LTs were performed at 22 Italian Centers. Of these, 370 were performed at INT, and the 1- and 5-year survival rates were 95.4% and 84.4%, respectively, among the best in Italy. The median 1- and 5-year survival rates throughout the country were, in fact, 85.9% and 73.7%, respectively.

Only a highly selected patient population would benefit from transplantation

In 2014, 36 patients underwent LT at INT: 32 were affected by HCC within the Milan Criteria at first diagnosis or after successful downstaging. HCCs meeting the MC have been confirmed to be a separate prognostic category associated with good outcomes after LT: however, only approximately 30% of HCCs are diagnosed at an early stage (namely within the MC), and therefore the large majority of patients can be offered only palliative treatments. Several experiences suggested that such restrictive criteria may exclude LT patients with a more extended disease, but still in the range of a possible cure. This is a debated issue which has been ongoing for about two decades with a large number of proposals alternative to MC published, most of which are based on retrospective evaluations of postoperative pathology (4). Up to now, none have managed to replace the MC that hence have been termed "conventional criteria", while any criteria beyond the size-and-number assigned to HCCs within the MC, are deemed as "extended" (Fig. 1).

Up to now, none have managed to replace the Milan Criteria that hence have been termed "conventional criteria"

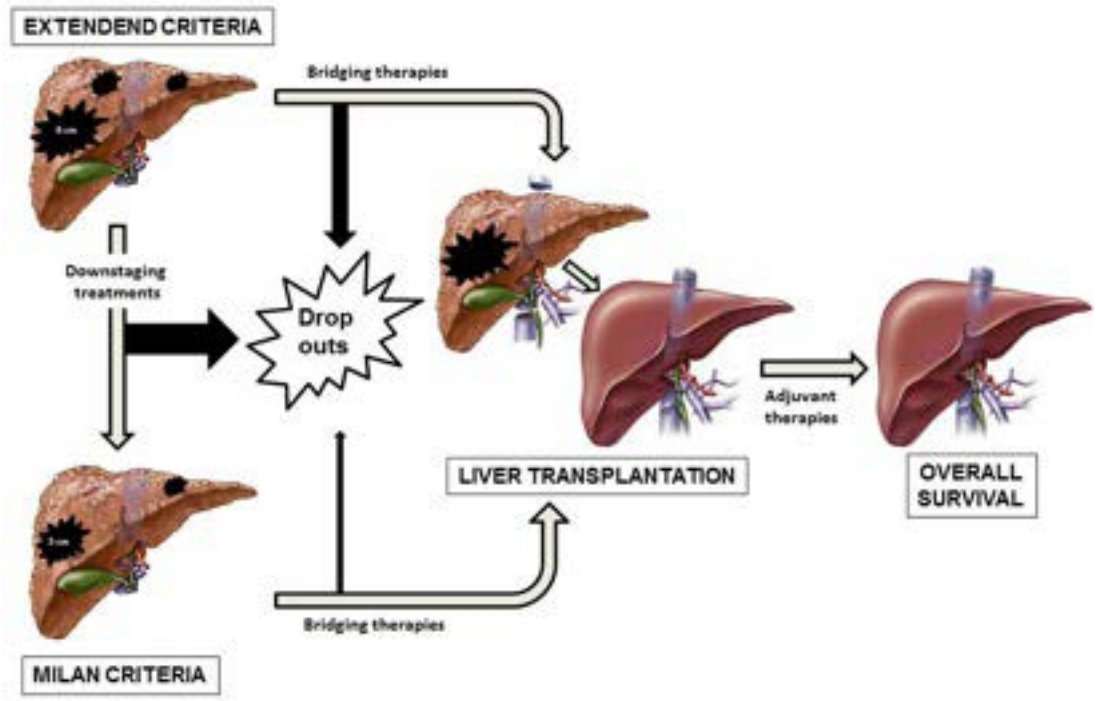

FIGURE 1
Tumor-related factors affecting prognosis of patients undergoing LT for HCC.

Another possible way of expanding the criteria for LT for HCC is through downstaging treatments. Downstaging is defined as a treatment given to HCC patients that are not eligible to LT because of tumors beyond conventional criteria, with the objective of reducing tumor burden (in terms of number, size, or tumor vitality) within a priori established conventional limits (generally MC) considered acceptable for LT. This strategy was initially suggested by the group in Hopital Paul Brousse, Paris, who retrospectively observed higher rates of survival in trans-arterial chemoembolization (TACE) responders than in non-responders in an analysis of patients with more than three nodules or nodules larger than 3 cm (5). Since then, few specific (and mostly retrospective) studies on downstaging before LT have been produced: the large differences in the criteria used, both to include patients in downstaging protocols and to subsequently decide on listing for transplantation, led to heterogeneous results, and up to now precluded from a common agreement on the feasibility and efficacy of downstaging protocols as a way to expand transplant criteria for HCC (6).
In 2011, our group designed a multicenter randomized clinical trial (RCT) to investigate whether or not LT following a successful downstaging may provide a survival benefit with respect to pure downstaging procedures. This

was the first RCT ever that sought to evaluate the outcomes of LT in patients with HCC. The protocol "Controlled Expansion of Conventional Criteria for Liver Transplantation in Hepatocellular Carcinoma Through Downstaging Procedures: a Randomized Trial" or "XXL trial" has involved the most important Italian Centers dealing with LT, and patient enrolment has ended on December 31th, 2014. The study enrolled only patients with a confirmed radiological diagnosis of HCC in cirrhosis (Child-Pugh A-B7), exceeding MC, with no extra-hepatic spread (EHS) and with at least >50% 5-year estimation of survival after liver transplantation according to the Metroticket Calculator (www.hcc-olt-metroticket.org/). Those patients who achieved a radiological partial or complete sustained response after downstaging procedures were randomized in a 1 to 1 fashion to receive or not LT.
At INT, the XXL trial has enrolled a total of 35 patients. At diagnosis, all were beyond the MC, being median size of the largest nodule 40 mm (13—80) and median number of nodules 3 (1—6). After downstaging procedures (mainly TACE), 74.3% of patients showed a partial or complete response, while 25.7% demonstrated a progressive or stable disease that impeded randomization; those latter patients dropped out from the study and were followed up until death. Of the 26 patients who were randomized, 13 underwent LT while 13 patients were treated according to the best available care. Preliminary results showed similar 3-year survival rates of 64.9% in the LT group and of 64% in the No LT group (p=0.81). Conversely, LT patients showed significantly fewer tumor recurrences as compared to the No LT group, being recurrence-free survival at 3-years 87% in the LT group and 0% in the No LT group, respectively. Actually, it is likely that follow-up period is too short to observe significant differences in terms of survival. However, considering recurrence-free survival as a surrogate endpoint of the efficacy of LT for HCC patients responding to downstaging, these results highly support the study hypothesis and may open the doors for an expansion of LT selection criteria after successful downstaging.

Liver transplantation for metastatic neuroendocrine tumors
Neuroendocrine tumors (NETs) originate from different parts of the widespread neuroendocrine system. Heterogeneity of biological features and clinical outcomes present significant challenges for diagnosis and treatment (7). Delayed diagnosis is common and tumors are often discovered when liver metastases have occurred often associated with the paraneoplastic "carcinoid syndrome". (8) Limited therapeutic options are available for these patients, and liver metastases represent the leading cause of death. Therefore, the perspective enabled by liver transplantation has been repeatedly explored, but selection biases and variegated resource allocation issues have made the interpretation of results difficult. (9) At INT, a systematic application of restrictive criteria for selecting transplant candidates with liver metastases from NETs was started in 1995. (10)
INT Criteria for Liver Transplantation in Patients with Liver Metastases from NET are:

- Confirmed histology of low-grade (G1-G2) neuroendocrine tumor
- Primary tumor drained by the portal system and removed with all extrahepatic deposits in a separate curative resection prior to transplant consideration
- Metastatic diffusion to <50% of the total liver volume
- Stable disease/response to therapies for at least 6 months prior to transplant consideration
- Age < 60 (relative criteria)

Since then, all patients presenting with tumors fulfilling such criteria have been considered for liver transplantation and eventually enlisted according to wait-list capability, patient compliance, and absence of contraindications. In 2014, our research has been focused on investigating survival outcomes of a series of patients with metastatic NETs who underwent LT at INT according the aforementioned criteria, collected over 20 years. Moreover, we sought to evaluate if LT provides a significant survival benefit compared

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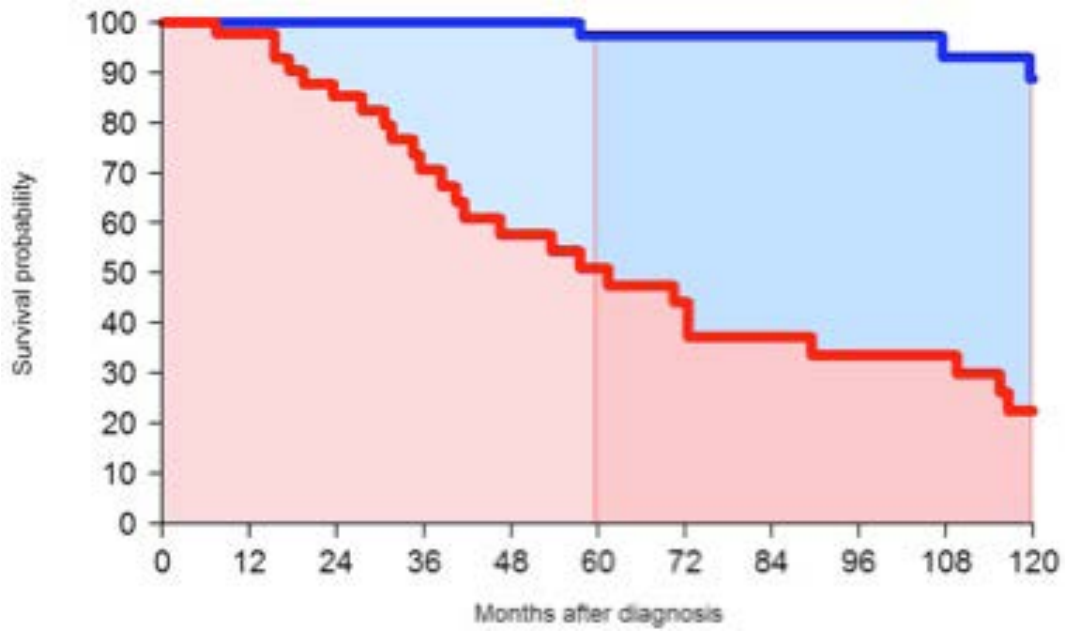
to a therapeutic strategy that does not include LT. The results of our investigations were presented at the American Association for the Study of Liver Diseases congress 2014 (plenary session), and are currently submitted for publication.

Of 280 patients referred for transplantation, a prospective cohort of 88 NETs with restrictive tumor characteristics was selected on the aforementioned pre-determined criteria. Allocation to transplant (n=42) versus no transplant treatment (n=46) depended on wait-list availability, patient disposition, and age considerations. Long-term outcomes were compared between groups after matching made through multiple Cox models and adjustment for propensity score built on logistic models based on patient age, stage of primary tumor, and serum chromogranin A. Survival benefit was the difference in mean survival between liver transplant versus non-transplant options. Transplant patients were younger (40.5 vs. 55.5 years; p<0.001). There was no difference in tumor burden. No patient was lost to follow-up or died without recurrence. Marginal quality grafts were used in 86% of transplants; 89% of non-transplanted patients received systemic therapies. Median follow-up was 122 months.

The transplant group had a significant advantage over non-transplant at 10 years for survival (88.8% vs. 22.4%; p<0.001) and time-to-progression (13.1% vs. 89%; p<0.001). After adjustment for propensity score, survival advantage in transplanted patients was maintained (HR: 10.67; 95%CI: 3.48-32.72; p<0.001). Adjusted transplant survival benefit was 6.82 months and 38.43 months at 5 and 10-years, respectively (p<0.001) (Fig. 2).



We demonstrated that LT for metastatic NETs under restrictive criteria provides an excellent long-term outcome, and that survival benefit increases over time in transplanted patients with respect to non-transplant options, justifying enlistment of these patients as recognized exceptions.

FIGURE 2

The magnitude of transplant benefit calculated as the difference in mean survival time at 5 and 10 years between study groups increases over time and is maximized at distant post-transplant intervals.

blu line = transplanted patients

red line = non transplanted patients

ACTIVE SURVEILLANCE IN PROSTATE CANCER

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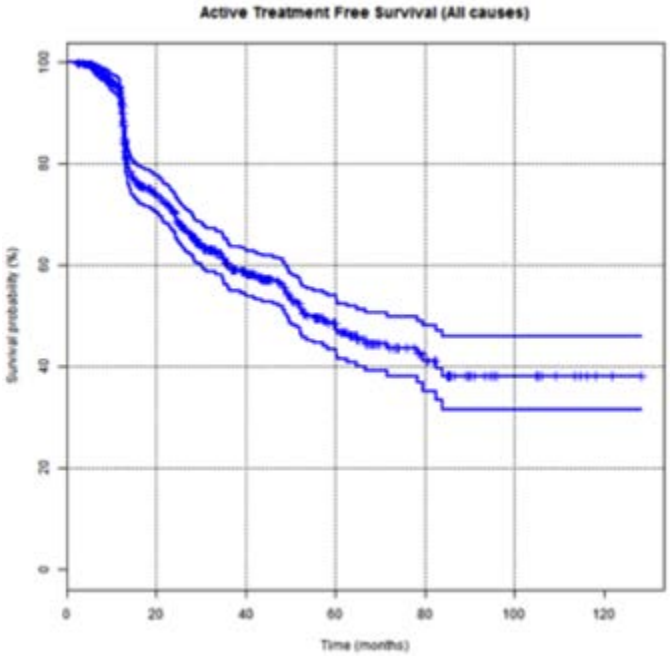
The Prostate Cancer (PC) Program is acknowledged worldwide to have important expertise in managing Active Surveillance (AS), an observational program proposed to patients with low and very low risk of PC as an alternative to radical treatment.

In fact, the extensive use of PSA as a screening tool, which started in the early 1990s, led to a dramatic increase in diagnoses of PC and to overtreatment of slowly progressing, potentially indolent, clinically insignificant tumors that would otherwise have remained clinically undetected during the patient's lifetime.
Since the early 2000s, AS is worldwide being offered to selected patients with particularly favorable prognostic factors in alternative to radical prostatectomy, radiotherapy and brachytherapy, which are the gold standard radical approaches but which may cause side effects that can potentially impact the patients' quality of life. AS is being proposed by the PC Program Multidisciplinary Clinic Team at INT since March 2005.
The first study was a single-center cohort protocol named SAINT (Sorveglianza Attiva INT). In November 2007, we joined PRIAS (Prostate cancer Research International: Active Surveillance), a multicenter prospective observational study coordinated by the Erasmus University Medical Center (Rotterdam, The Netherlands). Due to the limited understanding of PC aggressiveness at diagnosis, the current protocols, which are active, are slightly different in terms of inclusion criteria. Both accept patients with histologically confirmed adenocarcinoma of the prostate, suitable for radical treatments, untreated, with initial PSA (iPSA) ≤10ng/ml, clinical stage (T category) ≤T2a (2002 TNM, no T1a and T1b in PRIAS), and Gleason Pattern Score (GPS) ≤3+3. SAINT allows inclusion of patients with ≤25% positive cores as long as the maximum core length containing cancer is ≤50%. In contrast, inclusion in PRIAS requires maximum 2 positive cores and PSA density <0.2 ng/ml/cc. Eligible patients are examined and selected during multidisciplinary consultation with a urologist, radiation oncologist, and psychologist (the medical oncologist is on demand for castration-resistant, advanced and metastatic PC patients) and confirmed in the interdisciplinary and multiprofessional team meeting dedicated to case discussion. In addition to curative options (radical prostatectomy, external beam radiation, brachytherapy), patients with low and very low PC are offered AS after confirmation of sizing and grading of diagnostic biopsy by the uro-pathologist of the PC Program.
Patients on AS are monitored over time with PSA, digital rectal examination, and repeated biopsies. The latter are aimed to periodically confirm the histological characteristics of disease and discontinue patients who show upsizing or upgrading over time and thus are considered reclassified. SAINT and PRIAS apply slightly different follow-up schemes with respect to timing of rebiopsy. SAINT schedules biopsies at 12 and 24 months after diagnosis and then every 2 years, while in PRIAS biopsies are taken at 1, 4, and 7 years. Between March 2005 and December 2014, 639 patients were enrolled in AS, 227 in SAINT, and 412 in PRIAS. Over time, 275 patients were discontinued, mainly due to changes in histological parameters: upgrading (GPS >6) and/

Eligible patients are examined and selected during multidisciplinary consultation with a urologist, radiation oncologist, and psychologist

or upsizing (number of positive cores exceeding the criteria for AS and/or maximum core length containing cancer >50% in SAINT). Active treatment-free survival (ATFS) curves, assessed by the Kaplan-Meier method, show discontinuation rates (Fig. 1).



The group of patients on AS at INT is the largest in Italy and one of the largest worldwide. In fact, the PC Program is the top recruiting center in the PRIAS consortium. The cohort represents a good reservoir for investigation on the pathogenesis and natural history of PC as patients are free from treatment manipulations. In this regard, research is urgently needed to improve selection and monitoring criteria for AS. To date, patients have been identified and followed based on clinical and pathological parameters, which are suboptimal. Several problematic issues are the focus of our research:

- Is it possible to predict reclassification or progression and detect the presence of GPS 4 in an early stage?
- Is it possible to identify patients with indolent/insignificant cancer?
- Can new reliable tools (biomarkers and imaging instruments such as multi-parametric MRI) be implemented to distinguish indolent from aggressive and potentially evolving prostate cancer?
- How is life with an untreated cancer?
- What is the long-term outcome of patients on AS?

To date, patients have been identified and followed based on clinical and pathological parameters, which are suboptimal

In the attempt to answer these questions, multiple studies are being proposed to AS patients.
Starting November 2008, the PROCABIO-INT side study is collecting biological material (blood) prospectively (at inclusion in AS and then once a year during follow-up). This biobank has made possible the activation of studies focused on improving selection criteria for AS. The preclinical research group, directed by Nadia Zaffaroni (Vice Director of the PC Program), is evaluating novel circulating biomarkers. The aim is to develop non-invasive approaches for disease monitoring during AS. There are two fields of interest:

Circulating microRNAs. We are currently evaluating microRNA (miRNA) profiles in plasma samples obtained from 300 patients at inclusion in AS. The aim is to correlate them with clinical outcome and assess whether specific miRNAs/miRNA signature are able to predict disease reclassification/progression better and/or in advance compared to conventional markers. The overall series has been divided into a training set and a validation set (150 patients each). miRNAs identified in the

training set of patients as associated with disease reclassification / progression will be validated in the second set. Upon confirmation of results in an independent patient cohort, the final aim of this study will be the integration of selected miRNAs in an updated and improved model for prediction of truly indolent PC.

miRNAs identified in the training set of patients as associated with disease reclassification/ progression will be validated in the second set

Genomic aberrations in circulating cell-free DNA. Since the genomic lesions that characterize indolent PC are currently unknown, the search for point mutations and copy number aberrations will be initially carried out in positive core biopsies from a subset of 60 AS patients by a whole exome sequencing approach with the aims to: i) compare such genomic alterations with those characteristic of clinically significant PC; ii) identify specific DNA alterations associated with disease reclassification/progression during AS. Once detected in tissue samples, specific genomic aberrations will be looked for in blood samples of the same patients with the aim to identify genomic lesions in circulating cell-free DNA associated with disease reclassification/progression during AS. DNA alterations characteristic of very low-risk PC will be validated in independent series of tumors from patients followed in the context of PRIAS in other medical centers by using a targeted sequencing approach.

DNA alterations characteristic of very low-risk PC will be validated in independent series of tumors from patients followed in the context of PRIAS in other medical centers

Starting September 2007, a research project run by dedicated psychologists in the PC Program is centered on the quality of life (QoL) of patients on AS. If avoidance of therapy-induced side effects and a positive impact on QoL are among the advantages of AS, it can be argued that the idea of "living" with PC might be associated with high levels of psychological distress and anxiety which would impair QoL and eventually lead men to discontinue AS. Patients enrolled in PRIAS and SAINT are asked to complete standardized self-reported questionnaires assessing QoL at inclusion and 6 times during a 5-year follow-up period (10, 12, 24, 36, 48, and 60 months). About 75% of patients enrolled in AS accepted to participate in the QoL study. Assessment of QoL in PC patients is most often based on the presence of symptoms, but although physical impairment represents one of the main concerns, patients' well-being should be considered by taking into account equally important factors such as overall health status, coping strategies, emotional well-being, and social interactions. As such, we used different assessment tools to tackle different aspects of patients' QoL in order to have a comprehensive evaluation of patients' perceived well-being. Our data, consistent with studies published by other research groups across Europe, North America, and Australia, showed that the idea of living with untreated cancer does not represent relevant psychological burden for patients. Only a minority of patients are more likely to be exposed to the risk of poor QoL due to vulnerability factors that include specific personality traits, lack of a partner, and inadequate communication with physicians. In addition, to demonstrate that AS is a valid alternative to radical therapies in low and very low risk PC patients and that long-term outcome is favorable, data on follow-up are being collected from patients who discontinued AS and underwent surgery, radiotherapy, and brachytherapy.

The idea of living with untreated cancer does not represent relevant psychological burden for patients

Acknowledgements of the PC Program Multidisciplinary Team

- Starting December 2009, the PC Program coordinates the 8 Italian institutions participating in PRIAS under the name of SIUrO PRIAS ITA
- The chief psychologist of the PC Program is chair of an international Task Force on QoL in AS promoted and supported by the European School of Oncology
- The PC Program is the only Italian center that was invited to participate in the Global PC AS Initiative funded by Movember Foundation, aimed to unite the world's 15 leading research and clinical groups focusing on AS to develop a new therapeutic guidelines for men diagnosed with low risk PC by integrating clinical, imaging, and biomarker data in the global central database GAP3.

EARLY DIAGNOSIS

PROGRAM/PROJECT MEMBERSHIP

G. SOZZI (COORDINATOR),
M. BOERI, M. GARIBOLDI, E. LEO, E. TAGLIABUE,
M.G. DAIDONE, U. PASTORINO

Detection of cancer at an early stage offers the genuine potential to reduce mortality with new chances of cure. Discovery and validation of biomarkers is central to this goal.

Understanding the biological changes in early tumor and stroma could have a profound impact on how cancer is detected, prevented, and treated, and might provide blood and tissue-based biomarkers that are able to identify progressing lesions. Such a novel perspective might improve early cancer detection and allows identification of aggressive tumors, thereby overcoming the well-known limitations of current screening and diagnostic approaches that, apart from causing anxiety, exposure to potentially harmful amounts of radiation or surgical procedures and additional expenses to the healthcare system, are also unable to predict the biological aggressiveness of the detected lesion. Goal of our translational studies is the implementation of highly sensitive molecular tests that could be used within screening programs to improve both early detection and clinical management of different cancer types. Institutional efforts are ongoing for three major cancer types (colorectal, lung, and breast) which represent the most significant malignancies in terms of clinical and economic burden.

LUNG CANCER (Gabriella Sozzi and Ugo Pastorino)

Lung cancer still remains a highly aggressive disease, accounting for almost 30% of cancer deaths worldwide. Lung tumors are typically asymptomatic in the early stages and are often diagnosed at a late stage, at a metastatic phase, and thus failing in successful treatment. Considering that 5-year survival for stage Ia patients is over 70%, it appears clear that advances in early detection are crucial to enable timely curative surgery. The implementation of molecular markers for risk stratification appears a priority, and microRNAs (miRNAs) constitute an extremely promising new class of blood-based biomarkers for cancer detection and prognosis.

Highlights

- We recently reported that specific miRNA signatures can be identified in plasma samples of patients up to two years before spiral-CT detection and are able to classify tumors according to aggressiveness. We have completed an extended retrospective validation of a miRNA signature classifier (MSC) in plasma samples of 1,000 cases and control subjects enrolled in the MILD trial. The diagnostic performance of MSC for lung cancer detection was 87% for sensitivity and 81% for specificity. For all subjects, MSC had a negative predictive value of 99% and 99.86% for detection and death-by-disease, respectively. Low-Dose CT (LDCT) had a sensitivity of 79% and a specificity of 81% with a false positive rate of 19.4%. Combination of both MSC and LDCT resulted in a 5-fold reduction of LDCT false positive rate to 3.7%. MSC risk groups were significantly associated with survival (χ 2=49.53, p<0.0001) (G Sozzi et al. JCO 2014; O Fortunato et al. Molecules 2014).

We have completed an extended retrospective validation of a miRNA signature classifier (MSC) in plasma samples of 1,000 cases and control subjects enrolled in the MILD trial

Future outlook

- The MSC test will be employed to monitor disease status during follow-up in longitudinal plasma samples obtained from patients before and after surgical resection of primary lung tumors. For this purpose, changes of MSC risk profiles at follow-up will be assessed for 31 patients of the MILD cohort with longitudinal plasma samples (n=86) collected after curative surgey (median time from diagnosis up to 4 years).
- In collaboration with the Thoracic Surgery and Radiology Units, the bioMILD trial (www.biomild.org) is ongoing in INT. The bioMILD is a truly innovative study testing the efficacy of a combined molecular and imaging approach, where blood miRNAs (MSC) and LDCT are both applied at baseline screening, and their results establish the intensity and modality of subsequent investigations. The BioMILD trial aims to define the individual risks of cancer among a cohort of heavy smokers, modulate the screening program on this basis, and reduce the number of unnecessary diagnostic investigations and useless surgery for benign disease. As of January 2015, we enrolled 2,063 volunteers and performed 2,854 miRNA tests and 2,550 low dose CT evaluations according to a proprietary BioMILD decisional algorithm.

www.biomild.org

BREAST CANCER (Elda Tagliabue and Maria Grazia Daidone).

Regular screening tests (mammographic screening and breast ultrasound scan) reduce the chance of death from breast cancer. However, to demonstrate that abnormal areas are malignant, biopsy is required. The procedures for a biopsy are invasive for the patient and expensive for the healthcare system, and this may present a problem, especially for high-risk younger women who need early breast cancer screening. Therefore, a simpler, valid alternative is highly desirable. The solution may reside in the monitoring of circulating molecular markers in blood. The identification of reliable circulating biomarkers that could track tumor behavior and anticipate diagnosis of unfavorable events in potentially curable disease such as early breast cancer may also represent a paradigm shift for personalized treatments.

Highlights

- We started from the hypothesis that the interaction between a tumor and its microenvironment allows the release of extracellular matrix (ECM) proteins in blood. We then examined which ECM molecule might serve as a diagnostic marker for breast cancer (BC) by in silico analysis of gene expression profiles of normal and BC samples obtained from publically available datasets. We demonstrated that normal fibroblasts conditioned by breast carcinoma cells significantly improve the production and release of collagens COL11A1, COL10A1, and COL6A3, as well as COMP, a matricellular protein. The analysis of these molecules in plasma samples allowed us to discriminate BC patients from patients with benign breast diseases and healthy donors, independently of the clinico-pathological characteristics of tumors. These results suggest that circulating ECM molecules may be soluble markers of the stroma remodeling that occurs during tumor development.
- The presence of small peptides in plasma is likely due to proteases located in the tumor microenvironment. We investigated the presence of these peptides in BC patients and healthy subjects using high-throughput profiling by liquid chromatography-mass spectrometry (LC-MS). Several differences were observed and, in particular, the peptides f1696 and f1630 were detected only in BC patients, as also confirmed in the analysis of a test cohort. These results suggest that f1696 and f1630 may be used to discriminate BC patients from healthy subjects.
- The association between circulating miRNAs and disease progression was investigated in patients with stage I BC entered in the control arm of a randomized Phase 3 chemopreventive trial and followed-up for more than 15 years. Using a case-control approach, and controlling samples

Our results suggest that circulating ECM molecules may be soluble markers of the stroma remodeling that occurs during tumor development

for the confounding effect of hemolysis (V. Appierto et al. Bioanalysis 2014), plasma miRNA levels were compared in relapsed patients (plasma collected 0—1 months before the diagnosis of the event, n= 93) and in women that did not relapse during follow-up (no evident disease, NED, n=93). A panel of differentially expressed miRNAs was identified by class comparison in patients developing distant metastasis, and miR-1246 and miR-1290 were the top differentially expressed miRNAs, regardless of the applied normalization methods, with promising results in terms of internal cross validation. Such findings have been validated in two independent studies carried out on plasma of patients with early and advanced diseases. Moreover, in silico analysis performed on the METABRIC dataset confirmed the association of miR-1246 and miR-1290 with patient outcome in the $ER^{+}HER2^{-}$ luminal subtype. Such an association remained significant in multivariable analysis including other clinico-pathological features (lymph node status, age, type of surgery) and a proliferation signature, known to be prognostic in this subtype. Such findings indirectly support a causal involvement of these miRNAs in the metastatic process, in agreement with results obtained in blood.

Future outlook

We will validate the use of ECM molecules and of f1696 and f1630 peptides in discriminating BC patients from healthy subjects. This will be done by analyzing a new series of plasma samples obtained from BC patients, those with breast benign diseases, and healthy donors. In addition, we will investigate the presence of these molecules in the plasma of women undergoing core-needle biopsy 14G for a potentially neoplastic mammary lesion detected by ultrasound. We will then correlate the results with histopathological diagnosis.

COLORECTAL CANCER (Manuela Gariboldi).

Colorectal cancer (CRC) is the second most common tumor in women and third for men. If CRC is diagnosed at early stages, when the tumor is still localized in the colon, the survival rate is high. At this step of progression, removal of polyps or adenomas can even avoid the development of cancer. CRC screenings on healthy individuals, through tests for the detection of occult blood in stool (FIT) followed by colonoscopy in case of positivity, has increased the early detection of the disease and reduced deaths by 20—30%. However, the test currently used for screening has sub-optimal sensitivity and specificity, especially for precancerous lesions. A promising technology in this field is the identification of blood circulating miRNAs linked to the presence of tumor in patients with precancerous lesions/CRC.

Highlights

We have used qRT-PCR to analyze the expression levels of 381 miRNAs in plasma from subjects undergoing colonoscopy screening at INT after a positive fecal occult blood test (FIT), and identified 13 miRNAs that show significantly different expression in subjects with adenomas and/or CRC lesions compared to subjects without lesions. The association of miRNA expression to each specific lesion highlighted 4 miRNAs linked to initial adenoma, 1 to advanced adenoma, and 8 to cancerous adenoma or invasive adenocarcinoma. We are currently validating these miRNAs on a prospective cohort of 150 cases. We have also developed a normalization strategy for selecting reference miRNAs when working with circulating miRNAs for qRT-PCR data to be transferred in the relative quantification of promising miRNAs in subsequent studies (S Zanutto et al. Br J Cancer 2014; S Pizzamiglio et al. IJC 2014; P Verderio et al. Anal Biochem 2014).

We have developed a normalization strategy for selecting reference miRNAs when working with circulating miRNAs

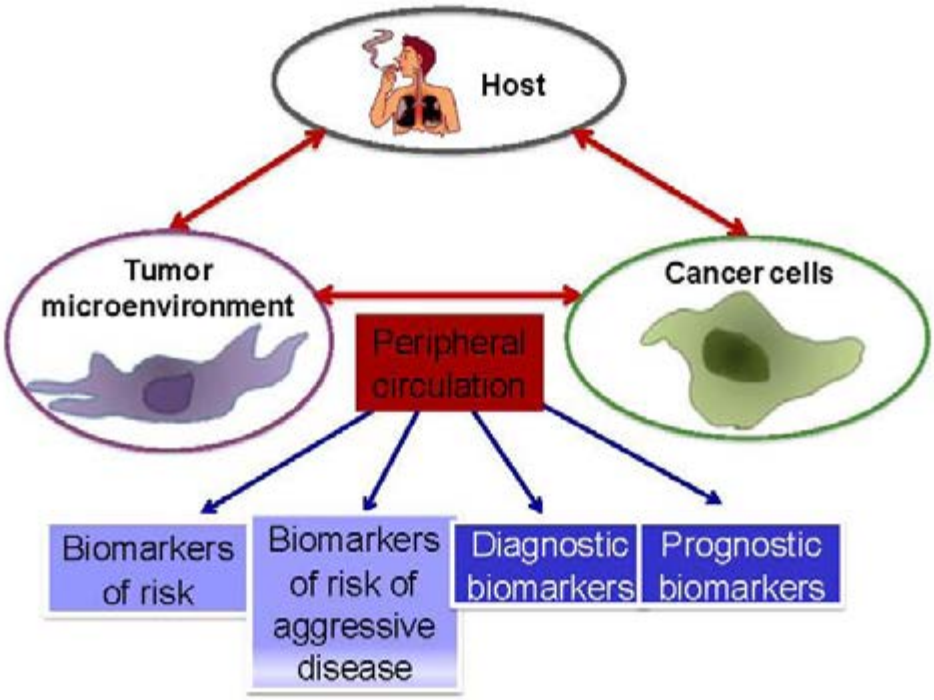
Future outlook

- To validate our results, a clinical study has been designed based on the collection of plasma samples, clinical information, and pathological specimens from subjects who undergo colonoscopy at hospitals

participating in the Milan CRC screening program. miRNAs that will confirm the differential expression will be tested by qRT-PCR on these samples for the larger external validation. To date, about 800 FIT+ subjects (from 9 hospitals) have been enrolled. Validation will also be extended to cases that will be collected at other ongoing CRC cancer screening centers in Italy.

- In parallel, we have designed a study for identification of miRNAs in plasma of individuals at high risk for CRC, such as those with familial CRC, to extend their use to subjects who are under close colonoscopic surveillance and who would greatly benefit from a non-invasive test. Subjects will be selected from the wide Heredo-Familiar CRC Registry at our Institution.

Sources of blood-based biomarkers.
Novel promising biomarkers are generated by cancer cells, tumor microenvironment, the host response and their dynamic interaction.



NEW DRUGS AND PERSONALIZED MEDICINE

PROGRAM/PROJECT MEMBERSHIP

M.C. GARASSINO (COORDINATOR), S. DI COSIMO, D. LORUSSO, P. PEREGO, G. SOZZI, E. TAGLIABUE, M. IORIO, N. ZAFFARONI

It's far more important to know what person the disease has than what disease the person has. – Hippocrates

The term "personalized medicine" describes the approach of providing "the right patient with the right drug at the right dose at the right time." Personalized medicine or "precision medicine" may be defined as the tailoring of medical treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up.
Emerging data from clinical studies suggest that the use of targeted agents in patients with targetable molecular aberrations improves clinical outcomes. Despite an increasing number of studies, gaps remain in identifying driver molecular alterations in patients with multiple aberrations and molecular networks that affect tumor development, metastatic spread, and drug resistance/response. Personalized medicine requires continuous scientific breakthroughs and technological improvements that are able to integrate preclinical, pathological, and clinical information. The INT is currently working on integrating knowledge at preclinical, clinical, and epidemiological levels with a large number of new drugs under investigation.
The main areas of research are focused on identification of new targets, identification of new biomarkers, and testing new drugs in small populations.

Emerging data from clinical studies suggest that the use of targeted agents in patients with targetable molecular aberrations improves clinical outcomes

At the preclinical level, some examples of research regarding new drugs and efforts towards personalized medicine are provided below.
The Tumor Genomics Unit (Gabriella Sozzi) is investigating the potential of miRNAs as novel tools for early detection and therapy of lung cancer. In particular, mir-660, one of the 24 miRNAs of a diagnostic signature, when over-expressed inhibited tumor growth in immunodeficient mice xenografted with human lung cancer cells. The MDM2 gene, a key regulator of p53 function, was identified as a new direct target of mir-660, thereby supporting its role as a tumor suppressor miRNA, and suggesting replacement of mir-660 as a new therapeutic approach for p53 wild-type lung cancer treatment (O. Fortunato et al. CDD 2014; O. Fortunato et al. Biomed Res Int. 2014).
The evolving paradigm of cancer stem cells (CSC) now suggests the existence of heterogeneous subsets of cells that are able to guide different steps of tumor initiation and metastatic progression, thus providing new therapeutic targets and prognostic biomarkers. The Tumor Genomics Unit is working on the identification of specific subsets of lung metastatic cells, e.g. $CD133^{+}CXCR4^{+}$ modulated by tumor microenvironment and associated with poor prognosis. The efficacy of novel peptide inhibitors of CXCR4 in blocking metastatic dissemination and preventing CSC enrichment induced by standard chemotherapy is being evaluated. The in vivo capacity of all-trans retinoic acid (ATRA) to force the CSC fraction to differentiate toward a cisplatin susceptible phenotype was also examined.

The in vivo capacity of all-trans retinoic acid (ATRA) to force the CSC fraction to differentiate toward a cisplatin susceptible phenotype was also examined

In collaboration with the Thoracic Oncology Unit (Marina C. Garassino) and Medical Oncology Department, the identification of KRAS mutations in lung cancer with a more aggressive phenotype is ongoing. KRAS mutations are thought to confer a more aggressive phenotype in lung cancer, although clinical observations are often controversial to support this evidence. Since a fraction of these patients have worse prognosis than those with wild-type KRAS, it is being investigated if the co-presence of KRAS and LKB1 mutations can confer a more unfavorable prognosis. Furthermore, this population accounts for at least 10% of all NSCLC patients and might be treated with combinations of drugs including metformin.
On a similar hypothesis, the Thoracic Oncology Unit and Oncology Department, in collaboration with several European institutions (University of Ulm, IRCCS Mario Negri, University of Athens) are working on the possibility that patients harboring mutated KRAS have an unbalancing in DNA repair at several levels. Theoretically, these patients can be excluded from therapy with platinum compounds.
The Molecular Target Unit of Experimental Oncology and Molecular Medicine Department (DOSMM) (Elda Tagliabue) is actively working to gain insight into the molecular pathways that are relevant for progression and response to therapy of breast carcinomas, especially those with HER2 overexpression and triple-negative (TN) features. In collaboration with the AIRC Start Up Unit (Marilena V. Iorio), they demonstrated that TN tumors, defined based on the absence of HER2 and hormone receptor expression, have the ability to generate blood lacunae lined by tumor cells. This feature is associated with poor outcome and PDGFR β- and FGFR2-mediated pathways and has been identified as relevant in mediating this characteristic, thus potentially representing valid targets for specific therapy of this breast cancer subgroup.

Triple Negative tumors, defined based on the absence of HER2 and hormone receptor expression, have the ability to generate blood lacunae lined by tumor cells

Concerning the identification of a robust predictor marker of the benefits of trastuzumab, the Molecular Target Unit uncovered the relevance of a splice isoform of the HER2 receptor which lacks exon 16 (Δ16HER2) in susceptibility of HER2-positive breast tumors to trastuzumab treatment. Specifically, they provided evidence in transgenic mice that expression of Δ16HER2 is sufficient to accelerate mammary tumorigenesis and improve the response to trastuzumab. Δ16HER2 was optimally functional through a link to SRC activation (pSRC). Clinically, HER2-positive BCs from patients who received trastuzumab exhibited a positive correlation in Δ16HER2 and pSRC abundance, consistent with the mouse results. Moreover, patients expressing high pSRC or an activated "Δ16HER2 metagene" were found to derive the greatest benefit from trastuzumab treatment.
In addition, in collaboration with the Medical Oncology Department (Serena Di Cosimo), they analyzed by DASL technology in archival tumor blocks from HercepTest 3+/2+ FISH-positive patients treated with adjuvant trastuzumab at the INT. The estimated association between gene expression and relapse-free survival allowed the development of a trastuzumab risk (TRAR) model based on a 41-gene signature. Application of the TRAR model to tumors treated with neo-adjuvant trastuzumab indicated that it is predictive of trastuzumab response, but not to chemotherapy alone. Pathway analysis revealed that TRAR-low tumors expressed genes of the immune response, with significantly higher CD8-positive cells detected immunohistochemically compared to TRAR-high tumors. Based on these results, a study aimed to explore whether the TRAR model is useful for predicting/monitoring therapeutic response to different anti-HER2 agents has been recommended for endorsement by the Steering Committee of the phase III, randomized trial Neo-ALTTO including women treated with trastuzumab or the EGFR/HER2 tyrosine kinase inhibitor lapatinib, either alone or in combination.

The estimated association between gene expression and relapse-free survival allowed the development of a trastuzumab risk (TRAR) model based on a 41-gene signature

The Molecular Pharmacology Unit (Nadia Zaffaroni) actively worked on the molecular alterations implicated in sustaining tumor cell survival that may provide opportunities for new drug development. In particular, XPO1/CRM1, which mediates nuclear protein export, is targeted by selective

drugs (e.g. selinexor) that inhibit highly metastatic cell aggressiveness in prostate carcinoma models, and reduced bone metastasis and cell spread in orthotopic models (GL Gravina et al. J Hematol Oncol. 2014). G-quadruplex (G4) structures occur in different regions of the genome. Naphthalene dimide derivatives emerged as G4 ligands that are able to impair tumor cell proliferation by interfering with telomere maintenance mechanisms and inhibiting the expression of oncogenes bearing G4-forming sequences in their promoters. A platinum complex (TriplatinNC) with non-covalent DNA binding produced p53-independent nucleolar targeting in tumor cells and a shift in the antitumor drug structure-activity paradigms.
Furthermore, in an attempt to provide the molecular basis for personalized drug combinations to be clinically exploited and to define biomarkers for patient selection, the following was demonstrated: a) efficacy of namitecan/topotecan-cetuximab combinations in squamous cell carcinoma as a function of EGFR gene copy number (M De Cesare et al. Clin Cancer Res. 2014); b) synergistic interaction between the RET inhibitor sunitinib and cisplatin in RET-driven medullary thyroid cancer (A Lopergolo et al. J Clin Endocrinol Metab. 2014); c) chemosensitizing effect by the survivin suppressant YM155 in DR5-expressing triple-negative breast cancer exposed to membrane TRAIL; d) synergistic interaction of sanguinarine/arsenic trioxide/TRAIL in platinum-resistant NSCLC cells (L Gatti et al. J Pharmacol Exp Ther. 2014); e) increased ovarian carcinoma cell sensitivity to platinum compounds by pharmacological targeting of the ERK1/2 pathway in selected molecular backgrounds (G Cossa et al. Cancer Lett. 2014), and f) therapeutic potential of vorinostat in combination with temozolomide in mutant BRAF melanoma models (L Gatti et al. Oncotarget. 2014).
At the clinical level, in the Medical Oncology Department several new drugs are under investigation, aimed towards a personalized medicine approach. Most are directed towards targeted sub-populations. In breast cancer, the Medical Oncology Department has the unique chance to treat patients not only with the milestone of breast cancer therapy represented by anthracycline and taxane, but also with novel and promising agents, including eribulin and the taselisib inhibitor of PIK3CA alpha in a neoadjuvant setting. In tight collaboration with pathologists and researchers at the Experimental Oncology and Molecular Medicine Department (DOSMM), residual cancer samples from breast cancer patients treated with primary systemic therapy are being analyzed with the Ion AmpliSeq Comprehensive Cancer Panel for mutational analysis of more than 400 genes and validation of detected mutations by digital PCR. Furthermore, in collaboration with DOSMM and the Senology Unit, circulating miRNAs able to predict outcome and guide treatment of breast cancer patients are being examined.
For gynecological tumors, several investigations are ongoing. For ovarian cancer, where knowledge of phenotypes and presence of BRCA mutations is important, aberrant methylation and HER2 status are useful to identify the subpopulations for individualized treatment. In particular, trabectedin is under investigation in BRCA mutated and BRCAness phenotypes, temozolamide in MGMT hypermethylated ovarian cancer, trastuzumab in mucinous ovarian cancer, and the PARP inhibitor rucaparib and antiangiogenic agent bevacizumab in the first-line treatment of ovarian cancer. In addition, immunotherapy (MK-3475-anti PLD 1 Inhibitor) is under investigation in recurrent, platinum-resistant BRCA mutated ovarian cancer. A large part of new drugs under investigation in several diseases are represented by immune checkpoint inhibitors.
In principle, every Department and every Unit is attempting personalized approach in both clinical practice and research. Therefore, these are only examples and are not representative of the entire institutional contribution. The chapters reffering to specific Units provide more complete understanding of the research projects and clinical trials focused on personalized medicine.

For ovarian cancer, where knowledge of phenotypes and presence of BRCA mutations is important, aberrant methylation and HER2 status are useful to identify the subpopulations for individualized treatment

METASTATIC DISEASE: THE SURGICAL MANAGEMENT

PARTICIPATING/PROGRAM MEMBERSHIP

U. PASTORINO (COORDINATOR), J. COPPA AND R. LUKSCH

Surgical management of liver metastases

[JORGELINA COPPA]

Colorectal cancer is the third most common cancer in the Western world and approximately 25% of these cancers present with liver synchronous disease, while another 25% will develop liver metastasis (CRCLM) during the course of disease (1). Liver resection is a worthwhile therapeutic aim and provides the best opportunity for long-term survival (2). The management of CRLM has changed dramatically in the past two decades. In the early 1990, liver resection was associated with a surgical mortality of 5% and was offered to only 10% of patients, leading to a 5-year survival of 2.5%. Dramatic progress in management of CRLM has taken place, with complementary and often synergistic results. Improvement in surgical techniques and the increased effectiveness of new chemotherapies has allowed for a R0 surgery from 20% to 35% of patients with stage IV CRC. The global result has been a 5-year survival rate of 35% to 63%, according to severity of disease, and response to therapy (3). Major advances have been made in the chemotherapeutic management of advanced CRC. Systemic chemotherapy can reduce tumor size in some cases and convert the disease from unresectable to resectable. The introduction of agents targeting the VEGF (bevacizumab) and EGFR (cetuximab) pathways in combination with cytotoxic therapies have improved outcomes for patients, but it remains unclear whether the increased efficacy of these regimens in terms of long-term survival can be extrapolated to improved rates of secondary liver resection.

Surgical management for secondary liver cancer represents approximately 80% of our activity, and colorectal cancer (CRC) is one of the most frequent causes of cancer related death in Italy

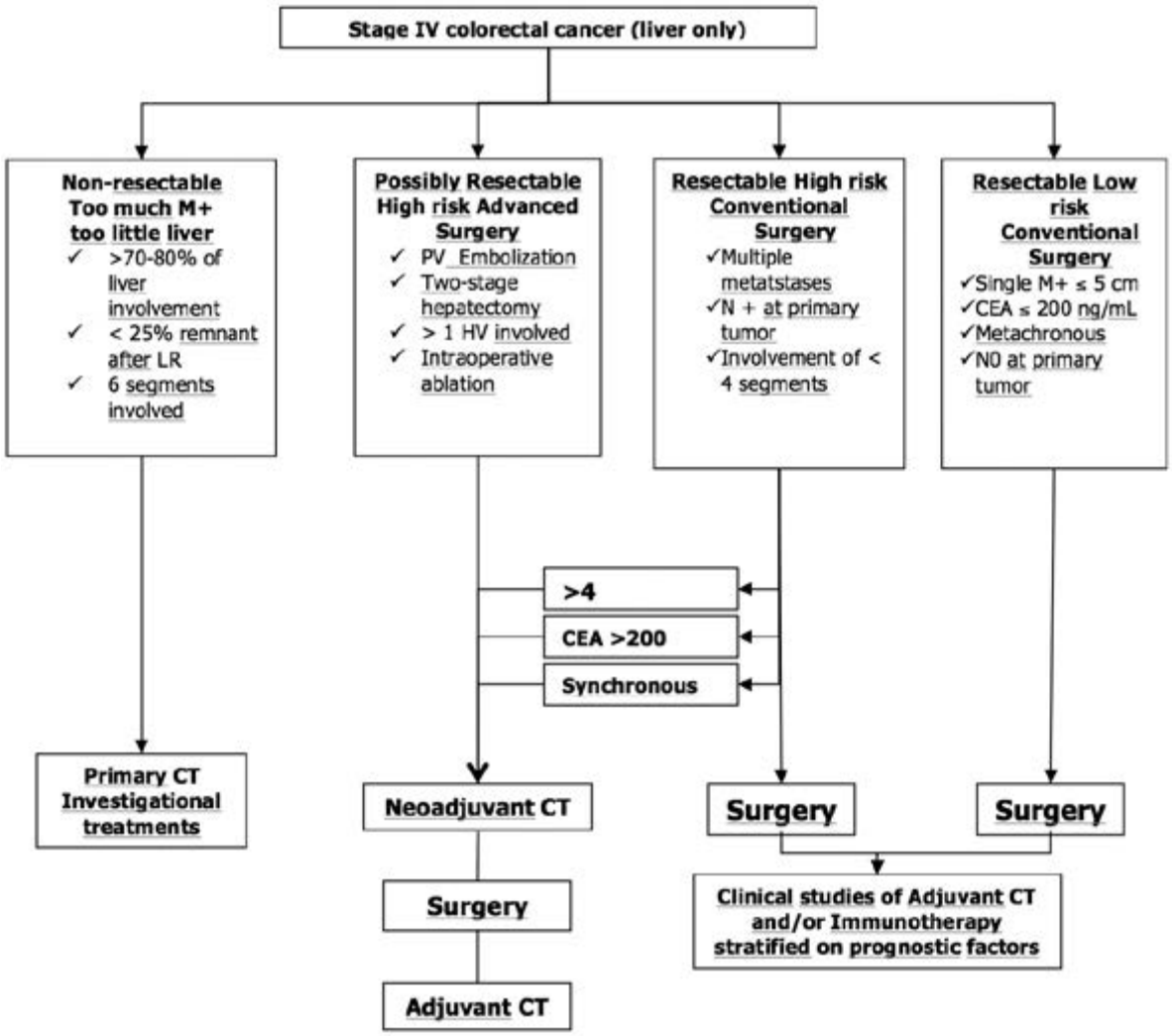
In our experience, a multidisciplinary team approach favors management of the disease. The model includes surgeons, oncologists, radiologists and pathologists. In this way, we are able to choose the best timing and indications for surgery and chemotherapy. As reported in literature, important patient benefits have been observed, including greater accuracy of disease staging, fewer treatment and referral delays, individualized evidence-based practice for greater continuity of care, enhanced quality of life, and better clinical and survival outcomes.

In our experience, a multidisciplinary team approach favors management of the disease. The model includes surgeons, oncologists, radiologists, and pathologists

As part of this work, we present our internal guidelines for management of CRLM below (see figure below). On the left side, clear conditions of non-resectable liver disease (too much liver involvement and <25% remnant liver after resection) lead to primary chemotherapy; at the right side, clearly resectable situations with patients at low risk (single nodule <5 cm, CEA <200 mg/ml, metachronous, and N0 at primary tumor) follow liver surgery as a first option. In the middle of the figure there are conditions frequently called 'borderline' and at high risk of recurrence. We have focused our studies on these latter situations.

Principal current strategies

Chemotherapy and its role in peri-operative setting. Chemotherapy given to unresectable patients to convert the disease to resectable



CRCLM is known as 'conversion chemotherapy', with the aim of achieving resectability. Neoadjuvant chemotherapy is reserved for patients with resectable (at high risk) or/and potentially resectable disease, prior to surgery. Several trials have demonstrated improved progression–free-survival after liver resection using peri-operative chemotherapy, although the real benefit of this on overall survival and the role in liver injury remain to be addressed (4). In the last 10 years, overall survival of patients with CRCLM has improved substantially, and reflects the increased number of available therapies (5-FU, FOLFOX, FOLFIRI regimens). More recently, chemotherapy with monoclonal antibodies targeting EGFR, (cetuximab, panitumumab) in patients with RAS wild type, and anti-VEGF (bevacizumab) improve outcomes (2).

In collaboration with the Medical Oncology Department, we have conducted 2 studies with patients affected by CRCLM that is potentially resectable although at high risk of recurrence. Patients were treated with triplet chemotherapy (capecitabine, oxaliplatin, irinotecan) associated with erbitux (COI-E) or becacizumab (COI-B). In the COI-E trial, a total of 40 patients were recruited and treated for 4 cycles of therapy followed by surgery and then another 4 cycles. In the COI-B study, we treated 20 patients and to date all cases underwent radical surgery. We are planning to complete the accrual after 44 patients.

Disappearing (no visible on imaging) liver metastases (DLM). DLM refers to the complete response or disappearance of a liver metastasis on imaging after administration of preoperative chemotherapy. This phenomenon occurs in 5—38% of patients who undergo preoperative systemic therapy (4), and in our experience are not less than 20% of patients following liver

resection after favorable response to chemotherapy. Undoubtedly, the quality and type of imaging and the parenchymal liver changes the damage due to chemotherapy (steatosis and steatohepatitis) in this situation. The management of this situation is challenging because a complete response on imaging does not necessarily correlate with complete clinical or pathological response. Results of studies regarding the outcome of DLM are discrepant and conflicting. Elias et al. (5) reported 62% of patients remained recurrence-free at 51 months. In contrast, Benoist at al. (6) found macroscopic residual disease in more than 25% of DLM during surgery. The extent of surgery needed in cases of DLM remains unclear; there are several proposed management strategies such as resection of all initial sites of DLM when possible, surgical removal of residual macroscopic disease while leaving the disappeared lesions in situ if the resection would be too extensive, resection followed by additional chemotherapy, continuing systemic chemotherapy alone, etc. We personally prefer removing of initial sites of disease. However, there is no strong evidence from randomized trials to support any of these management options, particularly extensive resections. We recommend use of best judgment and adopting a risk-benefit approach to establish the extent of surgical treatment.

The liver-first approach. This is the reverse of the classic approach and begins with systemic chemotherapy, directed against the CRCLM, followed by liver resection; the treatment of rectal cancer is considered in a subsequent step. This approach is proposed for patients with important synchronous liver involvement and asymptomatic primary tumor, given the prognostic decisive role of CRCLM in long-term survival. From a theoretical point of view, this approach has an advantage, underlying the importance of prioritizing treatment of the most problematic component of the patient's disease. Data that support this argument are limited. In some circumstances, we consider this strategy for patients whose prognosis is related to prominent liver involvement, followed by systemic chemotherapy for the liver and primary tumor.

The liver-first approach is proposed for patients with important synchronous liver involvement and asymptomatic primary tumor, given the prognostic decisive role of CRCLM in long-term survival

To date, no randomized, controlled studies have assessed the benefits of this modern strategy or its effects on recurrence and long-term survival. An adequately-powered randomized controlled trial examining the effect of the liver-first approach on recurrence and long-term survival might be worthwhile, but complexity of the study design limits this possibility.

Two-stage hepatectomy. This strategy achieves curative resection in a selected group of patients with multiple bilobar liver metastases in which complete resection would not have been possible with a single procedure. Sometimes, in case of insufficient volume of the liver, this approach combines portal vein embolization (PVE) with the tumor resection of the future remnant liver, followed by major resection when the liver has achieved sufficient size. We recommend tumor clearance of the non-embolized hemi-liver before the application of PVE to avoid the risk of stimulating tumor growth. However, we have seen that about 25% of patients do not proceed to planned hepatectomy because of disease progression or inadequate hypertrophy. A large series reported operative morbidity for first and second stage as 14% and 54% respectively, and 5-year survival for those who complete the two stages of 32% (7).

Portal vein embolization (PVE). Improved knowledge of liver regeneration has allowed devising new solutions for patients who, after liver resection, would be left with an insufficient functional liver parenchyma. PVE has clearly contributed to increasing the number of patients who can undergo major hepatectomy with lower risk of postoperative liver failure. We perform PVE for conditions that will leave less than 35—40% of functional parenchyma as a rule in patients who received intense chemotherapy. In general, two types of approaches are utilized: in the first, an interventional radiologist performs percutaneous super-selective PVE using microcatheters and embolic agents (cyanoacrylate + lipiodol). In the second option, intraoperative PVE during the first step of liver resection is performed as preparation for major hepatectomy. It should be emphasized

Improved knowledge of liver regeneration has allowed devising new solutions for patients who, after liver resection, would be left with an insufficient functional liver parenchyma

that adding segment IV embolization to a right PVE may contribute to a better hypertrophy of segments 1, 2,and 3 in case of extended right hepatectomy.

Ablation associated with liver resection. To increase treatment options for patients with unresectable disease, local ablation can be performed during hepatectomy for non-resectable lesions (<2 cm), or in patients at high risk of morbidity mortality.

The positive impact of ablation on long-term outcomes has been independently demonstrated by 2 prospective studies. EORTC 40004 compared systemic chemotherapy vs. chemotherapy + ablation for patients with unresectable disease, and 3-year disease-free-survival (DFS) was improved in the combined ablation +chemotherapy arm (10%, p=0.025) with a trend towards improved overall survival (OS) (median 45.3 months vs. 40.5, p=0.22)(8). Another French study (ARF2003) treated patients with unresectable, limited liver disease with a combined ablation + resection strategy; 1 year DFS was 46%, while 5-year OS was 43%, demonstrating that ablation and resection can lead to good long-term survival (9).

However, there remains a lack of clarity surrounding the role of ablation in the management of metastatic CRC: to date there is no high-quality data published for this technique, which limited its application, nevertheless, liver resection is considered as the gold standard for the treatment of CRCLM.

Surgical management with simultaneous liver and lung metastases. The management of simultaneously diagnosed liver and lung metastases from CRC is a matter of debate. A number of studies have suggested potential benefits from resecting both liver and lung metastases, supported by better outcomes for patients with lung metastasis compared with metastasis at other extra-hepatic sites, although contradictory outcomes have been reported.

Liver resection for metastases from neuroendocrine tumors (NET)

Liver metastasis occurs in 50—75% of patients affected by NETs, and complete resection is only possible in 7—15% of cases. Surgical treatments of NET consist in curative resection, cytoreductive resection, and liver transplantation, and provide effective symptomatic relief and improved overall survival (10). Complete surgical resection is possible in a minority of cases, and few prospective studies comparing different types of treatments have been published. Surgical management is considered the best approach for resectable hepatic metastasis from NET, because it is the only approach with intent to cure, even though the incidence of recurrence after surgery remains high (11). Patients suitable for liver resection include those whose primary tumor was resected or resectable, grade 1 or 2 (G1-G2), without the presence of other extrahepatic disease, anticipated liver remnant of at least 30%, and especially intent of curative surgery. In our experience of 75 patients resected radically, 5- and 10-year OS are 85% and 73%, respectively. As reported in the literature, despite long-term survival, recurrence free-survival (5- and-10 year 50% and 24%) is a strategic point to consider in future studies.

Many advances in liver surgery, diagnostic and interventional radiology as well as medical oncology contributed to the creation of multidisciplinary specialized teams who are able to offer patients the best chances of cure. Despite advanced disease at presentation, current outcomes include cure in more than 20% of cases, and a survival rate of 30—60%, with a surgical mortality of <1% at a specialized Hepatobiliary Centre. These outcomes were unimaginable only two decades ago, and represent a remarkable collective achievement.

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Surgical management of lung metastases

[ROBERTO LUKSCH]

In an autopsy series of patients who died from extrathoracic malignancies, 20—50% had pulmonary metastasis at death, and among these, 10—15% had metastatic disease limited to the lungs. The presence of lung metastatic disease dramatically lowers the probability of survival and the majority of patients have non-resectable locally advanced disease or concurrent metastases to other organs, which excludes therapeutic metastasectomy. In this situation, chemotherapy and radiotherapy permit a median survival of 9—12 months, with long-term survival probabilities around 5%.

Around 30% of patients with cancer develop lung metastases, and in half of cases the lung will be the only site of metastatic diffusion

Lung metastases are the expression of the presence of circulating disease, and theoretically the surgical resection of metastatic lung nodules seems a paradox. However, since 1926 when the first lung metastasectomy was described, many case reports have surprisingly shown that surgical resection of lung metastases could improve survival in selected patients. In 1947, Alexander and Haight published a series of lung metastasectomies and were the first to describe aggressive control of metastatic disease in the chest by carrying successive metastectomies. They proposed the preliminary selection criteria for lung metastasectomy with curative intent: good performance status, absence of extra pulmonary metastases, and good control of the primary tumor. In the following 40 years, Mayo Clinic, Memorial Sloan-Kettering, the INT and a few other highly-specialized centers worldwide emphasized the curative value of surgery in the treatment of metastatic lung disease in different settings, and demonstrated the importance of limited resections for salvage iterative surgery.

In 1990, the INT established the International Registry of Lung Metastases to create a database and exchange information with major thoracic surgery centers across Europe and North America. This Registry also served for a homogeneous analysis of results to identify prognostic criteria and other information on this type of surgery. The Registry collected data on 5206 lung metastasectomies of various primary tumors, defined the long-term survival after metastasectomy, and strengthened the idea that lung metastasectomy is potentially curative, showing that survival after complete resection (R0) was 36% at 5 years and 26% at 10 years, compared with survival after incomplete resection (R1) that was 13% at 5 years and 7% at 10 years. The results of multivariate analysis revealed that complete resectability, disease-free interval, and number of metastases were independent prognostic factors, thus providing a new classification system combining anatomical and biological features to assess prognosis in various primary tumors. Furthermore, the idea born in INT to launch this International Registry permitted, at that time, to demonstrate the inaccuracy of radiologic staging in a large proportion of cases, and the importance of intraoperative exploration by an experienced surgeon to optimize resection of all metastases.

In the years following the publication of the results of the International Registry of Lung Metastases (1997), prognostic factors were validated with prospective studies. The "law of 3" (3 cm diameter, 3 year disease-free interval, and 3 as diameter ratio) as a tool was identified for the planning for adequate indications of lung metastatic resections; the best outcome was confirmed in the germ cell tumors, but the surgical approach to pulmonary metastatic disease permitted observing improvement of clinical outcome even in other histotypes.

At present, some debate remains on the best indications for lung metastasectomy for each single histotype, especially in a context of a multidisciplinary approach in highly specialized and dedicated teams

At present, some debate remains on the best indications for lung metastasectomy for each single histotype, especially in a context of a multidisciplinary approach in highly specialized and dedicated teams. Furthermore, the availability of new tools for the radiological diagnosis, PET and EBUS, brings new insights and questions. These considerations,

together with the continuous advances in bioinformatics that offer rapid and precise technological support for sharing of data, led to new prospective studies, including the creation of a prospective National Registry of Lung Metastases, with as a leading position of the INT of Milan.

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PEDIATRIC TUMORS

PARTICIPATING/PROGRAM MEMBERSHIP

M. MASSIMINO (COORDINATOR),
A. FERRARI, M. CASANOVA, R. LUKSCH, D. PEROTTI

Brain tumors are the leading cause of cancer-related mortality and morbidity in pediatric age. We have ended the procedures for the National Coordination of the SIOP (International Society of Pediatric Oncology) trials for medulloblastoma and ependymoma whose scientific coordinator is a member of this Unit. For ependymoma, we will also lead, in Italy, the European side study called BIOMECA with the aim of studying, in a uniformly staged and treated cohort, prognostic markers already described in the literature and by us in retrospective series, and to validate new markers in discovery research. We have published, moreover, the results of our institutional trial on diffuse intrinsic pontine glioma (DIPG), which are the best ever in this dreadful disease. A study of biopsy surrogate serum biomarkers in DIPG is ongoing, as well as a miRNA profile. More than 24 patients and 300 serum samples have been archived. Cytokines, growth factors, and sonic hedgehog ligands (Sonic, Indian, Desert) are being profiled consecutively and providing a light on tumor extension, response to treatment, relapse, and prognosis. A preliminary report on association with progression-free survival allowed us to identify a signature of 10 miRNAs that is able to stratify high and low risk patients. At present, this is the first study that aims at investigating circulating miRNA levels in pediatric patients with DIPG. As a result of collaboration with McGill University in Montreal, we will also embark in the analysis of specific DIPG mutation, namely p.Lys27Met (K27M) histone H3.3 or p.Lys27Met histone H3.1 mutation that nearly 80% of these tumors harbor, in the serum samples collected. Recent studies showing a mitogenic effect of H3 mutations when expressed in neural progenitor cells and their oncogenic activity in cooperation with other alterations (such as activated PDGFA and loss of p53) support this model. Within this patient population, whose serum samples have been collected as specified above, we selected 10 patients (5 long-term survivors and 5 fast-progressors) with the largest series of serum samples. Specifically, samples from 5 long-term survivors were obtained within a time frame of 1—2 years after beginning of treatment. Samples from fast-progressing patients were obtained in a time frame of 4 months up to 1 year after beginning of treatment. This collection will be used in Dr. Jabado's lab for the identification of H3 mutations thanks to specific assays that are being developed, including those based on the droplet digital PCR (ddPCR) approach. These assays allow sensitive and quantitative detection of H3 mutations in serum and plasma from DIPG patients.

Cytokines, growth factors, and sonic hedgehog ligands are being profiled consecutively and providing a light on tumor extension, response to treatment, relapse, and prognosis

A prospective frozen cephalo-spinal-fluid biobank (CSF) from patients with pediatric brain tumors and non-Hodgkin lymphoma (controls) was established as CSF is a very valuable source of biomarkers for brain tumors and other diseases affecting the CNS, which could offer new important

CSF is a very valuable source of biomarkers for brain tumors and other diseases affecting the CNS, which could offer new important insights for diagnosis, prognosis, and novel treatments

insights for diagnosis, prognosis, and novel treatments. The CSF collection has over 100 samples from 92 patients and 30 controls with lymphomas. Pairing capturing hydrogel nanoparticles, poly(NIPAm-co-AA), technology with LTQ Orbitrap mass-spectrometer allows us to identify proteins at extremely low concentration. The unsupervised selection procedure identified, according to the Fisher exact test and/or to the univariate logistic regression model, 34 and 41 significant (alpha = 0.05) proteins comparing 27 cases versus 13 controls and 10 metastatic cases versus 13 controls, respectively. Combining a unique dataset of CSF from pediatric cancer patients with novel nanotechnology allowed us to identify promising CSF proteins that are possibly linked to CNS tumors.

The Unit also continues the National Coordination for stage 4 and poor prognosis **neuroblastoma (NBL)** trial that is a particular engagement including intensive chemotherapy, autologous hemopoietic stem cell transplantation, surgery, radiotherapy, and immunotherapy with anti-GD2, a hard phase of the overall strategy, for which some patients are referred from other centers for the well-known experience gained at our Unit. In the pipeline, there is an immunotherapy project involving the creation of tumor specific CARs (chimeric antigenic receptors) that maintain the antigenic specificity of the antibody that has generated and the transmembrane part of the T receptor. In NBL, CARs against GD2 antigen trasduced in activated T-cell or EBV-specific CTL have been used in protocols of adoptive immunotherapy and have shown strong anti-neoplastic activity. We aim to identify new tumoral targets such as NY-ESO-1. Another target, called PRAME, has shown immunogenicity in vitro and is expressed by advanced stage neuroblastoma.

Due to the deep involvement in the ITCC (Innovative Therapies for Children with Cancer) network, we have offered our relapsing patients a major number of further line therapies with **new drugs** contributing to some clinical success. Clinical Cancer Research has published a paper identifying a characteristic gene-signature selecting medulloblastoma patients that can respond to the SHH inhibitor LDE225, which is now applied in a phase 3 trial whose protocol is coordinated by our Unit. Two studies for first-line (randomization for the inclusion of bevacizumab to standard therapy in metastatic patients) and relapsed rhabomyosarcoma (randomization for the inclusion of temozolomide to standard vincristine and irinotecan) have been concluded (our Institution being the leader center in Italy), as well as the first-line randomized trial for malignant glioma with or without bevacizumab where our center was the national coordinator and the largest recruiting center worldwide (14/120 patients in over 80 open centers). We have also recruited, as the largest enrolling center, two adolescents in a phase 1 study of vemurafenib for unresectable and stage IIIC or IV tumor with di BRAFV600 mutations. We have continued the screening and enrolment in the phase 1 pediatric - first in child - study with LDK378, an ALK inhibitor. We are the only Italian center joining the study. We also began enrolment in a phase I/II study with nab-paclitaxel (Abraxane) for relapsed and resistant solid tumors in children. Our Unit is the national Coordinator for this study. There are at least 3 other new drugs suitable for initiating phase 1/2 trials for pediatric solid tumors.

We have offered our relapsing patients a major number of further line therapies with new drugs contributing to some clinical success

The Youth Project, a clinical, social, and political awareness project to help cope with the poor prognosis of **adolescents and young adults** affected by pediatric tumors, has promoted the creation of a new scientific Italian society: SIAMO, (www.progettosiamo.it), that unifies the efforts of AIEOP (Associazione Italiana Ematologia e Oncologia Pediatrica), FIAGOP (parents association), AIOM (Associazione Italiana Oncologia Medica), and SIE (Società Italiana Ematologia) towards better care with inclusion in controlled trials and tailored post-treatment return to normal life with fertility, psychology, sport, education, and job programs. There is a strong national movement leaded by one of us to highlight this problem and

A clinical, social, and political awareness project to help cope with the poor prognosis of adolescents and young adults affected by pediatric tumors, has promoted the creation of a new scientific Italian society: SIAMO

modify patient access to care and clinical behaviors that will be the aim of future efforts.
This last aspect is pioneered in our **"cured patients" clinic** that receives around 300 patients a year taking into account the late effects reported after cancer impact and iatrogenic sequelae. An interview related to job and social activities is also accompanied by specific clinical questions, visit, and care. When needed, guided referral to other childhood or adult specialists is made. In the last year, particular care has been given to premature ovarian failure risks and subsequent female infertility. We aim to study, by dosing anti-mullerian hormone (AMH), prematural ovarian failure in a pilot series of girls that will be assessed at the beginning of therapy, 6 months after, and 2 years later. Candidates will be those with osteosarcoma, lymphoma, localized medulloblastoma, or localized rhabdomyosarcoma.

For **Wilm's tumor** (WT), the most common kidney tumor in children, we will continue National Coordination of both clinical and biological trials with a tumor bank containing over 350 tumor, blood, and urine samples, and activities concerning referral for particularly difficult cases from surgical or radiotherapy standpoints. The analysis of new putative genes involved in WT has been completed and significance has been attributed to the mutations found. The occurrence of familiar cases of WT has been analyzed. The whole exome sequence has been completed and all genetic variables have been validated by classic sequencing. In 58 non-pre-treated tumors, gene sequencing has been correlated to high-risk of relapse. The aim for near future is to complete a whole genome analysis of 200 cases, in addition to analysis of samples from relapsed patients in a European context of 25 cases/year.

The analysis of new putative genes involved in Wilm's Tumor has been completed and significance has been attributed to the mutations found

Our Unit is also in charge of National Coordination for **germ cell tumors, metastatic Ewing sarcoma, and soft tissue sarcomas** different from rhabdomyosarcoma.
With particular reference to **rhabdomyosarcoma**, we are performing cytogenetic/genetic analysis (Targeted Next Generation Sequencing, t-NGS) to find new molecular alterations and possibly new therapeutic targets. To prove the existence, feasibility, and vulnerability of these targets, pre-clinical models will be prepared. This will be obtained through cell culture preparation from surgical samples of pediatric rhabdomyosarcomas that will be submitted to several pharmacologic inhibitors. We also aim to prepare in vivo xenograft models to confirm the possibility of tumor cell inhibition.

We are performing cytogenetic/genetic analysis (Targeted Next Generation Sequencing, t-NGS) to find new molecular alterations and possibly new therapeutic targets

In the field of children and adolescent **soft-tissue sarcomas** of interest, we also have a project to study a selected series of children and young adults with sarcoma with the same histology but different patient ages at diagnosis. The aim of this research is to understand if the prognostic differences already observed clinically between younger – more favorable – and older patients is justified by different molecular alterations. We will use a high-throughput t-NGS with IonTorrent AmpliSeq™ Comprehensive Cancer Panel to identify recurrent gene mutations. Moreover, we will use comparative genomic hybridization to identify deletions and amplifications.

In the field of **psychological and psychodynamic studies** and **support**, we will study the effects of continuous **sport training** during oncological treatment, **the quality of life of bone tumor patients** at diagnosis and during/after treatment, the **action-observation-therapy** for patients with post-cerebral tumor morbidities, and the effects of patient **communication** during phase 1/2 trials.

HEMATOLOGICAL MALIGNANCIES, BONE MARROW TRANSPLANT AND NEXT GENERATION SEQUENCING IN HEMATOLOGY

PROGRAM/PROJECT MEMBERSHIP

P. CORRADINI (COORDINATOR)

Treatment options for patients with hematological malignancies include chemotherapy, radiotherapy, immunotherapy, and high-dose chemotherapy followed by autologous and allogeneic stem cell transplantation (auto- and allo-SCT).

Highlights

This project will address currently unmet clinical needs in the management of hematological malignancies. New biomarkers for the upfront identification of patients with aggressive, refractory and/or relapsing disease and new treatments tailored to target cancer-driving lesions are mandatory. Although a variety of genetic and epigenetic lesions as well as microenvironmental features have been mechanistically implicated in the pathogenesis and progression of hematological malignancies, the pathogenesis of chemo-refractoriness remains unclear. Major improvements in sequencing technologies could provide the opportunity to discover genomic alterations and therapeutic targets accounting for chemo-refractoriness and early relapse. This project will also define preclinical models mainly for Peripheral T Cell Lymphomas (PTCLs) that reliably predict the clinical activity of novel compounds specifically targeting the key genetic lesions identified. The potential role of genes/proteins as diagnostic tools and novel biomarkers with prognostic and predictive value will be assessed.

Major improvements in sequencing technologies could provide the opportunity to discover genomic alterations and therapeutic targets accounting for chemo-refractoriness and early relapse

Program Membership

The goals of this project will be achieved by integrating the complementary and synergistic skills and facilities of members (clinicians, researchers and data managers) of the Hematology-Bone Marrow Transplantation Unit. The clinical staff (Prof. Paolo Corradini, Dr. Anna Dodero, Dr. Vittorio Montefusco, Dr. Lucia Farina, Dr. Francesco Spina, Dr. Giulia Perrone) has been working in the field of hematological malignancies and stem cell transplantation for many years and will be instrumental in designing clinical studies and selecting patients for biological analysis. All clinical information necessary to correlate biological results with outcomes will be collected by our data managers (Dr. Debora Degl'Innocenti, Dr. Anisa Bermema). Well characterized bio-repositories of biospecimens (blood, plasma, biopsies) from patients enrolled in several clinical trials are available to the research team as a biobanking system, which is ongoing within the Unit and coordinated by Dr. Cristiana Carniti. The biobank will provide a sufficient number of samples for analysis and validation of results. The expertise for the use of new sequencing technologies is increasing in our

Unit. Specifically, Dr. Silvia Gimondi of the Hematology Branch attended the Ion PGM teaching course at Life Technologies laboratories, Darmstadt, in Germany and learned the use of this technology, completing her bioinformatic skills. Other members of the team include researchers (Dr. Antonio Vendramin, Dr. Alessandra Cavanè, Dr. Sara Rizzitano) with different but synergistic expertise who have been selected according to their proven well-defined scientific and technical skills.

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DIET AND PREVENTION

PROGRAM/PROJECT MEMBERSHIP

V. KROGH (COORDINATOR),
A. VILLARINI, P. PASANISI

The Diet and Prevention research program is structured in two main investigative approaches: 1. prospective cohort studies, to define individual risks related to diet; 2. intervention studies, to test strategies for prevention and recurrence of cancer and other chronic-degenerative diseases.

The **European Prospective Investigation into Cancer and Nutrition (EPIC) study** was designed to investigate the relationships between diet, lifestyle, genetic, and environmental factors and the incidence of cancer and other chronic diseases in 23 centers across 10 European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom. Data were collected from more than 520,000 healthy volunteers on diet, physical activity, reproductive history, lifetime consumption of alcohol and tobacco, previous and current illnesses, and current medication. Blood samples were also collected, processed, and stored in liquid nitrogen at –196°C. Anthropometric measurements were taken according to a standard protocol. Follow-up is based on linkage with population cancer registries or a combination of methods including health insurance records, cancer and pathology registries, and active follow-up. The EPIC project represents an ideal natural laboratory thanks to the very heterogeneous dietary habits still to be found in different European populations. At the same time, the incidence of several major cancer sites varies substantially across countries and even more across regions. Another crucial element of statistical power, which was central in the design of EPIC, is the study size.

The main results on diet and cancer risk published in 2014 were:

- **renal cell carcinoma**: red and processed meat consumption increase the risk in women; higher circulating concentrations of vitamin B6 are associated with lower risk and improved survival following diagnosis;
- **head, neck and esophageal cancer**: elevated circulating levels of homocysteine, which indicate low B vitamin status, are associated with increased risk of developing squamous cell carcinoma of the head and neck; tea and coffee consumption is associated with decreased risk of esophageal squamous cell carcinoma among men and current smokers;
- **pancreatic cancer**: higher plasma concentrations of β-carotene, zeaxanthin, and α-tocopherol are inversely associated with risk;
- **hepatocellular carcinoma**: coffee and tea consumption is associated with decreased risk;
- **gastric cancer**: adopting several healthy lifestyle behaviors (not smoking, limiting alcohol consumption, eating a healthy diet, and maintaining a normal weight) is associated with decreased risk;
- **colorectal cancer**: high dietary glycemic index and high carbohydrate intake from high glycemic index foods increase the risk; combined lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, and a healthy diet) are associated with lower risk; elevated plasma total and LDL-cholesterol are associated with increased risk; body mass index (BMI) is associated with colon cancer risk; pre-diagnostic general and abdominal adiposity are associated with lower survival after colorectal cancer diagnosis;

- **bladder cancer**: the dietary intake of flavonols and lignans is associated with reduced risk; the Mediterranean diet reduces risk among current smokers; weight, BMI, waist, and waist to hip ratio are inversely associated with risk;
- **breast cancer**: dietary folate intake is associated with a lower risk of overall breast cancer and a lower risk of sex hormone receptor-negative breast cancer in premenopausal women; high total fat is associated with greater risk of ER^+PR^+ disease, high saturated fat is associated with increased ER^+PR^+ HER2- disease; combined lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption and a healthy diet) reduce the risk of breast cancer among postmenopausal women; adult weight gain is associated with increased risk, especially for cancers diagnosed before age 50;
- **mortality**: raw vegetable consumption is associated with lower cancer mortality; alcohol consumption is positively associated with overall upper aerodigestive tract, liver, colorectal, and female breast cancer mortality.

The **ORDET study** is one of the first prospective European studies on the role of hORmones and Diet in the Etiology of breast Tumor. A total of 10,786 healthy women, aged 35–69 years, residents in Varese province, Northern Italy, were recruited in 1987—1992. At recruitment, several sources of hormone variability were controlled for by both inclusion criteria and highly standardized conditions at blood drawing. Women with bilateral ovariectomy, those currently pregnant or breast-feeding, those on oral contraceptives or hormone replacement therapy, or those affected by liver diseases were not eligible for the study. Information on lifestyle characteristics, menstrual and reproductive history, dietary habits, and anthropometric measurements have been collected at baseline. Moreover, blood samples were collected after 12 hours of fasting. All blood samples were processed and stored at –80°C. Women are followed through the local cancer registry (Lombardy Cancer Registry, Varese Province) characterized by high completeness and quality.
The ORDET study is participating the "Pooling Project of Prospective Studies of Diet and Cancer", an international collaboration that involves 28 European and North American cohort studies, with more than 2,000,000 volunteers, coordinated by Harvard University.

The **COS study** is a randomized controlled trial of diet and physical activity in BRCA mutation carriers. The aim of the study is to test whether moderate caloric and protein restriction (including avoidance of milk protein) together with physical activity, decrease IGF-I, insulin, and insulin resistance in women with a genetic susceptibility to breast cancer. The study intends to recruit a cohort of 300 BRCA mutation carriers and 160 women have been already randomized. This cohort of women belonging to high genetic risk families will represent the starting point of a prospective study to test potential modulators of penetrance and prognosis.

The **TEVERE (Diana-4) study** is a blinded randomized controlled trial of diet and metformin for primary prevention of breast cancer. The study is recruiting healthy women aged 45—74 years, with waist circumference ≥85 cm, and at least one feature of metabolic syndrome. The aim of the study is to test the effect of metformin, an antidiabetic drug, on breast cancer occurrence. The study hypothesis is that study participants treated with metformin (1700 mg/day) will have a lower incidence of breast cancer in comparison with women given placebo on breast cancer prevention during 5-year follow-up. Participants also receive dietary recommendation to reduce the risk of metabolic syndrome and insulin resistance. At the moment, we have recruited 470 women and more than 300 are under treatment.

The aim of the study is to test the effect of metformin, an antidiabetic drug, on breast cancer occurrence

The **MeMeMe study** is a randomized controlled trial of diet and metformin for primary prevention of age-related chronic diseases (ArCD). The plan is to carry out a randomized controlled trial on 2,000 healthy men and women, 55-74 years of age, at high risk of ArCD because of metabolic syndrome. The aim of the study is to evaluate the effect of comprehensive life-style intervention (including moderate physical activity and Mediterranean/ macrobiotic diet with moderate caloric restriction), and treatment with metformin for prevention of ArCD.

The **DIANA-5 study** is a multicenter randomized controlled trial of the effectiveness of a diet based on Mediterranean and macrobiotic principles, associated with moderate physical activity, in reducing additional breast cancer events in women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu. The intervention is expected to reduce serum insulin, sex hormones, serum IGF-I, and metabolic syndrome (defined by the presence of at least three among abdominal obesity, hypertension, low plasma HDL-cholesterol, high plasma glucose, and high triglycerides), which were associated with breast prognosis in previous studies.
The study enrolled 2,356 women diagnosed with invasive breast cancer within the previous 5 years who had not developed distant metastasis, local recurrence or second primary breast cancer. All participants were asked to change their diet according to the WCRF/AICR (2007) guidelines for prevention of cancer and were allocated to one of three different groups. Women with no metabolic/endocrine traits of high recurrence risk (ER- tumor, metabolic syndrome, high serum testosterone or insulin level) were allocated to an observational group (n=681). Women with one or more of the above high risk traits were randomly assigned to a control group (n=833), which received only WCRF/AICR recommendations, and an active intervention group (n=842) requested to participate in kitchen courses and physical exercise sessions. Compliance assessments in control and intervention group include repeated 24-hour food frequency and physical activity diaries, anthropometric measures, impedance evaluation of body fat distribution, one week registration of energy expenditure integrating the measure of movement, and several other physiological signals collected with a SenseWear Armband, plasma glucose, cholesterol, triglycerides, insulin, SHBG, and sex hormones. At baseline and after 12 months, blood samples are collected. The collection of additional blood samples is planned at 36 and 60 months.

The DIANA-5 study enrolled 2,356 women diagnosed with invasive breast cancer within the previous 5 years who had not developed distant metastasis, local recurrence or second primary breast cancer

DEVELOPMENT, PRECLINICAL, AND CLINICAL VALIDATION OF ANTIBODY-BASED REAGENTS FOR DIAGNOSTIC AND THERAPEUTIC USE

PROGRAM/PROJECT MEMBERSHIP

M. FIGINI (COORDINATOR)
E. TAGLIABUE

Antigen-specific monoclonal antibodies (MAbs) with direct pharmacological effects as naked antibodies, conjugated with chemotherapy/toxic agents, or able to stimulate immunological responses are promising therapeutic agents for various cancers, either as frontline treatment or in maintenance of remission.

The main purpose of this area of research is the preparation, characterization, and optimization of antibody-based reagents using antibody engineering to better respond to clinical needs. All research projects presented herein are the result of collaboration between biotechnologists, biologists, chemists, and clinicians. For the design of a good antibody-based reagent and for optimization of its clinical use, it is important to know the mechanism by which the antibody exerts its activity, the biology of the target, and the characteristics of the targeted disease. The results obtained in 2014 are summarized below.

Antibody-based reagent directed to alpha folate receptor (α FR). The α FR has the characteristics of a tumor-associated antigen with limited normal tissue distribution and altered expression after chemotherapy, thus making it a potential target even in previously treated relapsing tumors. On the other hand, it is over-expressed in many tumors, such as epithelial ovarian cancer (EOC), mesothelioma, lung cancer, head and neck and in a significant subgroup of ER/PR-negative and triple-negative breast cancers, indicating that a reagent directed against this target may have a great spectrum of applicability.

Completely human Fab fragments against α FR were generated in our laboratory using antibody phage display libraries obtained from EOC patients. One of the selected human fragments has been considered as a suitable agent for radio-immunotherapy in EOC, and recently, spherical magnetic iron oxide nanoparticles 20 nm in diameter were conjugated with this fragment for preclinical in vivo studies in mice bearing orthotopic or subcutaneous targetable tumors. Elemental and histological analyses showed that these targeted magnetic nanoparticles have enhanced tumor accumulation retention demonstrating a good therapeutic window as carriers of therapeutic agents, thus reducing side effects and toxicity due to systemic distribution. Moreover, the nanoparticles have superparamagnetic property and if exposed to a magnetic field will overheat, thus opening up the possibility of their use for hyperthermia treatments.

The conversion of this antibody fragment into an IgG molecule allowed the recruitment of effector cells through the Fc fragment thus inducing ADCC (80% ADCC in an EOC cancer cell line using PBL from donors at an E:T ratio of 6:1).

Completely human Fab fragments against α FR were generated in our laboratory using antibody phage display libraries obtained from EOC patients

The possibility to use antibodies for lymphocyte retargeting is a very promising application which can be exploited using chimeric antigen receptors (CARs) by T-cell engineering or by using bispecific antibodies (BsAbs). In collaboration with the University of Pennsylvania, we recently obtained a fully human CAR with potent activity against cancer cells but reduced risk for off-tumor toxicity using the human scFv anti αFR C4 previously selected in our laboratory.

BsAbs anti TRAIL-RII\anti CD3. By simultaneously recognizing target antigen and T cell activating receptor, BsAbs provides an alternative opportunity to redirect immune effector cells against cancer cells. With the advent and advances in recombinant DNA technology, new BsAb formats overcame the problems of the complexity of antibody pairing. In an AIRC 5x1000 research framework (PI AM Gianni), we developed a BsAb directed against TRAIL that demonstrates potent cytotoxic effect in many different types of cancer including EOC, melanoma, and breast carcinoma. The two scFv, anti TRAIL-RII and anti CD3, have been joined in a single chain format. This format can be purified to near homogeneity and being a small molecule of only 55 KDa, induces the formation of an immunological synapse between T cells and tumor cells that results in T-cell activation and proliferation as well as potent T-cell mediated anti-tumor activity.

Antibody-based reagent directed against prostate specific membrane antigen (PSMA). PSMA is an antigen specifically expressed on prostate cancer. Moreover, several studies have shown that anti-PSMA antibodies bind to the vasculature associated with many solid malignant tumors suggesting wider use of this reagent is possible. Starting from the property of our anti-PSMA mouse MAb D2B, we converted it into a single chain Fv (scFv) format (PCT /IB2009/005326). ScFvD2B was analyzed in vitro for activity, stability, internalization ability, and in vivo for targeting specificity. This scFv was used for the construction of a second generation of CAR that is able to exert relevant cytotoxic activity by engagement with PSMA$^+$ prostate tumor cells. Upon transfer in tumor-bearing mice, CAR-transduced T cells were capable of completely eradicating disseminated neoplasia in the majority of treated animals, thus supporting the translation of such approach in a clinical setting (Zuccolotto et al. PlosONE 2014).
Moreover, the therapeutic potential of a recombinant immunotoxin composed of this scFv and the de-immunized PE toxin is under evaluation in collaboration with Prof. Colombatti (University of Verona).
In clinical practice, the role of imaging in PC diagnosis and treatment is three-fold: tumor localization, staging of disease, and detection of recurrence. The development of a suitable reagent is therefore an actual need.
Maintenance of function and immunoreactivity as well as extremely high radiolabeling efficiency and radiochemical purity were demonstrated by in vitro assays. Despite its monovalent binding mode, scFvD2B retained a good strength of binding. In vivo we showed its ability to specifically target only PSMA-expressing prostate cancer xenografts. Three different radioisotopes were used to label scFvD2B (^{111}In, ^{131}I and ^{123}I) with comparable tumor localization. ^{123}I was chosen as the best imaging reagent for potential in vivo applications.
Design and implementation of a phase I clinical study to assess safety, tolerability and dosimetry of ^{123}I-scFvD2B GMP administered i.v. and followed by scintigraphy is ready to be submitted to the Ministry of Health.

Several studies have shown that anti-PSMA antibodies bind to the vasculature associated with many solid malignant tumors suggesting wider use of this reagent is possible

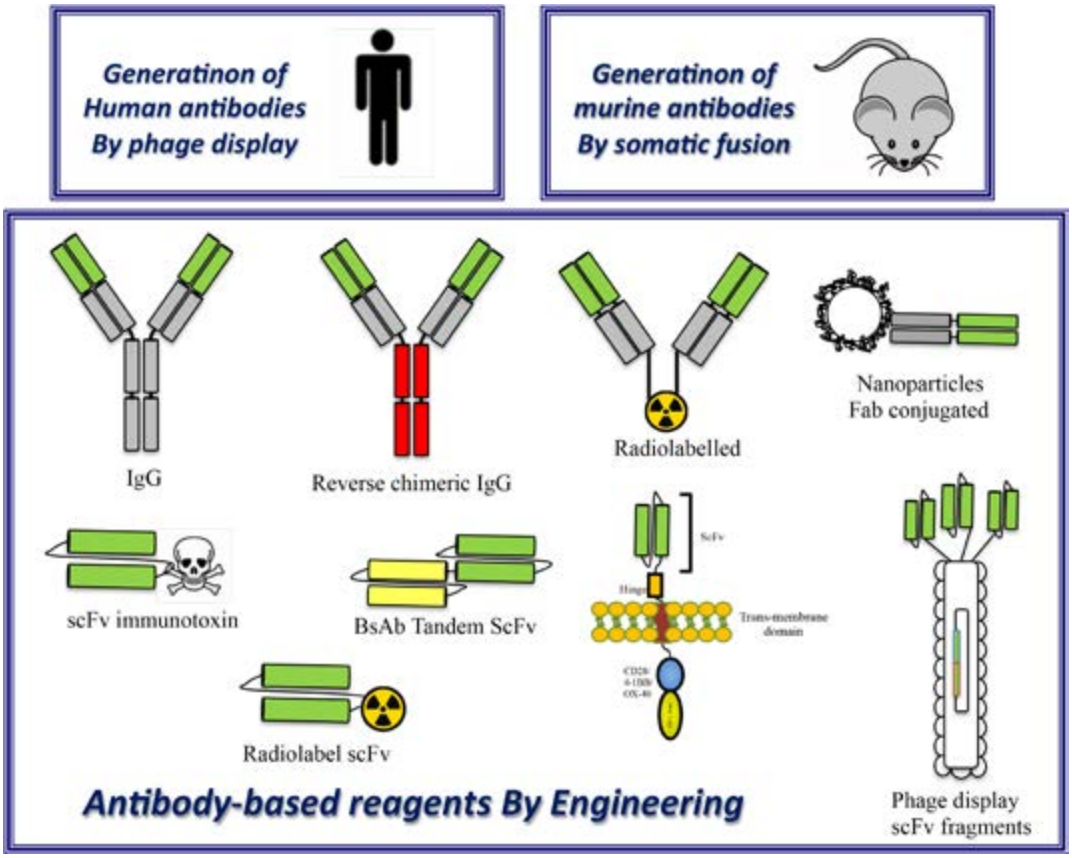
Production of monoclonal antibodies against maspin. From microarray supervised analysis on a dataset of chemotherapy-treated breast carcinoma patients, maspin, a member of the serpin protease inhibitor family, has been the foremost variable identified in non-responsive versus responsive tumors. Accordingly, in a series of human BCs, we detected high maspin expression in tumors that progressed under doxorubicin

In a series of human BCs, we detected high maspin expression in tumors that progressed under doxorubicin (DXR)-based chemotherapy

(DXR)-based chemotherapy. Our analysis of the role of maspin in response to chemotherapy in human BC cell lines transfected to overexpress maspin and injected into mice showed that maspin overexpression led to DXR resistance through the maspin-induced collagen-enriched microenvironment. Therefore, using recombinant GST-maspin protein as an immunogen, we derived 10 monoclonal antibodies that are specific for recombinant maspin by ELISA assay and one (MPI1) able to neutralize maspin activity. Treatment of mice, injected with maspin-overexpressing cells, with this antibody decreased collagen content and, as a consequence, overcame maspin-induced DXR resistance decreasing tumor volume upon DRX treatment. These findings suggest the promise of this antibody in combination with a standard chemotherapeutic agent, such as DXR, as a novel therapeutic strategy to overcome drug resistance induced by the tumor microenvironment and to consistently achieve objective responses in breast carcinomas that progress after traditional therapy (Triulzi T. et al. Int J Cancer 2014).

FIGURE

Novel promising biomarkers are generated antibody based reagents for diagnostic and therapeutic use.



HEREDITARY CANCER AND MEDICAL GENETICS

PROGRAM/PROJECT MEMBERSHIP

S. MANOUKIAN, P. RADICE, M. VITELLARO, S. SIGNORONI, G. DEL CONTE

Hereditary Breast and Ovarian Cancer syndrome (HBOC)

[PAOLO RADICE AND SIRANOUSH MANOUKIAN]

The project is carried out in collaboration among Molecular Bases of Genetic Risk and Genetic Testing Unit, Medical Genetics Unit of the Department of Preventive and Predictive Medicine, and the Unit of Anatomic Pathology 1 of the Department of Diagnostic Pathology and Laboratory Medicine and takes advantage on the collaboration with National and International research groups, including consortia and scientific societies.

While we will pursue the decryption of the complex landscape of the molecular basis of breast cancer susceptibility and of the associated risks, we plan to exploit recently developed technological approaches, including Next Generation Sequencing. This will be applied to the examination of selected gene panels or of the entire exome or genome. More specifically, we intend to verify the occurrence of additional pathogenic founder mutations in population enriched in genetic isolates. Furthermore, we seek to investigate breast cancer patients who survived from pediatric malignancies. These will be screened for constitutional pathogenic mutations in a panel of seven breast cancer predisposing genes. The analysis will include, in addition to coding exons, all non-coding regions spanning the genes of interest. In fact, little information is available on the role on cancer predisposition of variants in such regions. Identified variants will be prioritized through bioinformatics analyses and their pathogenicity assessed by functional assay. The occurrence of specific correlations between the detected mutations and the characteristics of the patients will be verified, in particular as concerned the age of breast cancer onset and type of treatments for childhood cancer. The main outcomes expected from this project are an increase of the current knowledge on the contribution of breast cancer predisposing genes to pediatric cancer onset and the development of genetic tests to identify specific subgroups of cancer prone individuals. Since compelling evidences indicate that a subset of cancer predisposing alleles have a preferential geographic distribution, we will foster the constitution of a nation-wide network of cancer genetic laboratories with the aim of promoting the development of collaborative project specifically addressed to the Italian population and of facilitating the connections with the above mentioned international consortia.

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The diagnostic activity is integrated with several research programs, taking advantage from the continuous recruitment through genetic counseling of selected individuals and families with evidence of genetic predisposition to cancer. In particular, the consolidated and long lasting clinical activity of the Medical Genetics Unit has allowed the assembling of the largest Italian collection of HBOC patients and relatives, including at present more than 8,750 individuals belonging to about 4,150 different HBOC families collected. When available, all relevant data have been recorded in the Medical Genetics HBOC database. Actually, more than 707 BRCA1/BRCA2

mutated families have been collected, including 1,314 gene carriers (150 men and 1,164 women), of which 879 women affected by breast and/or ovarian cancer. Moreover data on 142 families with variants of unknown significance and 1,846 high risk families tested negative for BRCA1/BRCA2 mutation, are available. Tumor specimens and blood samples are routinely collected from all patients treated at INT. Taking advantage of the high number of families maintaining a long lasting contact with the Unit, all new clinical, familial, pathological and molecular data of the individuals belonging to HBOC families are constantly updated.
Major relevant studies are:

- genetic characterization of HBOC (penetrance, survival, disease features and presentation, tumor features, as well as genetic and environmental risk factor modifiers)
- long-term efficacy, clinical and psychological impact of surveillance, risk reducing measures and treatment in HBOC individuals
- biological and clinical significance of BRCA gene mutations with unknown significance
- genomic and transcriptomic analyses for the identification of modifier risk factors and new genes involved in genetic predisposition to HBOC
- effective strategies for identification and referral to risk evaluation of women at increased genetic risk for breast and ovarian cancer.

Hereditary Digestive Tract Tumors

[MARCO VITELLARO, STEFANO SIGNORONI AND GABRIELE DEL CONTE]

Recently, several genetic factors associated with hereditary susceptibility to cancer have been identified. Genetic test is routinely applied in clinical practice to search for germline cancer predisposing alleles. This allows clinicians to identify, within cancer-prone families, at-risk individuals. Once the gene carriers are identified, it is possible to offer them the appropriate surveillance programs and/or other measures of risk reduction, such as chemoprevention or prophylactic surgery. Conversely, family members not found to be mutation carriers may be advised to follow the same recommendations of the general population. We are devoted to the counselling, molecular testing, and clinical management of individuals with genetic predisposition to the major hereditary syndromes of gastrointestinal cancer. These include Lynch Syndrome (or Hereditary Non-Polyposis Colorectal Cancer -HNPCC-), Familial Adenomatous Polyposis (FAP) and its variants Attenuated-FAP or MAP, Peutz Jeghers Syndrome, Juvenile Polyposis and Hereditary Gastric Cancer. Individuals with evidence of hereditary susceptibility to cancer are counseled and informed about personal and relatives risk. Depending of the fulfillment of defined clinical criteria, individuals who receive genetic counseling are offered the possibility to undergo molecular testing for identification of specific genetic alteration(s) that may be associated with the increased risk of cancer in their families. These criteria include personal and family history of cancer, specific clinical phenotypes, and tumor characteristics. The screened genes at present include: MLH1, MSH2, MSH6, and PMS2, cumulatively referred to as DNA mismatch repair (MMR) genes [Lynch Syndrome]; APC and MUTYH [FAP and attenuated FAP]; STK11 [Peutz-Jeghers Syndrome], PTEN [Cowden Syndrome], CDH1 [Hereditary Gastric Cancer] and p53 [Li Fraumeni Syndrome]. During 2014, about 400 individuals were counselled and screened for germline mutations in cancer predisposing genes. This diagnostic activity is integrated by several research programs.
Beyond the already identified hereditary genes, there is an amount of CRC cases that present familial aggregation for the disease without a known germline genetic cause. Moreover, CRC can be also considered a complex disease in which the combinations of genomic variants with rare-to-

Once the gene carriers are identified, is possible to offer the appropriate surveillance programs and/or other measures of risk reduction, such as chemoprevention or prophylactic surgery

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common prevalence and high-to-low penetrance could play a role in the etiology of the disease. In the recent years, new sequencing technologies including whole-exome sequencing have provided further insights into familial CRC revealing new candidate susceptibility genes for CRC predisposition.

The identification of predisposing variants for CRC could have substantial implications for disease risk assessment, management, and surveillance in family members with a strong CRC family history, without a detectable germline mutation in the known predisposition genes. Moreover, it could represent an important tool to improve the efficiency and the efficacy of treatment and surveillance protocols of selected patients/individuals, reducing costs and improving compliance and quality of life. At present a discovery phase of whole exome sequencing is in progress on selected patients with the support of the Functional Genomics and Bioinformatics - Department of Experimental Oncology and Molecular Medicine.

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BIOSPECIMEN REPOSITORY - BIOBANK

PARTICIPATING/PROGRAM MEMBERSHIP
G. PELOSI AND M.G DAIDONE

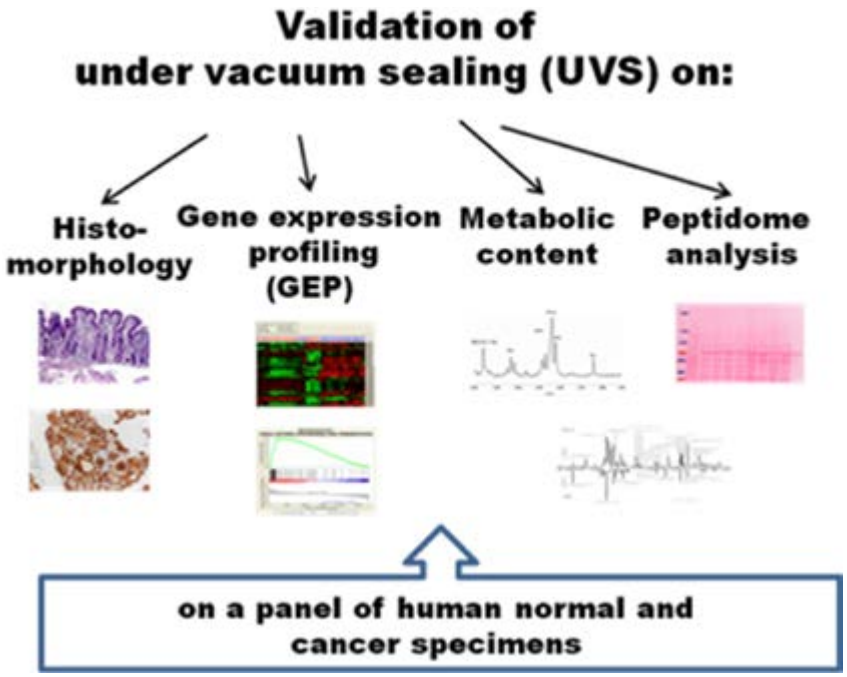
Since 2002, the INT Biobank (INT-BioB) has been dedicated to the collection and distribution of neoplastic, preneoplastic, and normal tissues from human subjects for research projects.

More recently, starting from 2012, collection and processing of blood samples have been implemented for selected tumor types. This resource is a project of INT Scientific Directorate, with day-to-day staff supervision provided by personnel from the Departments of Pathology and Experimental Oncology and Molecular Medicine. The activities are overseen by an interdepartmental advisory committee, which evaluates and approves research projects depending on the availability of tissue specimens. Adopting TUBAFROST procedures, although slightly modified to comply with local conditions, the INT-BioB stores frozen samples (primary and metastatic lesions, with corresponding normal tissues) and blood samples (whole blood, plasma, serum, red cells and buffy coats) and contributes specimens to a large number of specific research projects dealing with almost all tumor types. All patients/subjects sign an informed consent document (approved by the Independent Ethics Committee and filed in the patients' records) to donate leftover tissue/biological specimens from diagnostic procedures to the INT-BioB for future studies. It is a one-time general consent with a two-step decision process that allows patients to control the use of their samples and foster important research. Guidelines have been proposed to define responsibilities for INT-BioB management, policies, and procedures to protect patient confidentiality and privacy, and establish priorities for specimen distribution. In 2014, INT-BioB was certified to implement and maintain a Quality Management System that fulfils the requirements of ISO 9001:2008 standards, and become a member of BBMRI (www.bbmri.it).

The activities are overseen by an interdepartmental advisory committee, which evaluates and approves research projects depending on the availability of tissue specimens

During 2014, much effort has been dedicated to investigating the potential of novel pre-analytical tissue handling procedures to allow optimal morphologic and reliable antigenic preservation, and integrity of nucleic acids, proteins, and metabolites to enable reliable molecular testing for personalized treatments, even in the context of multicentric studies. The evidence that formalin fixation may lead to extensive degradation of nucleic acids prompted the development of an alternative approach by Under Vacuum Sealing (UVS) and cooling specimens at 4°C to transfer fresh tissues to pathology labs (Bussolati G, et al. PLoS One. 2011;6(6):e21043). Using a panel of 18 human normal and tumor samples (including breast, colon, lung cancers and sarcomas), we evaluated the UVS approach in terms of: a) histomorphology, Ki-67 and vimentin expression; b) Gene Expression Profiling (GEP) by Illumina HT12_v4 platform and Gene Set Enrichment Analysis (GSEA); c) high resolution NMR spectroscopy of metabolic content; d) peptidome analysis by SELDI and WB. Morphology and immunohistochemical reactivity were perfectly preserved (up to 72 h at 4°C) and unaltered over the entire observation period, thus permitting transport of fresh surgical specimens from distant Institutes. GEPs showed tissue-related changes over time, while GSEA indicated that some pathways

Morphology and immunohistochemical reactivity were perfectly preserved and unaltered over the entire observation period, thus permitting transport of fresh surgical specimens from distant institutes



were eventually deregulated. Degradomic behaviors by peptidome analysis revealed a negligible contribution of storage time on proteolysis, and stability of phosphorylation sites for up to 24 hours. Conversely, metabolic changes occurred after 1 hour of UV storage of breast and lung cancers, and after 24 hours in normal and colon cancer tissues. Notwithstanding some tissue heterogeneity, the study confirms the validity of UVS for histologic and molecular analyses.

In addition, during 2014, a strong collaboration was activated in INT among the Analytical Epidemiology and Health Impact, ICT and Breast Surgery Units and INT-BioB to integrate the institutional breast cancer clinical registry with the different repositories (e.g., bio-banks and blood exam database). Such an initiative represents an asset in a comprehensive cancer centre since it can be used for an assessment of bio-bank specimens with specific characteristics, and thus is instrumental for translational studies.

PATIENT-DERIVED XENOGRAFTS

PARTICIPATING/PROGRAM MEMBERSHIP

G. SOZZI (COORDINATOR),
M. MORO, N. ZAFFARONI

Studies based on cell lines have been found to be poor predictors of clinical effects, and thus in many cases clinical translation of results has failed. A major determinant for the poor performance of cell lines is the observation that they do not reflect the entire complexity and heterogeneity of primary tumors.

In fact, tumors contain not only tumor cells but also stromal cells of different types. Furthermore, tumor cells within a tumor might be heterogenous, in some cases organized along a differentiation hierarchy, and in other cases organized as different subclones with differing molecular characteristics reflecting ongoing clonal evolution. Taken together, the different cells in a tumor form a complex tissue-like structure. Therefore, preclinical models that more precisely reflect these characteristics are needed. A growing body of work suggests that patient-derived xenografts (PDX) represent a more informative cancer model, providing a faithful representation of the patient's original tumor.

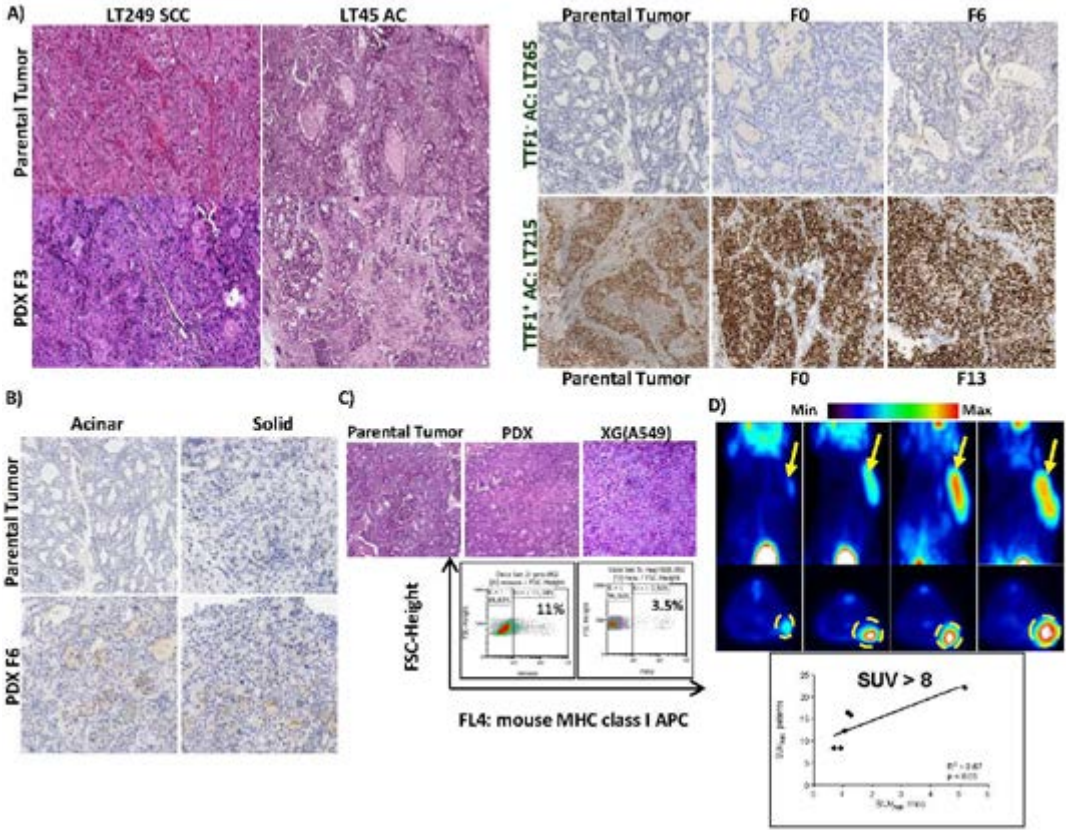
PDX at Tumor Genomics Unit (Gabriella Sozzi and Massimo Moro)

We have recently developed in vivo lung cancer PDX models by directly implanting fragments of the patient's primary tumor in the flank of immunocompromised mice. We have so far successfully grafted 39 non-small cell lung cancer PDXs (25 ADC, 8 SCC), among which 9 PDXs were obtained from LDCT screen-detected (MILD and bioMILD studies) patients. Additional PDXs are being continuously established. Characterization of these mouse models confirmed that they closely recapitulate the parental primary tumors in terms of tumor histology and expression of specific markers for several passages in mice (Figure A). Interestingly, the prevalent histological pattern (i.e. acinary or papillary for AC) was generally maintained (Figure B), although a progressive drift towards a solid pattern for some models was noticed. Moreover, the percentage of stroma and necrosis within PDXs reflected the characteristics of the primary tumor, in contrast to classical xenografts, obtained from cell line injection, which developed subcutaneous tumors with very low stromal content (Figure C). Of note, the parental tumor's stromal cells are gradually substituted by murine cells. In order to use these models for testing novel treatments, we set up metabolic imaging in vivo of PDXs using weekly [18F]FDG-PET and performing coronal and 3D-reconstruction at different days. We noted good correlation of metabolic activity between patient's tumors and PDXs thus supporting the use of these "human in mouse" models for functional studies (Figure D).

The percentage of stroma and necrosis within PDXs reflected the characteristics of the primary tumor, in contrast to classical xenografts

Moreover, PDXs are similar to a patient's tumor also in terms of the content of Cancer Initiating Cells (CICs); this feature allowed us to study the in vivo ability of all-trans retinoic acid (ATRA) to force the CICs fraction to differentiate to a more CDDP susceptible phenotype.

Our Unit is also actively involved in a collaborative project on pediatric rabdomyosarcoma with the team of Andrea Ferrari (Pediatric Unit). This project aims to investigate genetic alterations in druggable genes, such as ALK, MET, and others, to identify novel target treatments for this incurable disease. Within this collaboration, we have started to develop PDXs from



pediatric rhabdomyosarcoma patients and have successfully grafted 1 PDX derived from a child harboring a fusion positive, ALK positive alveolar rhabdomyosarcoma.

FIGURE

Characterization of PDX from lung cancer.

Tumor derived PDX closely recapitulate the parental primary tumor in terms of histology (A), morphology (B), stroma content (C), metabolic activity (D).

PDX at Molecular Pharmacology Unit (Nadia Zaffaroni)

Thanks to strict collaboration with surgeons and pathologists, we generated a small panel of patient-derived xenografts (PDXs) in SCID mice through the direct implant of surgical specimens obtained from patients carrying rare diseases, including Diffuse Malignant Peritoneal Mesothelioma (DMPM) and solitary fibrous tumor (SFT), for which preclinical models are currently unavailable. Since PDXs retain the molecular, genetic, and histologic heterogeneity of their donor tumors, they represent enhanced preclinical models compared to established cell line-derived xenografts, and provide information on tumor biology useful for identifying novel therapeutic targets and mechanisms of resistance suitable for specific inhibition with pharmacological and/or genetic tools. Such findings appear of utmost importance for several tumor types, such as DMPM and SFT, for which limited therapeutic options are clinically available. To date, 4 orthotopic DMPM PDXs, which properly recapitulate the dissemination pattern in the peritoneal cavity of human DMPM and the occurrence of ascites, and 1 s.c. dedifferentiated-SFT PDX have been successfully grafted. Additional PDXs are currently being established. DMPM PDXs have already been used to preclinically develop novel CDK1, Hsp90, and XPO-1/CRM1 inhibitors, and are currently employed to validate selected miRNAs shown to be deregulated in clinical DMPM as novel therapeutic targets through the use of miRNA mimics and LNA-based inhibitors. The SFT PDX has been used to comparatively assess the activity of different available antiangiogenic compounds, indicating regorafenib as the best drug for the disease, and to develop novel drug combinations of conventional and targeted agents.

CLINICAL CANCER REGISTRY

PROGRAM/PROJECT MEMBERSHIP
M. SANT (COORDINATOR) AND P. BAILI

Clinical registries are available in many oncological Institutes and are mainly aimed to facilitate clinical and translational research, although they can also be useful for patient management and follow-up.

The utility of cancer registration encompasses several research fields, e.g. clinical validation of potentially prognostic biomarkers; estimate of number of cases needed for clinical studies; monitoring clinical procedures and adhesion to guidelines; comparative studies between clinical and population sets of patients; studies on cancer prognosis and survivorship.
A large amount of information is produced in daily clinical activity, yet researchers or clinicians do not have straightforward access to it and the data format is not always suitable for statistical analyses. Tumour morphology, for instance, is not always coded according to international classifications such as the International Classification of Disease for Oncology (ICDO).
For this reason, it is often necessary to inspect many clinical notes to identify patients with specific characteristics who are eligible for a given study, with a considerable utilization of personnel time and resources. Furthermore, the scattered availability of data in non-homogeneous formats leads to the creation of many ad-hoc datasets, with duplication of efforts and limited comparability of results.
Disease-specific INT-based registries would allow researchers and clinicians to identify and access specific cases of their interest, providing a set of pre-defined anagraphic and clinical-biological variables (i.e., disease-specific "core information") to which further information for specific studies can be added. The linkage between clinical registry and institutional bio-repositories facilitates clinical translational research, observational studies, and generation of novel study hypotheses.

The Breast Cancer Clinical Registry (B-CCR) at INT. The feasibility of systematic cancer registration has been demonstrated with the creation of the institutional clinical registry for breast cancer (B-CCR) in place since 1st October 2011. The B-CCR systematically collects clinical, pathological, and biomolecular data of all cases operated at the INT Breast Surgery Unit. To date, the B-CCR contains data on about 4,000 patients for whom we plan to start registering follow-up information in 2016. The registry is updated weekly with clinical data of patients undergoing surgery the previous week, and with bio-molecular data from pathological reports.
The B-CCR is accessible through a web-based interface which guarantees direct control on data during insertion and allows performing systematic control of the quality of data, e.g., on completeness and internal consistency of variables. The available variables are listed in Table 1.
The B-CCR is connected with the INT blood bank, which contains samples donated by breast cancer patients at their first hospital admission; the registry is also linked to the INT blood exam database which contains the results from blood exams performed in the pre-admission phase, before surgery.

To date, B-CCR data are in use for two studies: *i*) "Time trends in SLND use and axilla management among breast cancer patients: persisting major variation in clinical practice across European centers" and *ii*) "Association between dysmetabolic and inflammatory conditions and breast cancer subtypes".

Variable domain	Input databases	Notes
Identification codes		
Clinical record number	Included in all database	Linking key
Patient identification for the B-CCR	• Breast Surgery Unit • SDO (through diagnosis field)	-
Personal data		
Sex, age, address	SDO and clinical records	-
Contact data	SDO and other INT databases	Data will be available when a specific study on active follow-up will start
Confidentiality		
Informal consensus data	Clinical records	Data collection is manual
Tumor characteristics		
Laterality	Extracted from AP and ROL	Linking key in order to assign surgery to the correct breast
Incidence date	Medical history in clinical records and ROL	Data collection is manual
Disease phase[a]		
Other cancers[b]		
Stage cT, cN and M	Clinical records	Data collection is manual
Morphology	AP diagnosis field	Text mining
Stage (y)pT and pN[c]		
Subtype[d]		
All Treatments performed at INT		
Surgery: date, type, axillary dissection, sentinel lymph node	ROL treatment field	Text mining
Neoadjuvant chemio and target therapy: date, type, duration	Clinical records	
Other Treatments performed at INT (only in follow-up data collection)		
Adjuvant chemotherapy and targeted therapy: date, type, duration	Clinical records	
Radiotherapy, hormonal treatment: date, type, duration	Clinical records	Data collection is manual
Follow-up		
Follow-up	• Clinical records • New AP, ROL, SDO records of patients already included in B-CCR	Data collection is mainly manual
Metabolic variables		
Height, weight, waist circumference, blood pressure, glycaemia, insulin, cholesterol, C-reactive protein, triglycerides	Blood exams database Clinical records	Other blood exams performed routinely at INT are available
Blood bio-bank		
Data of B-CCR cases are also connected with the INT blood bio-bank and with the blood exam database		

TABLE 1

List of variables collected in the B-CCR (Breast clinical cancer registry at INT)

AP Pathological reports; SDO: Hospital Discharge Records; ROL: Discharge letter for the patient

a Phase of the disease in which the patient was at the moment of the his/her inclusion in the B-CCR

b Including previous, synchronous and metachronous breast cancers

c Measured through size, number of metastatic lymph nodes, number of lymph nodes examined, presence of isolated tumor cells, presence of nodal micrometastases, presence of sentinel lymph node and its outcome

d Measured through estrogen and progesterone receptors, Fer-2, FISH, Ki-67

The INT Clinical Registry. The Institutional Clinical Registry at INT (ICR) will be based on the consolidated experience of the B-CCR and aims to extend registration to additional neoplasms. During the first year, the neoplasms to be considered for registration will be identified in agreement with all relevant clinicians.

The data collection and storage procedures that proved effective for the B-CCR will be adopted for the registration of additional neoplasms, and any necessary changes to these procedures will be applied where relevant. The following steps will be taken for the implementation of the ICR:

a) available clinical and administrative databases to be exploited to the maximum extent in the construction of the registry
b) open source software should be used in the implementation phase
c) a web-based interface guarantees access to all INT specialists interested in using the ICR data (under appropriate regulation)
d) the ICR must be an open system, able to be connected with other INT data repositories
e) the ICR should be compatible with population-based CR data in order to ease a future link.

The basic information necessary to construct the clinical registry at INT will be extracted from the institutional administrative databases which are centralized by the Communications Technology Unit (ICT) and periodically delivered to the CCR team listed below.

- **Database of the Pathology Department**, containing all histological examinations carried out at INT. Diagnoses are mostly reported in a narrative form (international classification codes, useful for statistical analyses on the data, are not largely present). For this reason, in a first phase (and for large morphology grouping, only) text mining algorithms should be developed for automated coding, allowing us to analyze tumor morphology.
  In the future, it is desired that Pathology Department Units will adopt the systematic coding of morphological diagnoses following international classifications. The feasibility of the systematic ICDO coding will be explored during the second year of the present project and will be coordinated with the Unit directors of the Pathology Department.
- **Hospital admission records (SDO)**, which contain all main therapeutic and diagnostic procedures carried out during hospitalization.
- **Pharmaceutical records (File F)**, containing the information on drugs administered to patients during hospitalization or as outpatients.
- **ROL** (Oncology Network of Lombardy Region): in some INT clinical Units, the hospital discharge letter is prepared using the ROL predefined template, which allows recording all information in a database. Text mining algorithms will be developed to extract relevant clinical information.
- **OECI form**: in 2015, INT clinical Units will start collection of all coded data (i.e. disease, presence of previous tumors, type of treatment, disease phase, etc.) for each discharge letter.

A specific scheme of connections between input databases will be designed to define the necessary SQL (Structured Query Language) linking algorithms. The data flow and connection can be briefly described as follows: the list of INT cases should be provided by the INT Units or by ICT through the SDO files. ICT will also periodically provide the files deriving from the AP, ROL, and FILE F. The key for linking all these input databases is the clinical record number, which is assigned to each patient when they first access the INT. The disease phase (i.e. diagnosis, post- or pre-surgical adjuvant treatment, recurrences, etc.), to which the available data refer will be established using the dates of each specific procedure and their temporal sequence.

The integration of automated data collection with manual collection of clinical data through examination of the patient's clinical records or EPR is envisaged at least during the feasibility and kick-off phases of the registration of each new neoplasm considered suitable for registration.

Dedicated personnel at AEHI Unit will be in charge of this task, prior to agreement with directors of the relevant units.

Regulation for data access and ethical issues. In principle, a Steering Committee (SC) will be established, including the directors of the Units providing data to the registry, or their representatives, the clinical registry scientific and technical director, and representatives of AEHI Unit analysts who will carry our main statistical analyses.

Study protocols envisaging the use of ICR data will be submitted to the INT Ethical Committee and will follow the usual procedure for approval.

During the first year of activity, the SC composition and its tasks, as well as the main study regulations will be defined. Regulations for possible data access or release will also be defined, as well as SOP for accessing or obtaining data from the samples stored in the INT biological bank and linked to the clinical registry.

TABLE 2

Plan of activities for the first 3 years of the Institutional Clinical Registry (ICR) program.

YEAR		
1	2	3
• Establish the Steering Committee composition and rules for data release/ analyses; • Agreement on modalities for connections with bio-banks	Planning, discussion, and agreement on systematic coding of Pathology Department diagnoses, according to ICDO	
• Finalize the draft article on association between metabolic variables and breast cancer subtype; • Plan new studies on breast cancer and develop the relevant study protocol;	Start analyses of new studies as envisaged by the study protocol	Finalize analyses of new studies on breast cancer and preparation of manuscript
	Start follow-up of breast cancer patients diagnosed in 2011—2012	Start analyses on disease free survival of BC patients diagnosed in 2011—2012
Meetings with directors of INT clinical Units to individuate cancers suitable for registration, e.g. cancer a)	• Develop and test procedures for registration and data analyses of the additional tumor a); • start registration of tumor a); • discuss study protocol based on tumor a data	Start analyses on data available for tumor a), as envisaged by the study protocol
	Meetings with directors of clinical units to individuate additional cancers suitable for registration, e.g. cancer b)	• Develop and test procedures for registration of tumor b); • start registration of tumor b)

MULTIDISCIPLINARY PROGRAMS

THE MULTIDISCIPLINARY APPROACH FOR HEAD AND NECK CANCER

PROGRAM/PROJECT MEMBERSHIP

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PARTICIPATING UNITS

RADIOTHERAPY 2
MEDICAL ONCOLOGY HEAD AND NECK
OTOLARYNGOLOGY/HEAD AND NECK SURGERY
SUPPORTIVE CARE
PALLIATIVE, PAIN AND REHABILITATION THERAPY

Overview

Multidisciplinarity is the basis of a modern therapeutic approach in Oncology; the simultaneous interaction of various medical specialties is very essential in order to provide the most appropriate care to cancer patients and is emerging as the best strategy to allow a comprehensive evaluation of cancer patients. In the last few years, several studies showed the positive impact of this overall evaluation on many diseases, thus ensuring even better treatment outcomes and improving patients' satisfaction.
In Head and Neck Cancer, this approach is even more important given the many therapeutic options that modern oncology can offer in a very heterogenous cancer patient population. This complex scenario strongly suggests a full and prolonged interaction of many disciplines.

Objectives

- To offer the most appropriate evidence based care to Head and Neck Cancer patients
- To optimize the management of Head and Neck Cancer patients
- To contribute to scientific production
- To perform educational activities
- To contribute to the definition of Regional, Italian and European guidelines of Head and Neck Cancer management

Activities

The Head and Neck Cancer Unit of Fondazione IRCCS Istituto Nazionale dei Tumori performs its multidisciplinary activities through biweekly first visits and follow-up outpatient clinics. During these visits a surgeon, a radiotherapist and a medical oncologist see the patient together.
Since 2008, on average, 259 new patients have been seen per year (297 in 2014).
In 2014, 320 multidisciplinary first visits and 962 multidisciplinary follow up visits were performed. Once a week a multidisciplinary meeting for case discussion takes place. Every week a dedicated radiologist joins the meeting. From time to time other INT professional figures (nutritionist, cardiologist, pneumologist, dentist, supportive and palliative Unit, psychologist, social worker, nurse etc) are needed and they are asked to participate at the case discussions. The simultaneous work of all these different figures is needed to optimize and tailor the best evidence-based treatment, to manage the less typical clinical cases and to assess all the specific clinical needs.
The optimization of Head and Neck Cancer management depends on their cooperation within the complex care process. Every patient gets a leading doctor that coordinates all the activities during the diagnostic and therapeutic phase.

In 2014, 320 multidisciplinary first visits and 962 multidisciplinary follow up visits were performed

In December 2014, the Head and Neck Cancer Unit has been awarded by AIOM (Associazione Italiana Oncologia Medica) for a project about the leading doctor's activity. In 2015, this activity will be monitored and objectively measured. This project aims to define the leading doctor's activity and give some practical solutions for the organisation of a multidisciplinary Head and Neck Cancer team.
Due to the relative rarity of the disease, research can only be performed in collaboration with other centers. In this regard, the connection with national (e.g. CNAO) and international Centers resulted in the activation of many clinical studies:
In 2014 the Head and Neck Cancer Unit was involved in 36 clinical trials. One third were activated in 2014 and total of 128 patients were enrolled. The clinical trials concerned:
- Curative treatment (6 trials)
- Recurrent/metastatic disease (7 trials)
- Thyroid cancer (12 trials)
- Non melanoma skin cancer (2 trials)
- Salivary glands cancer (2 trials)
- Quality of life and supportive care (7 trials)

Two on site international and one national educational courses were held in 2014.
Two International Consensus Conferences were organized. Both events were supported by the Italian Association of Medical Oncology (AIOM), Radiation Oncology (AIRO) and Head and Neck Surgery (AIOCC).
In 2014, the scientific production of Head and Neck Cancer Unit resulted in 29 papers published with a total impact factor index of 171,345.

In December 2014, the Head and Neck Cancer Unit has been awarded by AIOM (Associazione Italiana Oncologia Medica) for a project about the leading doctor's activity

The Head and Neck Cancer Unit was involved in 36 clinical trials

Relevant output
The Head and Neck multidisciplinary team's activity optimizes the complex management of Head and Neck Cancer patients. The very experienced involved professionals allow for efficient planning and decisions.
To date, the multidisciplinary work resulted in a high number of patients treated and in a very high number of patients enrolled in studies. This is rather unique due to the relative rare tumor and to complexity of the disease. However, INT investments are at present substantial in terms of dedicated physicians (6 surgeons, 6 medical oncologists, 3 radiation oncologists) and dedicated administrative workers (5).
The Head and Neck Cancer Unit contributes to establish the scientific knowledge in this evolving field.

Keywords
Multidisciplinary approach, head and neck cancer, leading doctor, research

MELANOMA MULTIDISCIPLINARY PROGRAM

PROGRAM/PROJECT MEMBERSHIP

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PARTICIPATING UNITS

MELANOMA AND SARCOMA SURGERY
IMMUNOTHERAPY OF HUMAN TUMORS
IMMUNOBIOLOGY OF HUMAN TUMORS
MEDICAL ONCOLOGY

Overview

The Melanoma Multidisciplinary Program has been active since 2013 by the Melanoma and Sarcoma Surgical Unit in collaboration with specialists of other participating Units, with special emphasis on a multidisciplinary approach to diagnosis and translational and clinical research. The goal is to implement research strategies and promote clinical and experimental studies to offer patients the best choice of therapy and the opportunity to access experimental treatments. The core of this multidisciplinary approach has been organized at a weekly meeting involving surgeons, medical oncologists, experimental oncologists, clinical study coordinators, data managers, and nurses. During the meeting, participants discuss several topics including new and ongoing clinical studies and scientific reports, and also share decisions and paths of care on clinical cases to plan the best therapeutic options for patients, including enrollment in experimental protocols. The constant interaction between experts in surgical, medical, and experimental oncology and the exchange of new experiences allows the development and/or the basis of new research projects to improve the management of the disease.

In 2014, about 40 meetings took place and more than 250 clinical cases were discussed. Throughout 2014 the activities of the participating units at the Melanoma Multidisciplinary Program were as follows:

In 2014, about 40 meetings took place and more than 250 clinical cases were discussed

Melanoma and Sarcoma Surgical Unit (MSSU). The Unit is involved in all aspects of melanoma and sarcoma treatment, i.e. diagnosis, primary and adjuvant therapy, and follow-up. The Unit conducts clinical trials in the field of adjuvant therapy for melanoma and pre-operative therapy for sarcoma. The Unit is the referring center for melanoma and sarcoma guidelines. It is organized in two Units: Surgery of Melanoma (MSU) and Surgery of Sarcoma, providing surgical activity in ordinary inpatient and day hospital regimens; outpatient visits for diagnosis and follow-up are performed in dedicated rooms as is specialist outpatient activity. The MSSU team is involved in the Melanoma Multidisciplinary Program.

Immunotherapy of Human Tumors Unit (IHTU). The Unit focuses its activities on the different interactions occurring between melanoma cells and the immune system, to dissect the pathways involved in tumor progression for identification of novel prognostic biomarkers and therapeutic targets.

Immunobiology of Human Tumors Unit (IBHTU). The research activity of the Unit is focused mainly on projects in the fields of immunology and target therapy of cutaneous melanoma. Most of these studies were carried out in collaboration with several Departments of the INT (Medical Oncology, Surgical Oncology, Pathology, Experimental Oncology, and Molecular Medicine) and with groups at the University of Milan (B. Venerando), University of Catanzaro (E. Carbone), and Regina Elena Institute, Rome (R. Falcioni).

Medical Oncology Unit (MOU). The clinical research activity of the Unit is focused mainly on projects in the fields of immunotherapy and targeted therapy of cutaneous melanoma. Most of these studies were carried out in collaboration with Departments of the INT and with national groups (IMI, Italian Melanoma Intergroup; NIBIT, Italian Network for Tumor BioTherapy).

Objectives

During 2014 in the MSSU the surgical approach of patients with melanomas stage III and IV improved considerably because many analyses confirmed the hypothesis that reduction of tumor burden through surgical resection can limit disease progression by interrupting the metastatic cascade associated with hematogenous seeding of cells to other sites. Moreover, the timing of surgery versus systemic treatment was another important endpoint. The development of new and effective drugs in the systemic treatment of stage IV melanoma patients such as the BRAF inhibitor vemurafenib, the monoclonal antibody ipilimumab, and the monoclonal antibody against programmed death 1 (PD-1) receptor constitutes a new therapeutic strategy combining new drugs with aggressive surgery in selected patients with metastatic melanoma.

During 2014 in the MSSU the surgical approach of patients with melanomas stage III and IV improved considerably

The development of new and effective drugs in the systemic treatment of stage IV melanoma patients constitutes a new therapeutic strategy combining new drugs with aggressive surgery in selected patients with metastatic melanoma

The IHTU developed studies to determine whether quantification of mutated BRAF in cfDNA may represent a predictive and surrogate marker of response for BRAF inhibitors treatment in melanoma patients. Genetic analyses included the study of germ-line genes and gene SNPs associated with melanoma susceptibility, in multiple, familial, and pediatric melanoma cases. Melanocyte senescence and biology of progression is studied in samples from multiple melanoma patients and sporadic controls. Moreover, for the definition of novel immunomodulating strategies to tilt the balance of tumor immunity, we set up a clinical Phase II trial to test whether administration of high dose esomeprazole (HDE) could mediate a direct and/or an immune-mediated antitumor effect in early melanoma patients. The Adesom2 trial, performed in active collaboration with the MSSU, consists in the treatment of stage III patients with HDE (2.5 mg/kg/day) for 5 weeks before surgery (phase A). A comparable group of untreated patients is enrolled as controls.

The main goals of the IBHTU studies were: a) to understand melanoma immune escape mechanisms associated with failure of immune checkpoint blockade therapy; b) to understand the role of cells belonging to the innate immune system in the response to advanced disease; c) to assess preclinical efficacy of combinatorial treatments that may overcome intrinsic resistance of melanoma to target therapy with BRAF inhibitors.

The main goals of the MOU clinical trials were: a) to compare combined targeted therapy (BRAF inhibitor + MEK inhibitor) versus mono-targeted therapy with BRAF inhibitor as first-line treatment of advanced BRAF mutated melanoma in terms of progression-free survival and overall survival; b) to compare a new immune checkpoint inhibitor nivolumab (anti-PD-1 mAb) versus chemotherapy in previously untreated metastatic melanoma patients and in patients affected by metastatic melanoma after disease progression following ipilimumab and/or BRAF inhibitor; c) to compare the efficacy of the combination of ipilimumab and fotemustine-based chemotherapy or ipilimumab and nivolumab versus fotemustine alone in terms of overall survival in patients with metastatic melanoma and brain metastases; d) to compare, in terms of overall survival, combined immunotherapy (nivolumab + ipilimumab) versus single therapy with nivolumab or ipilimumab in previously untreated patients with metastatic melanoma.

Activities

During 2014, the MSSU performed clinical and dermatoscopic examination on about 15,000 patients. More than 600 patients were hospitalized and underwent major surgery after a diagnosis of melanoma; these patients were submitted to 330 wide excision and sentinel node biopsies, 218

lymph-node dissections, 30 surgical excisions and skin grafts, 9 distant metastasectomies, 6 isolated limb perfusions, 13 electrochemotherapies, and 12 other various surgeries. About 1500 conventional surgeries and 30 electrochemotherapies were performed in day surgery. The MSSU was one of the clinical Units chosen to participate to the Lombardy Oncology Network (Rete Oncologica Lombarda ROL), a regional oncology network built in Lombardy to improve prevention and care for people with a diagnosis of all kinds of cancer. All patients who underwent surgery in 2014 were included in the ROL. The MSSU houses a perspective computerized database of all melanoma patients who were treated at this Institution from 2000 to date: the database contains more than 7,000 patients and represents one of the largest and more complete melanoma databases worldwide. The MSU organized a weekly meeting involving surgeons, medical oncologists, pathologists, radiologists, experimental oncologists, clinical study coordinators, data managers, and nurses to discuss clinical cases and plan the best therapeutic options for patients. The MSSU gave specific attention to pediatric melanomas and melanocytic tumors of uncertain malignant potential (MELTUMP) that typically occur in children and adolescents. About 420 pediatric patients were submitted to a clinical and dermatoscopic examination at out pediatric outpatient clinic during 2014 and 12 cases underwent major surgery for histological diagnosis of cutaneous melanoma or MELTUMP. The MSSU also was one of the referral centers in Europe for loco-regional treatments such as isolated limb perfusion (ILP) and electrochemotherapy (ECT) in melanoma patients.

The MSSU houses a perspective computerized database of all melanoma patients who were treated at this Institution from 2000 to date: the database contains more than 7,000 patients and represents one of the largest and more complete melanoma databases worldwide

The working hypothesis developed by the IHTU was that mBRAF plasmatic quantification, possibly reflecting tumor burden, might help to identify patients who are more likely to benefit from treatment, also allowing early detection of treatment failure and resistance onset. In addition, we aim to identify potential mutation profiles associated with treatment outcomes in tumor lesions from long-term responders and from non-responding patients obtained before treatment by the analysis of mutations in selected cancer genes or by whole exome sequencing.

The aim of these studies at the IBHTU is to understand the mechanisms of resistance to therapy with anti-CTLA4 antibody through characterization of pre- and post-therapy neoplastic lesions from several patients by both gene expression profiling and immunohistochemistry. To investigate the role of cells of the innate immune system in advanced disease, we used multiparametric flow cytometry to characterize frequency and phenotype of NK cell subsets in tumor-invaded and matched tumor-free lymph nodes from melanoma patients. To verify efficacy, at the pre-clinical level, of new approaches to combinatorial target therapy in melanoma, we used two different strategies: a) we developed a melanoma classification based on differential expression of genes coding for receptor tyrosine kinases and then assessed the anti-tumor efficacy of the association of BRAF inhibitors and multikinase inhibitors on tumor subsets with intrinsic resistance to BRAF inhibition; b) we developed an extensive drug interaction analysis to check whether the combination of target-specific inhibitors and of a biological molecule (TRAIL), with selective anti-tumor activity, can have synergistic anti-melanoma effects and overcome resistance to each of these agents.

The MOU worked on the possibility to surpass the limits related to the specific patterns of response of BRAF inhibitors and ipilimumab. The limit of mono-targeted-therapy is represented by the short median response duration (6-8 months), whereas ipilimumab requires less time to mount an efficient anti-tumor immune response. Another research topic consists of designing a new therapeutic algorithm for treatment of brain metastases, in the light of the new therapeutic weapons available.

Relevant output

The MMSU took part in a Phase 1 dose-finding study (Philogen) of tumor-targeting human monoclonal antibody-cytokine fusion protein L19TNFa

plus melphalan using isolated inferior limb perfusion (ILP) in patients with in-transit stage III/IV melanoma. ILP with L19-TNF had a favorable safety and promising activity profile at a dose of 650 µg of L19-TNF, supporting the exploration of higher L19-TNF doses and a Phase II trial comparing L19-TNF ILP with standard melphalan-containing ILP. In addition, the MSU was a Coordinating Center of a Phase III randomized double blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection, a two-arm, randomized, double-blind Phase III study. The MSU took also part in a Phase II clinical trial: "Intralesional administration of L19IL2/L19TNF in stage III or stage IVM1a melanoma patients: results of a phase II study". This study was based on the intralesional administration of L19-IL2 and L19-TNF in patients with stage IIIB/C and IVM1a metastatic melanoma who are not candidates for surgery. The preliminary results of the study were presented as a poster and published in the abstracts of the 2014 ASCO Annual Meeting, Chicago 29/05-02/06, 2014 [J Clin Oncol 32:5s, 2014 (suppl; abstr TPS9103)].

Assessing the molecular mechanisms underlying tumor immune escape and resistance to therapy, the IHTU identified a gene-expression profile in positive sentinel node predicting recurrence at 5 years follow-up (Vallacchi et al., Cancer Res 2014). The signature included selected immune-related genes, among which CD30 was confirmed to be significantly up-regulated in patients with recurrence. Studies on the role of CD30 as a potential novel checkpoint that could be inhibited by specific blockade in a clinical setting are presently ongoing. The role of the immune system in the onset of BRAFi resistance was also addressed using a gene-expression profile approach. BRAFi resistant cell lines, as well as melanoma lesions from BRAFi-treated patients, were found to display increased production of CCL2 together with a series of miRNA regulated by CCL2 via HIF-1. The evidence that in vitro inhibition of these pathways restores tumor cell apoptosis and BRAFi efficacy provides a rationale for the development of novel strategies aimed at improving sensitivity to BRAFi through modulation of the immune microenvironment (Vergani et al., manuscript in preparation).

The studies aimed at identifying immune-related prognostic factors for patient selection and therapeutic planning led to the recent identification of the circulating myeloid index score, which is associated with poor prognosis in patients with metastatic melanoma (Huber et al., manuscript in preparation). This immunological score may be of help in integrating commonly utilized clinical algorithms for therapeutic decision making. Parallel investigation of plasma-miRNA profiles allowed the definition of a miRNA signature associated with myeloid altered differentiation that was detected in circulating exosomes and myeloid cells from progressing melanoma patients. The prognostic impact of these miRNA and their potential role as target for immunomodulating strategies are currently under validation.

The relevant output of the IBHTU analysis was characterization of neoplastic lesions from non-responding patients treated with anti-CTLA-4 indicated loss of expression of HLA class I molecules by neoplastic cells, often associated with lack of infiltrating $CD8^+$ T cells (A. Anichini et al; manuscript in preparation). These results point to immune escape mechanisms as a main determinant of resistance to immune checkpoint blockade. We have contributed to the identification of a new subset of highly cytotoxic NK cells that is selectively enriched in tumor-invaded lymph nodes of melanoma patients. These results provide a rationale for future immunotherapeutic approaches that could exploit the anti-tumor functions of this novel NK subpopulation. In the field of target therapy of melanoma, by adopting a classification based on differential expression of receptor tyrosine kinase genes, we identified an $EGFR^+$ $ERBB3^-$ melanoma subset that included tumors with intrinsic resistance to BRAF inhibitors. Combination of a BRAF inhibitor with a multikinase inhibitor in this subset of melanomas exerted synergistic anti-tumor effects overcoming primary resistance to a single

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target-specific drug. In a different study, we found that co-targeting of oncogenic (by MEK or PI3K/mTOR inhibitors) and death receptor pathways (by TRAIL) has strong synergistic activity on most tumors, in a large panel of cell lines, and can overcome intrinsic resistance to target-specific inhibitors used in a clinical setting, as well as to TRAIL. These results provided proof of principle for the association of biological treatment with targeted therapy in melanoma.

The combination of a BRAF inhibitor and MEK inhibitor (dabrafenib + trametinib or vemurafenib + cobimetinib) developed by the MOU has met three main endpoints:

a) Improvement of the global clinical activity (up to more than 60% of response rate)

b) Increase of median duration of response (nearly double)

c) Significant reduction of the incidence of cutaneous squamous cell carcinoma (from more than 20% to less than 5%).

Anti-PD-1 monoclonal antibodies have ben demonstrated to induce faster clinical responses (within weeks) compared to ipilimumab, while maintaining a prolonged duration of response.

MOU and IBHTU collaborate to identify potential biomarkers that are predictive of response and resistance to immune checkpoint inhibitors.

Lastly, at MOU, in 2014 38 patients were treated with pembrolizumab (MSD anti-PD1 monoclonal antibody) and 30 patients with dabrafenib/trametinib according to compassionate use.

Keywords

Multidisciplinary approach, Melanoma, Immunotherapy, Target therapy

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A MULTIDISCIPLINARY APPROACH FOR THYROID PATHOLOGIES AND CANCER

PROGRAM/PROJECT MEMBERSHIP

G. GALMOZZI, E. SEREGNI

PARTICIPATING UNITS

MEDICAL DIRECTORATE
NUCLEAR-MEDICINE
OTOLARYNGOLOGY SURGERY
RADIOLOGY AND DIAGNOSTIC IMAGING
ANATOMIC PATHOLOGY
LABORATORY MEDICINE
EXPERIMENTAL ONCOLOGY AND MOLECULAR MEDICINE: MOLECULAR MECHANISMS;
HEAD AND NECK CANCER MEDICAL ONCOLOGY
PEDIATRIC ONCOLOGY

Overview

Thyroid alterations, i.e. endocrine dysfunctions and nodular pathologies, are frequently diagnosed in clinical practice. The wider use of neck ultrasound and laboratory tests can trigger intensive treatment with the risk of increasing costs and morbidity. Despite the availability of several guidelines for management of thyroid pathologies, different approaches are observed in daily practice. For this reason, in 2005 a multidisciplinary project was started at the INT to harmonize and coordinate the activities of different specialists towards an unique and well established clinical framework.

Since 2005 a multidisciplinary project at the INT harmonize and coordinates the activities of different specialists towards an unique and well established clinical framework

Objectives

The objectives of the project can be summarized as follows:
• Reduce the time interval between diagnosis and treatment for each patient, minimize diagnostic errors, unnecessary or repeated examinations, and the fragmentation of approaches and variability of judgment among clinicians.
• Contribute to increase the level of patient satisfaction and its perception of good clinical practice by reducing overlapping and confounding messages or information.
• Encourage enrollment of selected patients in innovative clinical trials.
• Improve clinical skills among different specialists.
• Improve the efficiency and qualification in institutional organization pathways.

Activities

The multidisciplinary project adopts different tools to achieve the above objectives. Among these:
• Internal guidelines for management of thyroid disease (diagnostic and therapeutic protocols)
• Multidisciplinary clinical for outpatients: in this structure otolaryngologist specialists, endocrinologists, and nuclear medicine physicians operate to define the most appropriate diagnostic work-up and treatment for the individual patient.
• Multidisciplinary board: during these boards different specialists (surgeons, pathologists, radiologists, nuclear medicine physicians, endocrinologists) discuss in a collegial manner all post-surgical patients and all patients to be submitted to thyroid surgery. The outcome of the group discussion is digitally signed and available for further evaluation and consideration. The ultimate goal of this work is to prospectively collect information and to obtain a basis for revisions of guidelines and currently adopted diagnostic and therapeutic protocols.
• Definition of a Diagnostic Therapeutic Care Pathway (PDTA) for patients with thyroid disease.
• Collaboration with extra-institutional thyroid cancer centers.

Relevant output

In the last year more than 1000 clinical visits were performed in the multidisciplinary clinic and many patients underwent thyroid surgery or radiometabolic treatment with radioiodine for thyroid carcinoma. Several studies are now ongoing regarding thyroid cancer, including:

- High activities of radioiodine in patients with advanced and metastatic thyroid cancer according to a tailored dosimetric individual approach
- Peptide receptor radiotherapy (PRRT) in patients with somatostatin-receptor positive thyroid cancer.
- Evaluation of ultrasensitive assays for thyroglobulin evaluation: analytical and clinical performance.
- Clinical significance of anti-thyroglobulin evaluation as a surrogate marker in thyroid cancer: analytical considerations
- Epidemiological and clinical evaluation of patients with a synchronous diagnosis of papillary thyroid carcinoma and medullary thyroid carcinoma
- Incidence, clinical impact, and therapeutic approaches of skeletal metastases in patients with thyroid carcinoma
- Diagnosis, evolution, and clinical management of pediatric thyroid cancer
- Identification of new target molecules in thyroid carcinogenesis

In the last year more than 1000 clinical visits were performed in the multidisciplinary clinic

Keywords

Multidisciplinary approach, thyroid cancer, laboratory tests, guidelines

PROSTATE CANCER PROGRAM

PROGRAM/PROJECT MEMBERSHIP

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SCIENTIFIC DIRECTORATE
DIAGNOSTIC IMAGING AND RADIOTHERAPY
EXPERIMENTAL ONCOLOGY AND MOLECULAR MEDICINE
MEDICAL ONCOLOGY
MEDICAL STATISTICS AND BIOMETRY
PALLIATIVE CARE, PAIN THERAPY, AND REHABILITATION
PATHOLOGY AND LABORATORY MEDICINE
PREVENTIVE AND PREDICTIVE MEDICINE
PSYCHOLOGY
SUPPORTIVE CARE IN CANCER
UROLOGIC SURGERY
PEDIATRIC ONCOLOGY

Overview and scientific goals

The Prostate Cancer (PC) Program is a translational multidisciplinary (MD) and multiprofessional (MP) program that started in September 2004. Endorsed by the Scientific Director, the PC Program has a decade long tradition of MD and MP approaches to the disease and expertise in epidemiology, experimental oncology, molecular pharmacology, pathology, imaging, urologic surgery, radiotherapy, medical oncology, palliative care, and psychology. The goals of the PC Program are: i) to outline and implement research strategies for the malignancy, including the study of mechanisms of PC development and progression as well as the identification/validation of novel therapeutic targets; ii) to promote clinical and experimental studies, also in collaboration with national and international partners; iii) to manage PC patients within a MD and MP team of specialists; iv) to run MD clinical activities; v) to organize educational activities (i.e. Grand Rounds, Multidisciplinary Team Meetings, conferences for clinicians, general practitioners, patients); and vi) to optimize the human and technological resources within a disease-focused MD and MP framework.

More than 20 research projects are currently on-going.

The rationale at the basis of the PC clinical program is that, depending on the state of disease, there are several therapeutic options and, for selected patients, observational strategies, namely active surveillance (AS) and watchful waiting. Radical therapies, namely surgery, radiotherapy, and brachytherapy, show no clear differences in cancer control rates in the same stage, but can induce adverse effects and negatively impact the patients' quality of life. On these assumptions, patients should receive objective, comprehensive information about the disease, therapeutic and observational strategies, and therapy-induced side effects. At the same time, patients and their significant others should be accompanied in the decision-making process, which might be a particularly difficult phase. To address the complexity of the disease, the PC Program has managed PC patients multidisciplinarily and multiprofessionally since its beginning.

Depending on the state of disease, there are several therapeutic options and, for selected patients, observational strategies, namely active surveillance and watchful waiting

In 2009, the MD and MP organizational model was formalized under the name of Prostate Cancer Unit (PCU) with the aim of identifying the personnel involved in PC research and care. Considering the feedback of voluntary evaluation of organizational model and activities, in 2013 the PCU document was updated. The latest release designated the MD activities, identified the core and non-core personnel involved in the care of PC patients, quantified contractual time for the MD activities, and included workflows to describe the paths of care and the interaction among services.

The MD clinical activities run by the PCU include the following:

• weekly first consultations for newly referred PC patients (345 MD visits in 2014) with the concurrent participation of an urologist, radiation

oncologist, and psychologist; a medical oncologist is on call for patients with locally advanced, hormone-refractory and metastatic PC; supportive care, rehabilitation, and specialist palliative care interventions are available on demand; PC patients are offered psychological support (decision-making support, counseling for individuals, couples, families, and self-help groups);

• biweekly follow-up visits for patients on AS and watchful waiting (617 visits in 2014): an urologist or radiation oncologist meets patients continuing in the observation in a monodisciplinary setting; a psychologist is on demand; a urologist, radiation oncologist, and psychologist in a MD setting meet patients whose observational setting is discontinued and who are addressed to treatment;

• weekly Multidisciplinary Team Meetings, a CME activity aimed to share decisions and paths of care on PC patients, tailor therapeutic and observational strategies, manage PC patients holistically and consider quality of life and psychological issues, enroll patients in trials, and verify adherence to guidelines and quality assurance. In 2014, 417 cases were discussed.

Weekly Multidisciplinary Team Meetings. In 2014, 417 cases were discussed

The PC Program is acknowledged worldwide to have important expertise in managing AS protocols. This observational option is being offered to patients with low and very low risk PC as an alternative to radical treatment since March 2005. The PC Program has 2 protocols open for enrollment and is the 15th top recruiting center in the PRIAS (Prostate cancer Research International: Active Surveillance) consortium with 412 patients in December 2014 and coordinates the 8 Italian institutions participating in PRIAS under the name of SIUrO PRIAS ITA. Significant attention is paid to the quality of life of patients on AS, which is the focus of a research project run by the PC Program dedicated psychologists. Considering the acknowledgements of expertise in the area, the PC Program chief psychologist is chair of an international Task Force on Quality of Life in AS promoted and supported by the European School of Oncology.

The PC Program has 2 protocols open for enrollment and is the 15th top recruiting center in the PRIAS consortium with 412 patients in December 2014 and coordinates the 8 Italian institutions participating in PRIAS under the name of SIUrO PRIAS ITA

The PC Program is the only Italian center invited to participate in the Global PC AS Initiative funded by Movember Foundation, aimed to unite the world's leading research and clinical groups focusing on AS to develop a new therapeutic guidelines for men diagnosed with low risk PC by integrating clinical, imaging, and biomarker data in the global central database GAP3.

Aware of the importance of translational research, the PC Program activated a biobank in 2005 and collects blood, urine, and tissue samples from different categories of PC patients, in order to have biological material for translational research.

Aware of the importance of translational research, the PC Program activated a biobank in 2005

Highlights

Research is focused on multiple areas, such as the interpretation of survival differences over time in Italy, development of novel therapeutic approaches based on the inhibition of relevant targets/pathways in preclinical PC models, identification of epithelial and stromal microRNAs regulating PC progression and metastasis and long non-coding RNAs governing prostate epithelial biology and tumor development, dissection of the role of mast cells and extracellular matrix proteins in prostate carcinogenesis, molecular characterization of indolent PC, quality of life of patients on AS, toxicity and quality of life in patients treated with radiotherapy, new drugs and drug combinations for locally advanced and metastatic PC, and new radiotherapy fractionation schemes.

A urgent need is related to the improvement of selection criteria for AS, which are currently suboptimal and rely exclusively on clinical and pathological parameters, by testing novel biological markers. In this context, we are currently evaluating microRNA profiles in plasma from patients on AS with the aim to correlate them with patient outcomes and assess whether specific microRNAs can predict disease behavior better and/or earlier compared to conventional markers. Upon confirmation of the

results in an independent patient cohort, the final aim of this study will be integration of selected microRNAs in an updated and improved model for prediction of indolent PC.
More in general, current understanding of low and very low risk, potentially indolent tumors is very limited due to a number of technical hurdles related to the analysis of these cancers. Because of the very favorable prognosis, an issue of debate is the possibility that these tumors could be regarded as non-malignant. In this regard, it can be hypothesized that molecular alterations characteristic of indolent PC may be different from those previously detected in clinically significant tumors. We are currently using whole exome sequencing technology to detect somatic DNA alterations in positive core biopsies from a subset of 60 AS patients with the aim to: i) compare genomic alterations with those characteristic of clinically significant PC; ii) shed light on the nature of such tumors; iii) identify specific DNA alterations associated with disease reclassification/ progression during AS. In addition, we have planned to investigate whether specific somatic DNA alterations associated with disease reclassification/ progression are represented in circulating cell free-DNA in order to develop non-invasive approaches for disease monitoring during AS.
The development of a non-invasive method to diagnose PC is long overdue. On this basis, we started collaborative research with the Bruno Kessler Foundation and the University of Trento that aims to measure volatile compounds in urine samples and identify and distinguish emission spectra in urine from PC patients and healthy specimens. If preliminary evaluation is positive, the substances contained in urine from PC patients will be more specifically identified in a larger group to implement the technique and produce low cost and non-invasive diagnostic kits.
Since 2008 the PC Program has promoted research in the field of predictive modeling of clinically significant endpoints. After starting with the prediction of gastrointestinal acute and late toxicity after radical radiotherapy for PC, the methodology developed was recently applied to predictive modeling of poor quality of life for men on AS. In 2014, the PC Program started its participation in the multicenter international project (funded by the European Union's Seventh Framework Programme) "REQUITE - Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality of Life in Cancer Survivors", which is aimed to validate known predictors of adverse reactions after radiotherapy for PC, breast and lung cancer, and to develop the statistical models that are clinically useful. This multi-center observational study will collect blood samples and standardized data longitudinally from 5,300 cancer patients. It is expected that 350 patients will be enrolled at our Institute, and 112 patients were included in 2014.

Keywords
Translational research, multidisciplinary approach, experimental therapeutics

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MULTIDISCIPLINARY RESEARCH IN THORACIC ONCOLOGY

PROGRAM/PROJECT MEMBERSHIP

U. PASTORINO

PARTICIPATING UNITS

THORACIC SURGERY
MEDICAL ONCOLOGY
RADIOTHERAPY
PNEUMOLOGY
ENDOSCOPY, RADIOLOGY
ANATOMIC PATHOLOGY
NUCLEAR MEDICINE

A multidisciplinary approach in Thoracic Oncology has been demonstrated to be one of the most important parameters of quality of care in patient management. Correct diagnosis, interaction, and definition of a therapeutic plan are key elements for an effective and efficient approach to every patient, from the simplest to the most complex.

To achieve this goal, a multidisciplinary group of specialists with specific experience in thoracic pathologies has been instituted that meets weekly to discuss clinical cases. The group includes specialists in thoracic surgery, medical oncology, radiotherapy, pneumology, endoscopy, radiology, anatomic pathology, and nuclear medicine.

The results of this activity have been progressive standardization of the diagnostic-therapeutic approach in complex cases, implementation of a working team, and training of medical personnel.

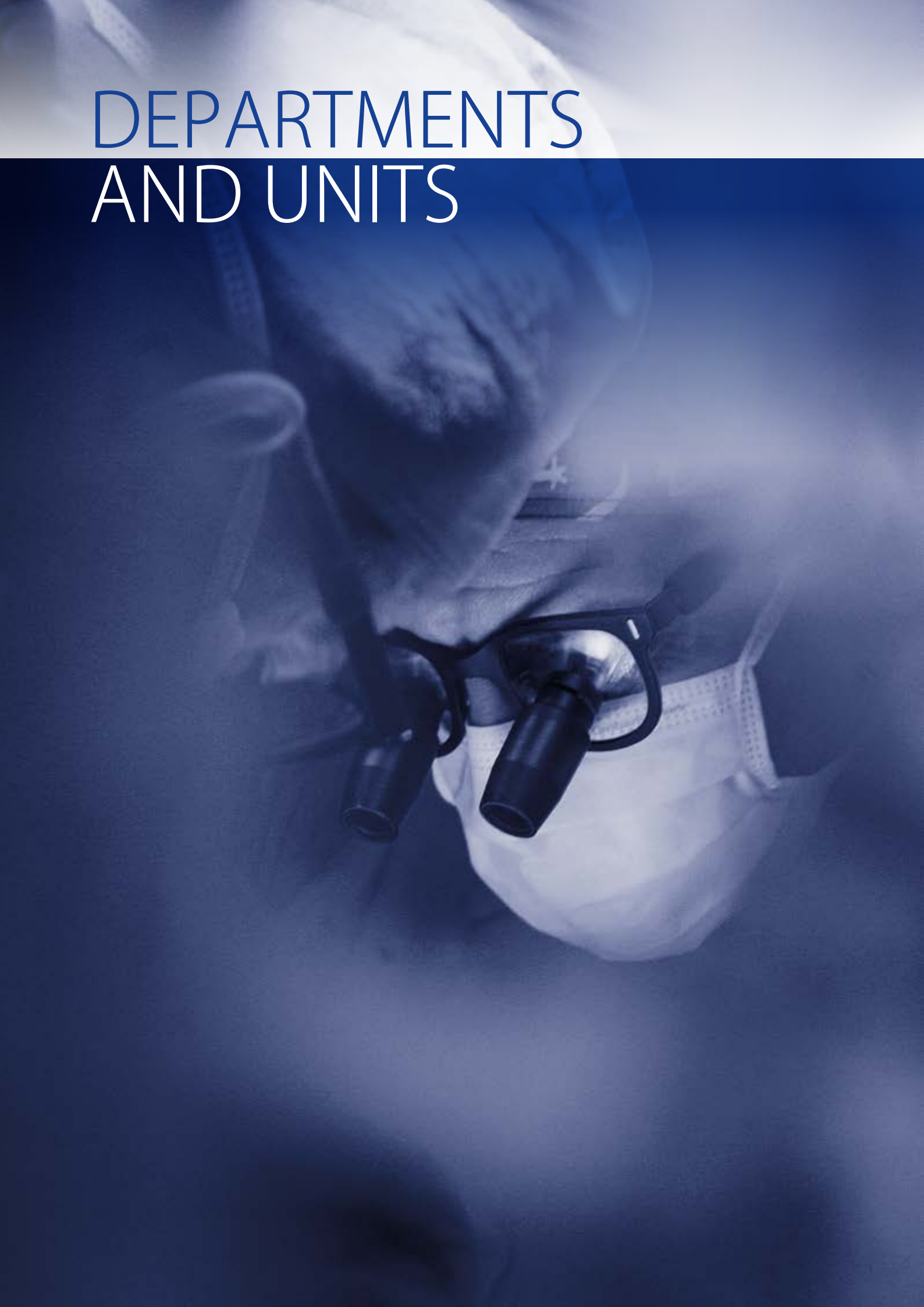
The multidisciplinary staff meets at the Thoracic Surgery Unit (block F, 6th floor) every Monday from 13:30 to 15:30. The meeting is open to all physicians of the INT as well as to external physicians who need consultation (by communicating this to the secretary).

This multidisciplinary program became active in October 2011. Since that time, over 1,000 clinical cases have been discussed. In 2012, the meeting received accreditation by the regional healthcare system for continuing education, with 50 credits per year, for the training offered.

This multidisciplinary program became active in October 2011. Since that time, over 1,000 clinical cases have been discussed

Keywords
Multidisciplinary approach, Quality of care, Training of medical personnel

DEPARTMENTS AND UNITS



SURGERY

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GASTROINTESTINAL, HEPATO PANCREATOBILIARY SURGERY, AND LIVER TRANSPLANTATION
VINCENZO MAZZAFERRO

COLORECTAL SURGERY
ERMANNO LEO

BREAST SURGERY
ROBERTO AGRESTI *(Until October 2014)*
MARCO GRECO *(From November 2014)*

MELANOMA AND SARCOMA
MARIO SANTINAMI

DIAGNOSTIC ENDOSCOPY AND ENDOSCOPIC SURGERY
ROBERTO SALVIONI *(Interim until September 2014)*
ENZO MASCI *(From October 2014)*

OTOLARYNGOLOGY SURGERY
GABRIELE SCARAMELLINI *(Until October 2014)*
VINCENZO MAZZAFERRO *(Interim from November 2014)*

GYNECOLOGIC ONCOLOGY
FRANCESCO RASPAGLIESI

THORACIC SURGERY
UGO PASTORINO

PLASTIC AND RECONSTRUCTIVE SURGERY
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MARCO GRECO *(Interim from November 2014)*

UROLOGIC SURGERY
ROBERTO SALVIONI

PEDIATRIC SURGERY
LUIGI PIVA

LASER THERAPY
ANNA COLOMBETTI

DAY SURGERY
ALDO BONO

The **Department of Surgery** is composed of 10 surgical divisions and 3 departmental units, organized for homogeneity of performance, with 240 inpatient beds and 14 outpatient beds. The Department treats oncological diseases that affect all areas of the body except for the brain, providing elective and emergency surgical activity, in ordinary inpatient and day hospital regimens, and specialistic oupatient activity for diagnosis and follow-up. Routine clinical activity ensures a high standard of care for all surgically-treated patients, providing conservative surgery (organ/function preserving or minimally invasive) for early stage disease and combined treatment modalities for advanced disease.

GASTROINTESTINAL, HEPATOPANCREATOBILIARY SURGERY, AND LIVER TRANSPLANTATION

The focus of the Gastrointestinal, Hepato-Pancreatobiliary Surgery and Liver Transplantation Unit is on treatment and research on tumors of the hepato-bilio-pancreatic tract, specializing in complex interventions including liver transplantation. This Unit, which was restructured about 10 years ago, provides treatment to patients from both Italy and abroad with tumors of the liver, pancreas, stomach, and upper gastrointestinal tract. Within the Unit a liver transplantation program is active which is known worldwide. This group was formed in the 1990s and established guidelines for selecting patients who are candidates for transplantation (known as the Milan Criteria). The Unit is operational 24 hours per day and is equipped with instrumentation for semi-intensive hospitalization, and about 800 patients are hospitalized each year with thousands of ambulatory visits. Over 850 surgical interventions per year are carried out in the hepato-bilio-pancreatic tract, and of these around 300 for primary or secondary liver tumors. To date, almost 600 liver transplantations have been performed in patients with tumors (mainly hepatocarcinoma, but also metastases from neuroendocrine tumors, hemangioendotheliomas, and other rare tumors) with a survival rate of 80% at five years after intervention. Over 600 surgical interventions have been performed for hepatic metastases from colorectal tumors as part of an innovative and coordinated protocol. Substantial focus is given to tumors of the stomach, pancreas, and bile ducts from both clinical and research standpoints. The Unit is a national referral center for study and treatment of patients with gastroenteric neuroendocrine tumors for which a wide range of therapies are used within a multidisciplinary context that was recently certified by the ENET. For transplant activities, the Unit refers to an interregional center that coordinates allocation of donor organs in Northern Italy. Clinical care is integrated with clinical research activities that have produced many scientific publications of international relevance, with continuous updates of the latest advances in treatment strategies. The most relevant clinical research projects concern:

- liver transplantation in oncology;
- integrated medical and surgical strategies for hepatic metastases;
- new molecular targets and integrated support strategies for patients with tumors of the pancreas and bile duct;
- new types of video-assisted interventions for pathologies of the stomach and upper digestive tract;
- development of supporting systems to improve the quality of life in patients with organ transplants and analysis of the risk-benefit ratio in patients with gastroenteric tumors.

HEAD

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6
PUBLICATIONS
AS FIRST/LAST AUTHOR

49.099
I.F. AS FIRST/LAST AUTHOR

50
H-INDEX HEAD OF UNIT

COLORECTAL SURGERY

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Ermanno Leo, MD

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The Colorectal Cancer Unit is a recognized European referral center. The case load of colorectal surgeries is about 600 per year. The Unit devotes special attention to tumors of the distal rectum and established very high standards of care for management of this subset of patients. Conservative, function preserving surgical techniques to avoid extensive resection and definitive colostomy have been perfected. During the last year, about 200 rectal resections were performed, and among these in 50% of cases a sphincter preserving procedure was exploited.
A further area of expertise is the treatment of complex local recurrences of rectal cancer and colo-rectal melanoma. Thanks to a muldisciplinary effort, we offer technically demanding surgeries to patients affected by extensive recurrent disease. Since the second half of 2012, the Peritoneal Surface Malignancies (PSM) program, active at INT since 1995, was attached to the Colorectal Surgery Unit. This program is responsible for the treatment of pseudomyxoma peritonei, peritoneal mesothelioma, and peritoneal carcinomatosis from colorectal cancers. Thanks to a vast experience of more than 600 procedures of cytoreduction associated with hyperthermic intraperitoneal chemotherapy, the program has achieved the highest standard in the management of peritoneal surface oncology and has become an important international reference center for this procedure.
The PSM program carried out several prospective multidisciplinary studies in collaboration with clinical and pre-clinical departments. Topics of interest are translational research in peritoneal mesothelioma, and translational research in pseudomyxoma peritonei [funded by National Organization for Rare Disorders (NORD) – 2011]. Furthermore, prospective randomized multicenter trials on patients with peritoneal carcinomatosis from colorectal cancer were planned.

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5
PUBLICATIONS
AS FIRST/LAST AUTHOR

41.186
I.F. AS FIRST/LAST AUTHOR

20
H-INDEX HEAD OF UNIT

BREAST SURGERY

HEAD

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The clinical activity of the Unit includes all aspects of breast cancer treatment: diagnosis, primary and adjuvant therapy, and follow-up. Treatment is performed by multidisciplinary teams involving other Units and Departments.

More in detail, 11,000 patients accessed to the out-patients services, ranging from the out-patients first examination to the pre-operative counseling to therapeutic planning, or the follow-up of operated patients.

In cooperation with the Medical Genetics Unit, an approach tailored for women at high genetic risk has been developed. During genetic counseling, genetic risk is estimated to design a personalized program including available preventive options and treatments.

Almost 1,100 patients underwent main surgery for breast cancer, ranging from breast conservative surgery to mastectomy (ev. NAC- or Skin-sparing) with plastic intervention for breast modeling or reconstruction. More than 350 patients underwent minor surgery for benign and suspicious malignant breast diseases.

In T1N0 breast cancer, the long-standing results from two different randomized clinical trials comparing axillary dissection with observation in patients under and over 65 years of age, respectively, have been published in the 2014.

A further study comparing FDG-PET with sentinel lymph node biopsy for identifying different biological and prognostic breast cancer populations was also published.

Among several joint studies started in the last years with other Units and Departments we completed the evaluation of PET as imaging tool for early prediction of pathologically response in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, as well as the evaluation of NAC-sparing mastectomy after neo-adjuvant chemotherapy, the relationship between breast cancer and metabolic syndrome, the impact of wound healing in triple negative or HER2-positive breast cancer, the breast conservative surgery in elderly patients with or without post-operative radiotherapy, subgroups of breast cancer with peculiar RMN imaging, or the psychologic distress in breast cancer patients.

Furthermore, we actively participate to multicentric clinical randomized trial comparing sentinel node biopsy vs. observation in early breast cancer (SOUND).

Following a recent pilot study at the INT on the feasibility of Selective Axillary Dissection (SAD) which preservs the lymphatic drainage of the arm, we started a randomized clinical trial to assess the prevention of lymphedema adopting selective axillary dissection.

The PREMIO trial on the efficacy of complementary treatment in women suffering from premenopausal induced by medical therapy of breast cancer, is almost completed and evaluation is in progress.

3
PUBLICATIONS
AS FIRST/LAST AUTHOR

10.374
I.F. AS FIRST/LAST AUTHOR

34
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Agresti R., Crippa F., Sandri M., Martelli G., Tagliabue E., Alessi A., Agresti R., Crippa F., Sandri M., Martelli G., Tagliabue E., Alessi A., Pellitteri C., Maccauro M., Maugeri I., Padovano B., Rampa M., Moscaroli A., Ferraris C., Carcangiu M.L., Bianchi G.V., Greco M., Bombardieri E.: Different biological and prognostic breast cancer populations identified by FDG-PET in sentinel node-positive patients: Results and clinical implications after eight-years follow-up. Breast 2014; 23: 334-340 [IF 2.581]

2. Agresti R., Martelli G., Sandri M., Tagliabue E., Carcangiu M.L., Maugeri I., Pellitteri C., Ferraris C., Capri G., Moliterni A., Bianchi G.V., Mariani G., Trecate G., Lozza L., Langer M., Rampa M., Gennaro M., Greco M., Menard S., Pierotti M.A.: Axillary lymph node dissection versus no dissection in patients with T1N0 breast cancer: A randomized clinical trial (INT09/98). Cancer 2014; 120: 885-893 [IF 4.901]

3. Martelli G., Boracchi P., Orenti A., Lozza L., Maugeri I., Vetrella G., Agresti R.: Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-Year results of trial and out-trial patients. Eur J Surg Oncol 2014; 40: 805-812 [IF 2.892]

MELANOMA AND SARCOMA

The Unit is involved in all aspects of melanoma and sarcoma treatment. The Unit conducts clinical trials in the field of adjuvant therapy for melanoma and pre-operative therapy for sarcoma. The Unit is the referring center for melanoma and sarcoma guidelines. It is organized in two Units: Surgery of Melanoma and Surgery of Sarcoma, providing surgical activity, in ordinary inpatient and day hospital regimens.

Surgery of Melanoma

This Unit performed clinical and dermatoscopic examination on about 15,000 patients. More than 600 patients were hospitalized during 2014 and underwent major surgery after diagnosis of melanoma. About 1,500 conventional surgeries and 30 electrochemotherapies were performed in day surgery. Our Unit gives particular attention to pediatric melanomas and melanocytic tumors of uncertain malignant potential (MELTUMP) lesions that typically occur in children and adolescents. Our Unit has built a perspective database of all melanoma patients who were treated at this Institution from 2000 to date: this database contains more than 7,000 patients and represents one of the largest and more complete melanoma database in the world. Several prospective randomized multicenter trials are planned during the next years.

Surgery of Sarcoma

We are reference center for soft tissue sarcomas of the extremities and trunk as well as for retroperitoneal sarcoma, gastrointestinal stromal tumor and desmoid type fibromatosis. In 2014, we carried out 306 major operations for new patients. We saw 1,200 new patients in consultation and performed follow-up visits for 4,000 cases. An institutional database is maintained containing over 7,500 patients affected by sarcoma treated in the last 30 years. International studies are ongoing focused on localized high-risk sarcomas of the extremities and trunk wall, retroperitoneal sarcoma, extra-abdominal sporadic desmoids tumors, sporadic desmoid-type fibromatosis.

HEAD

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Surgery of Melanoma

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Gabriella Nicolò

Surgery of Sarcoma

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Lorella Rusi (Scientific Secretary)

14
PUBLICATIONS
AS FIRST/LAST AUTHOR

72.12
I.F. AS FIRST/LAST AUTHOR

31
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Bauer S., Rutkowski P., Hohenberger P., Miceli R., Fumagalli E., Siedlecki J.A., Nguyen B.P., Kerst M., Fiore M., Nyckowski P., Hoiczyk M., Cats A., Casali P.G., Treckmann J., van Coevorden F., Gronchi A.: Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib - Analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol 2014; 40: 412-419 [IF 2.892]
2. Fiore M., Coppola S., Cannell A.J., Colombo C., Bertagnolli M.M., George S., Le Cesne A., Gladdy R.A., Casali P.G., Swallow C.J., Gronchi A., Bonvalot S., Raut C.P.: Desmoid-type fibromatosis and pregnancy: A multi-institutional analysis of recurrence and obstetric risk. Ann Surg 2014; 259: 973-978 [IF 7.188]
3. Gronchi A., Colombo C., Le Péchoux C., Dei Tos A.P., Le Cesne A., Marrari A., Penel N., Grignani G., Blay J.Y., Casali P.G., Stoeckle E., Gherlinzoni F., Meeus P., Mussi C., Gouin F., Duffaud F., Fiore M., Bonvalot S.: Sporadic desmoid-type fibromatosis: A stepwise approach to a non-metastasising neoplasm-A position paper from the Italian and the French Sarcoma Group. Ann Oncol 2014; 25: 578-583 [IF 6.578]
4. Gronchi A., Colombo C., Raut C.P.: Surgical management of localized soft tissue tumors. Cancer 2014; 120: 2638-2648 [IF 4.901]
5. Gronchi A., De Paoli A., Dani C., Merlo D.F., Quagliuolo V., Grignani G., Bertola G., Navarria P., Sangalli C., Buonadonna A., De Sanctis R., Sanfilippo R., Dei Tos A.P., Stacchiotti S., Giorello L., Fiore M., Bruzzi P., Casali P.G.: Preoperative chemo-radiation therapy for localised retroperitoneal sarcoma: A phase I-II study from the Italian Sarcoma Group. Eur J Cancer 2014; 50: 784-792 [IF 4.819]
6. Martin-Broto J., Gutierrez A.M., Ramos R.F., Lopez-Guerrero J.A., Ferrari S., Stacchiotti S., Picci P., Calabuig S., Collini P., Gambarotti M., Bague S., Dei Tos A.P., Palassini E., Luna P., Cruz J., Cubedo R., Martinez-Trufero J., Poveda A., Casali P.G., Fernandez-Serra A., Lopez-Pousa A., Gronchi A.: MRP1 overexpression determines poor prognosis in prospectively treated patients with localized high-risk soft tissue sarcoma of limbs and trunk wall: an ISG/GEIS study. Mol Cancer Ther 2014; 13: 249-259 [IF 6.107]
7. Maurichi A., Miceli R., Camerini T., Mariani L., Patuzzo R., Ruggeri R., Gallino G., Tolomio E., Tragni G., Valeri B., Anichini A., Mortarini R., Moglia D., Pellacani G., Bassoli S., Longo C., Quaglino P., Pimpinelli N., Borgognoni L., Bergamaschi D., Harwood C., Zoras O., Santinami M.: Prediction of survival in patients with thin melanoma: Results from a multi-institution study. J Clin Oncol 2014; 32: 2479-2485 [IF 17.879]

8. Morosi C., Stacchiotti S., Marchianò A., Bianchi A., Radaelli S., Sanfilippo R., Colombo C., Richardson C., Collini P., Barisella M., Casali P.G., Gronchi A., Fiore M.: Correlation between radiological assessment and histopathological diagnosis in retroperitoneal tumors: Analysis of 291 consecutive patients at a tertiary reference sarcoma center. EJSO-EUR J SURG ONC 2014; 40: 1662-1670 [IF 2.892]

9. Pastorino U., Duranti L., Scanagatta P., Leo F., Piccioni F., Collini P., Gronchi A.: Thoracopleuropneumonectomy with riblike reconstruction for recurrent thoracic sarcomas. Ann Surg Oncol 2014; 21: 1610-1615 [IF 3.943]

10. Patuzzo R., Maurichi A., Camerini T., Gallino G., Ruggeri R., Baffa G., Mattavelli I., Tinti M.C., Crippa F., Moglia D., Tolomio E., Maccauro M., Santinami M.: Accuracy and prognostic value of sentinel lymph node biopsy in head and neck melanomas. J Surg Res 2014; 187: 518-524 [IF 2.121]

11. Radaelli S., Desai A., Hodson J., Colombo C., Roberts K., Gourevitch D., Gronchi A.: Prognostic factors and outcome of spermatic cord sarcoma. Ann Surg Oncol 2014; 21: 3557-3563 [IF 3.943]

12. Radaelli S., Stacchiotti S., Casali P.G., Gronchi A.: Emerging therapies for adult soft tissue sarcoma. Expert Rev Anticancer Ther 2014; 14: 689-704 [IF 2.279]

13. Rossi C.R., Mozzillo N., Maurichi A., Pasquali S., Macripo G., Borgognoni L., Solari N., Piazzalunga D., Mascheroni L., Giudice G., Mocellin S., Patuzzo R., Caraco C., Ribero S., Marone U., Santinami M.: Number of excised lymph nodes as a quality assurance measure for lymphadenectomy in melanoma. JAMA SURG 2014; 149: 700-706 [IF 0]

14. Rossi C.R., Mozzillo N., Maurichi A., Pasquali S., Quaglino P., Borgognoni L., Solari N., Piazzalunga D., Mascheroni L., Giudice G., Mocellin S., Patuzzo R., Caraco C., Ribero S., Marone U., Santinami M.: The number of excised lymph nodes is associated with survival of melanoma patients with lymph node metastasis. Ann Oncol 2014; 25: 240-246 [IF 6.578]

DIAGNOSTIC ENDOSCOPY AND ENDOSCOPIC SURGERY

HEAD

Roberto Salvioni, MD *(Interim until September 2014)*

Enzo Masci, MD *(From October 2014)*

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Miria Faccini, Salvatore Morfeo, Rosanna Loi

The Unit is focused on diagnosis and endoscopic treatment of gastro-entero-pancreatic tumors and palliative treatment of advanced gastrointestinal neoplasia. Our main interest is advanced endoscopic imaging and new endoscopic devices. We are focused on the development of new endoscopic procedures for treatment of early neoplasia and management of surgical complications as well as palliative therapy of advanced gastrointestinal cancer.

In collaboration with the Unit of Hereditary Tumors of the Digestive System, we coordinate the endoscopic surveillance program of patients with hereditary tumors and high-risk subjects. The Unit participates in the program of the Local Health Service (ASL) of Milan for colorectal cancer screening and is involved in the management of upper gastrointestinal cancer. Moreover, our Unit is also part of a team of excellence involved in the diagnosis and treatment of neuroendocrine tumors certified by the European Neuroendocrine Tumor Society.

Endoscopic Ultrasonography (EUS) is one of the most common procedures in our Unit and during 2014 more than 600 EUS procedures, including nearly 200 EUS guided biopsies, were performed for staging and diagnosis of primary and metastatic cancer.

The Unit is interested in identification of circulating molecular biomarkers for early diagnosis of sporadic and familiar colorectal cancer to identify less invasive tests for screening and surveillance. New imaging techniques for endoscopic surveillance in patients with hereditary gastrointestinal cancer are being developed to evaluate the role of endomicroscopy in management of duodenal polyps (and adenoma of the papilla of Vater) in subjects with adenomatous familial polyposis.

In 2015, we will focus on evaluating the role of new endoscopes and extend therapeutic endoscopy to new procedures in which endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography are combined.

OTOLARYNGOLOGY SURGERY

The Otolaryngology Surgery Unit is involved in all types of tumors that affect the oral cavity (lips, tongue, gums, hard palate, cheek mucosa and oral floor), oropharynx (soft palate-uvula, tonsils, tongue base), larynx, hypopharynx (pyriform sinuses), cervical esophagus and adjacent trachea, nose and paranasal sinuses, salivary glands (parotid and submandibular glands), thyroid and parathyroid. The Unit is integrated with the involvement of radiologists, pathologists, radiotherapists, and medical oncologists who are dedicated to the head and neck region. This integration allows the possibility to offer patients multidisciplinary evaluation that permits the most adequate and effective choice of treatment, guaranteeing the best possible quality of life and periodic follow-up, and is aimed at the management of complications, early diagnosis and/or secondary tumors. For pathologies of the head and neck, the Unit has close collaborations with neurosurgeons at C. Besta Institute. The complex reconstructions required during the extensive resections needed for treatment of head and neck tumors are carried out together with plastic surgeons in order to provide the best possible solution in terms of preservation of function and esthetics, including the microsurgical use of revascularized free flaps. The Otolaryngology Surgery Unit also collaborates with specialists in nuclear medicine and endocrinology for diagnosis, treatment planning, and follow-up of thyroid and parathyroid pathologies as part of the Thyroid Project.

HEAD

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HEAD

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Cinzia Marretta, Rosella Zennoni

The Gynecologic Unit is involved in treatment of primary and secondary tumors of the female genital tract. Surgical research is carried out on the following techniques: nerve sparing radical surgery, debulking surgery, mini-invasive surgery, laparoscopic surgery in diagnosis, staging and treatment of early gynecological tumors, sentinel node detection in endometrial cancer. The Unit also carries out research to evaluate the efficacy of chemotherapeutic agents in gynecological cancers as part of national and international clinical trials, and especially in ovarian cancer. Staff is dedicated to clinical practice, research, and teaching (three tumor boards weekly, international meetings, three surgical master courses yearly). All surgical and medical treatments are coordinated on a weekly basis by a multidisciplinary team including surgeons, medical oncologists, pathologists, and radiotherapists. The research activity of the group involves both basic science and clinical studies. To improve the prognosis of early stage cancer, several studies are being conducted on the efficacy and safety of laparoscopic techniques in gynecologic oncology. We extended the concept of mini-invasiveness to laparotomy to reduce the complications of radical hysterectomy.

The clinical activity of Gynecologic Oncology is mainly focused on first entry gynecologic oncology evaluation, familial cancer, abnormal pap and colposcopy, HPV multidisciplinary office, 1st and 2nd level ultrasound, hysteroscopy, follow-up.

Surgical research was conducted on the following techniques:

- Nerve sparing radical surgery
- Debulking surgery
- Mini-invasive surgery
- Laparoscopic surgery in diagnosis, staging and treatment of early gynecological tumors
- Sentinel node detection in endometrial cancer
- Fertility-sparing surgery (cervical, ovarian, and endometrial cancer)
- Surgery in advanced cases and/or recurrences from all origins
- Photodynamic treatment of recurrent Paget's vulvar disease
- Vulvar, vaginal, and uterine melanoma surgical treatment
- Reconstructive surgery (in collaboration with Plastic and Reconstructive Surgery Unit)

We perform about 1,200 procedures each year in ambulatory surgery, and about 500 major surgical procedures are carried out per year.

9
PUBLICATIONS
AS FIRST/LAST AUTHOR

23.271
I.F. AS FIRST/LAST AUTHOR

28
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Ditto A., Martinelli F., Lorusso D., Haeusler E., Carcangiu M., Raspagliesi F.: Fertility sparing surgery in early stage epithelial ovarian cancer. J Gynecol Oncol 2014; 25: 320-327 [IF 1.6]
2. Ditto A., Martinelli F., Ramondino S., Lo Vullo S., Carcangiu M., Haeusler E., Mariani L., Lorusso D., Raspagliesi F.: Class II versus Class III radical hysterectomy in early cervical cancer: An observational study in a tertiary center. Eur J Surg Oncol 2014; 40: 883-890 [IF 2.892]
3. Lorusso D., Martinelli F., Mancini M., Sarno I., Ditto A., Raspagliesi F.: Carboplatin-paclitaxel versus cisplatin-ifosfamide in the treatment of uterine carcinosarcoma a retrospective cohort study. Int J Gynecol Cancer 2014; 24: 1256-1261 [IF 1.949]
4. Lorusso D., Petrelli F., Coinu A., Raspagliesi F., Barni S.: A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. Gynecol Oncol 2014; 133: 117-123 [IF 3.687]
5. Lorusso D., Ramondino S., Mancini M., Zanaboni F., Ditto A., Raspagliesi F.: Phase II trial on cisplatin-adriamycin-paclitaxel combination as neoadjuvant chemotherapy for locally advanced cervical adenocarcinoma. Int J Gynecol Cancer 2014; 24: 729-734 [IF 1.949]
6. Lorusso D., Ratti M., Ditto A., Raspagliesi F.: High-risk borderline ovarian tumors: Analysis of clinicopathological features and prognostic impact of different follow-up strategies. Oncology 2014; 87: 183-192 [IF 2.613]
7. Lorusso D., Sarno I., Di Donato V., Palazzo A., Torrisi E., Pala L., Marchiano A., Raspagliesi F.: Is postoperative computed tomography evaluation a prognostic indicator in patients with optimally debulked advanced ovarian cancer? Oncology 2014; 87: 293-299 [IF 2.613]
8. Papadia A., Bogani G., Bellati F., Raspagliesi F.: Oophorectomy and hysterectomy and cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstet Gynecol 2014; 124: 840-841 [IF 4.368]
9. Raspagliesi F., Zanaboni F., Martinelli F., Scasso S., Laufer J., Ditto A.: Role of paclitaxel and cisplatin as the neoadjuvant treatment for locally advanced squamous cell carcinoma of the vulva. J Gynecol Oncol 2014; 25: 22-29 [IF 1.6]

THORACIC SURGERY

High-standard clinical care and scientific research, translational research and continous education identified the Thoracic Surgery Unit.
Clinical activities cover all aspects of thoracic oncology, focusing on pulmonary, mediastinal, chest wall, and esophageal tumors. In the management of lung cancer, the mainstay of surgical treatment is maximal functional sparing. All patients undergo muscle-sparing thoracotomy, avoiding any muscular section. Lung-sparing procedures (bronchoplasty and/or angioplasty) are adopted to avoid the removal of the entire lung, when possible.
A clinical randomized trial is ongoing, searching for the best drainage strategy to limit postoperative air leak (airINTrial). In the domain of secondary lung tumors, the Thoracic Surgery cooperates with different INT Units (mainly with Medical Oncology, Pediatric Oncology and Sarcoma Units), performing standard metastasectomy by innovative parenchyma-sparing procedures. Extended resections are proposed when an acceptable postoperative impairment of the quality of life can be expected. Innovative techniques for tridimensional chest wall reconstruction have been developed (rib-like technique), permitting appropriate reconstruction even in case of removal of an entire hemithorax. In mediastinal surgery, Superior Vena Cava (SVC) replacement is performed by procedures not requiring SVC cross-clamping, avoiding intraoperative hemodynamic instability. Pleuro-pneumonectomy is proposed in limited malignant mesothelioma, after induction chemotherapy. In the more advanced disease, a clinical trial has been approved to measure the advantage of pleurectomy/decortication after chemotherapy in terms of disease-free survival and quality of life, compared to chemotherapy only (PASS trial). Esophageal surgery is performed in cooperation with different Units (Otorhinolaryngology, Gastrointestinal- Pancreatic Liver Surgery, Endoscopy).
Our group employs a multidisciplinary approach to better define the strategy for diagnosis and treatment for each clinical case. Every week we organize a meeting with the colleagues of the other competencies involved: radiology, oncology, endoscopy, pulmonology, radiotherapy and nuclear medicine.
Continuos education for Physician and Nurses is guaranteed by a structured program of more edition on particular aspects of clinical management (Thoracic Dreinage, Standard resections and different Approaches to thoracic surgery) and a course on the scientific editing (Writing a scientific article).

HEAD

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12
PUBLICATIONS
AS FIRST/LAST AUTHOR

58.425
I.F. AS FIRST/LAST AUTHOR

48
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Billé A., Giovannetti R., Calarco G., Pastorino U.: Tailored stent for bronchial stump fistula closure and omentoplasty for infection control: A combined approach with low morbidity. Tumori 2014; 100: e157-e159 [IF 1.09]
2. Billé A., Girelli L., Leo F., Pastorino U.: A false positive fluorodeoxyglucose lymphadenopathy in a patient with pulmonary carcinoid tumor and previous breast reconstruction after bilateral mastectomy. Gen Thorac Cardiovasc Surg 2014; 62: 195-197 [IF 0]
3. Billé A., Platania M., Pelosi G., Padovano B., Quattrone P., Pastorino U.: Gingival metastasis as first sign of multiorgan dissemination of epithelioid malignant mesothelioma. J Thorac Oncol 2014; 9: 1226-1229 [IF 5.8]
4. Bovolato P., Casadio C., Billé A., Ardissone F., Santambrogio L., Ratto G.B., Garofalo G., Bedini A.V., Garassino M., Porcu L., Torri V., Pastorino U.: Does surgery improve survival of patients with malignant pleural mesothelioma?: A multicenter retrospective analysis of 1365 consecutive patients. J Thorac Oncol 2014; 9: 390-396 [IF 5.8]
5. Marulli G., Duranti L., Cardillo G., Luzzi L., Carbone L., Gotti G., Perissinotto E., Rea F., Pastorino U.: Primary chest wall chondrosarcomas: Results of surgical resection and analysis of prognostic factors. Mol Biol Evol 2014; 45: e194-e201 [IF 14.308]
6. Pastorino U., Duranti L., Scanagatta P., Leo F., Piccioni F., Collini P., Gronchi A.: Thoracopleuropneumonectomy with riblike reconstruction for recurrent thoracic sarcomas. Ann Surg Oncol 2014; 21: 1610-1615 [IF 3.943]

7. Pelosi G., Haspinger E.R., Bimbatti M., Leone G., Paolini B., Fabbri A., Tamborini E., Perrone F., Testi A., Garassino M., Maisonneuve P., de Braud F., Pilotti S., Pastorino U.: Does immunohistochemistry affect response to therapy and survival of inoperable non-small cell lung carcinoma patients? A survey of 145 stage III-IV consecutive cases. Int J Surg Pathol 2014; 22: 136-148 [IF 0.961]

8. Scanagatta P., Duranti L., Billé A., Pastorino U.: Dynamic magnetic resonance imaging and postoperative motion of diaphragm. Ann Thorac Surg 2014; 98: 787 [IF 3.631]

9. Scanagatta P., Duranti L., Girelli L., Sestini S.: EComment. New frontiers of pulmonary resections: Possible usefulness of autologous adipose mesenchymal cells. Interact Cardiovasc Thorac Surg 2014; 18: 95 [IF 1.109]

10. Scanagatta P., Furia S., Billé A., Duranti L., Girelli L., Tavecchio L.D., Leo F., Giovannetti R., Pelosi G., Porcu L., Pastorino U.: Thulium laser versus staplers for anatomic pulmonary resections with incomplete fissures: negative results of a randomized trial. Tumori 2014; 100: 259-264 [IF 1.09]

11. Sozzi G., Boeri M., Rossi M., Verri C., Suatoni P., Bravi F., Roz L., Conte D., Grassi M., Sverzellati N., Marchiano A., Negri E., La Vecchia C., Pastorino U.: Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study. J Clin Oncol 2014; 32: 768-773 [IF 17.879]

12. Tavecchio L., Billé A., Pastorino U.: Cervical partial oesophagectomy and trans-oral direct end-to-end anastomosis. Eur J Cardiothorac Surg 2014; 46: 137-139 [IF 2.814]

PLASTIC AND RECONTRUCTIVE SURGERY

HEAD

Maurizio B. Nava, MD *(Until October 2014)*

Marco Greco, MD *(Interim from November 2014)*

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Luisa Morandi

NURSES

Maria Saracino (Coordinator), Samantha Fabiana Castelli, Marisa Labò, Cinzia Gentilini, Giovanna Melia, Caterina Pireddu, Irene Rossi, Raffaella Tupputi

The Plastic and Reconstructive Surgery Unit is a reference center for breast reconstruction, and carries out both surgical and research activities. The main focus of the Unit is oncoplastic surgery. Surgical reconstructive procedures are performed for mastectomy and for tumors of the head and neck, soft tissues, thorax, and other types of oncological ablations as well as surgical interventions and repair for skin tumors.

The department carries out the following types of surgeries:

- Breast and soft tissue reconstructions;
- Mastectomy;
- Microsurgical reconstruction;
- Germ cell transplantation;
- Reconstructive surgery of the head and neck;
- Thoracic reconstructive surgery;
- Gynecologic reconstructive surgery;
- Urologic reconstructive surgery;
- Pediatric reconstructive surgery;
- Cutaneous oncoplastic surgery;
- Advances techniques for wound healing.

SELECTED PUBLICATIONS

1. Rancati A., Dorr J., Irigo M., Peralta B., Gonzalez E., Angrigiani C., Zampieri A., Scuderi N., Nava M.: Breast implant explantation and simultaneous correction with inferior dermoglandular flap authoprosthesis technique. Cir Plast Ibero-Latinoam 2014; 40: 271-277 [IF 0]

2. Riggio E., Bianchi G.V.: Commentaries on data published by Riggio et al. and discussion by Otterburn on locoregional risk following mastectomy after lipofilling. Aesthetic Plast Surg 2014; 38: 608-610 [IF 1.189]

2
PUBLICATIONS
AS FIRST/LAST AUTHOR

1.189
I.F. AS FIRST/LAST AUTHOR

15
H-INDEX HEAD OF UNIT

UROLOGIC SURGERY

HEAD

Roberto Salvioni, MD

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The Urologic Oncology Unit is one of the largest in the Italy with around 1000 new urologic cancer referrals yearly. It is a national and international center with substantial experience in managing patients with germ cell tumors of the testes, penile cancer, urothelial cancer, kidney cancer, and prostate cancer. Multidisciplinary groups, including surgeons, clinical and medical oncologists, radiologists and basic scientists, work together in the clinical management of patients and in research activities. Over 8,000 clinical visits were performed in 2014 with more than 500 inpatient chemotherapy treatments administered. The Unit has extensive experience in mini-invasive surgical techniques such as laparoscopic surgery in the cure of testicular cancer and small renal masses and treats many patients with percutaneous cryoablation. The Unit is also involved in development of new therapies in urology focusing on new drugs including immunotherapy and targeted therapies. We are actively involved in training of young oncologists with international projects sponsored by ESMO.

During 2014, we participated in several international trials in urothelial carcinoma investigating new targeted therapies; we actively participated in transitional research with Memorial Sloan Kettering in New York (USA) in studies involving genomic profiling. In relapsed germ cell tumor we promoted two trials using antiangiogenetic (pazopanib) and targeted therapy as brentuximab (anti-CD30) antibody. We have international collaborations to collect data from patients with bone or brain metastases from germ cell tumors to permit evaluation of prognostic factors, treatment, and prognosis. We participated in an international collaboration to identify prognostic factors for systemic treatment for locally advanced/metastatic penile carcinoma. In renal neoplasms, we have a multidisciplinary approach with particular attention to biopsy and both conservative and radical treatments in advanced disease.

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PUBLICATIONS
AS FIRST/LAST AUTHOR

12.323
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4. Necchi A., Nicolai N., Mariani L., Lo Vullo S., Giannatempo P., Raggi D., Farè E., Piva L., Biasoni D., Catanzaro M., Torelli T., Stagni S., Milani A., Gianni A.M., Salvioni R.: Combination of paclitaxel, cisplatin, and gemcitabine (TPG) for multiple relapses or platinum-resistant germ cell tumors: Long-term outcomes. Clin Genitourin Cancer 2014; 12: 63-69.e1 [IF 1.693]
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PEDIATRIC SURGERY

HEAD
Luigi Piva, MD

The Pediatric Surgery Unit was created in July 2005. Specific aims of the Pediatric Surgery Unit of the Institute is the surgical treatment of the most frequent solid - non CNS - tumors in children and adolescents. The role of surgery is established according to ongoing European treatment protocols. The main clinical research area is represented by renal tumors.

Wilm's Tumor
The Pediatric Oncology Unit of this Institute represents the reference AIEOP (Associazione Italiana Ematologia e Oncologia Pediatrica) center for pediatric renal tumors, and is the coordinator of national clinical protocols and molecular studies. In this view, the surgeon of this Unit represents the referral surgeon for institutional patients as well as for children coming from other Pediatric Hospitals, especially for cases presenting with a complex clinical picture.

Neuroblastoma
Surgery plays an important role in the treatment of neuroblastoma, and its application in the treatment protocols of E-SIOP is well defined for both the diagnostic and the therapeutic phases. For high-risk neuroblastoma, surgery is difficult and time consuming. Surgery should be undertaken after the end of induction chemotherapy, with the aim to achieve complete excision of the tumor with minimal morbidity to improve local control. The role of surgery in high-risk neuroblastoma is one of the primary objectives of the ongoing European Protocol for high-risk neuroblastoma, opened in 2002 and coordinated in Italy by our Institute.

Teratomas and malignant germ cell tumors
Pediatric patients are treated according with the AIEOP TCGM 2004 protocol. Primary surgical resection was the treatment indicated for all patients with localized disease (ovary, testicular, and extragonadal tumor).

During 2014, 72 surgical interventions were carried out in cooperation with the other surgical Units of the Institute, including urological, gynecological and andrological procedures as well as surgeries on soft tissue sarcomas and rare tumors.

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1
PUBLICATIONS
AS FIRST/LAST AUTHOR
1.311
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LASER THERAPY

HEAD
Anna Colombetti, MD
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The Unit is dedicated to diseases where laser therapy is the first or the only treatment choice. The Unit features 5 lasers for a total of 23 wavelengths, allowing for both conservative and ablative therapies. Selective photothermolysis laser treatment is performed for keloids, pigmented and vascular lesions; laser ablation technique is used for mucosal and skin cancers lesions requiring histological evaluation.

Treated lesions can be conveniently classified into 5 groups:

- Tumor lesions: melanoma in-transit metastases in patient not eligible to other therapy, cutaneous and mucosal localizations of Kaposi's sarcoma, skin carcinomas of critical anatomical areas as eyelids, nostrils and ear, precancerous lesions such as actinic keratosis.
- Vascular lesions: flat-type congenital capillary angiodysplasia, angiomas, and venous lymphatic angiodysplasia.
- Nevi: giant melanocytic nevi. We have developed an intralesional innovative technique to treat selected vascular lesions and giant nevi.
- Traumatic and post-burn hypertrophic scars and keloids, radiodermatitis: in addition to laser therapy we associate in particular cases the lipofilling technique with implant of adipose tissue, to restore skin trophism and volume.
- Cutaneous localizations originating from complex syndromes, such as adenomas in tuberous sclerosis, angiodysplasias related to Sturge-Weber syndrome.

The Laser Therapy Unit is considered the national reference center for neurofibromas and cafe-au-lait spots in Neurofibromatosis disease (NF1). Our approach is multidisciplinary, and laser procedures are performed in collaboration with the Melanoma and Sarcoma Unit and Radiology Unit. In collaboration with the Department of Anesthesiology, 88 pediatric patients affected by giant nevi, post-burn scars, hemangiomas and congenital vascular pathologies were treated with laser procedures under general anesthesia. During 2014, about 2,000 patients were treated with laser therapy, more then 1,300 of which were in an ambulatory setting.

DAY SURGERY

HEAD

Aldo E. Bono, MD

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Maria R. Bignamini, Anna Corella, Loredana Orezzi

The Day Surgery Unit is devoted to surgical procedures performed in ambulatory and Day Hospital settings. The unit includes 10 beds, 2 operating rooms for general surgical activities, and one operating room for laser surgery. Surgical activity deals with different lesions involving skin, soft tissues, breast, as well lesions in gynecologic, urologic, and head and neck areas. During the year 2014, 5,644 surgical procedures were performed. Of these, 2,470 were performed in a Day Hospital setting, and 3,174 patients underwent outpatient surgery. Besides normal surgical activity, specialized procedures were performed such as electrochemotherapy of secondary skin tumors (in collaboration with Melanoma and Sarcoma Unit) and fat injection or lipostructure with the Coleman technique to lessen local skin and sub-cutaneous damage (in collaboration with Plastic and Reconstructive Unit).

Clinical research activity is, at present, mainly performed in cooperation with the Melanoma and Sarcoma Unit. The aim of this activity is to better define the initial clinical features of early melanoma to bring about curative surgery. In particular, many studies have been performed on the following topics: melanoma in situ, small melanoma, childhood melanoma, amelanotic melanoma, horizontal growth phase melanoma, nodular melanoma, spectrophotometry of melanoma, automated computerized diagnosis of melanoma. Recently, we have developed the concept of micro-melanoma: a melanoma with a diameter equal to or less than 3 mm. This lesion is so small that it is close to the limit of clinical relevance, but its detection is of the utmost importance because it is a de facto malignant lesion. A further scientific cooperation is currently ongoing with the Unit of Immunotherapy of Human Tumors, dealing, in particular, with blood measurements of circulating miRNA in patients bearing cutaneous melanoma.

MEDICAL ONCOLOGY

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MEDICAL DAY HOSPITAL
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RESPIRATORY PATHOPHYSIOLOGY
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The Department provides for comprehensive cancer treatments in adults with solid tumors and performs research focusing on new drug development and treatment strategies. Opportunities are maximized for inter-departmental and inter-institutional collaborations to ensure the forefront of patient care and oncology research.

The Medical Oncology Department comprises various clinical medical units and one centralized day hospital; outpatients visits are performed in dedicated rooms.

The Department is organized in the following Units:

- Medical Oncology 1: new drugs development (phase I, early phase II), breast cancer, gastrointestinal tumors (gastric, colorectal – neuroendocrine– pancreatic and biliary tract), melanoma, thoracic tumors (lung cancer – mesothelioma – thymoma), urogenital tumors (renal, prostatic, bladder, testis and penis cancer), solid tumors immunotherapy
- Adult Mesenchymal Tumor Medical Oncology: clinical research and care in sarcomas and peritoneal mesothelioma
- Medical Day Hospital: deals with adult patients referred by the clinical Units of the Department, as well as diagnosis, treatment and follow-up of neuroendocrine tumors
- Head and Neck Cancer Medical Oncology: clinical research and care in cancer, thyroid and salivary glands cancer
- Cardiology: evaluation of patients addressed to surgery and medical treatments. Follow up of cardiovascular toxicities due to antineoplastic treatments
- Respiratory Pathophysiology: evaluation of patients addressed to surgery, and medical treatments; follow up of pulmonary toxicities due to chemo-radiotherapy; hospital-based tobacco control policies as well as outpatient and inpatient smoking cessation clinic.

Highlights

New drug development (phase I and Ib studies) and the promotion of translational research projects. An entire Unit is fully dedicated to Phase I and early Phase II studies.

Translational research on prognostic and/or predictive biomarkers to investigate new therapeutic strategies for all solid tumors (upper and lower gastrointestinal tract cancer, non-small cell lung cancer, malignant pleural mesothelioma, thymoma, breast cancer, genitourinary tumors).

New generation targeted therapy and immunotherapy for malignant melanoma, lung cancer, gastrointestinal tumors, prostate cancer, breast cancer and neuroendocrine tumors.

Cardiologic surveillance to assess the cardiotoxicity of new experimental drugs (monoclonal antibodies, receptor tyrosine kinase inhibitors, BRAF inhibitors, MEK inhibitors).

Research interest focused on electronic cigarettes and their health effects in terms of second-hand exposure and concerning the physiological consequences of the “rib-like” technique, a semi-rigid tridimensional prosthesis reproducing the shape of native ribs for sarcoma patients.

INT is certified as a Center of Excellence by the European Society of Neuroendocrine Tumors (ENET).

MEDICAL ONCOLOGY

Our mission is to improve clinical care and outcomes of medical treatment of cancer through multidisciplinary management, personalized medicine, and development of new drugs and strategies by the Units fully dedicated to lung cancer mesothelioma and thymoma, gastrointestinal tract cancers, genitourinary tumors, melanoma and breast cancer. A major effort has been made to restore the infrastructure for inpatient care and renew the clinical research structure.
Major areas of interest are:

- A Unit fully dedicated to new drug development (phase I and Ib studies) and promotion of translational research projects. We will develop treatments using new molecular compounds, and to investigate new therapeutic strategies for solid tumors.
- Translational research on prognostic and/or predictive biomarkers in most solid tumors (upper and lower gastrointestinal tract, non-small cell lung cancer, malignant pleural mesothelioma, and thymoma).
- New targeted therapies and immunotherapies for malignant melanoma and lung cancer.
- Adjuvant and systemic treatment of patients with renal cell carcinoma and management of castration-resistant prostate cancer using new therapeutic approaches.
- Adjuvant and systemic treatments of breast cancer: identification and selection of subsets of patients to be treated differently according to the molecular profile of their disease (i.e. integrating targeted therapies with standard chemotherapy or with hormone treatment).
- Active involvement in research on antiemetic drugs.

The facilities available at Medical Oncology include a 28-bed inpatient ward, a day hospital area, 10 consulting rooms, and 2 research laboratories for pharmacokinetic, pharmacodynamic, and preclinical studies and evaluation of new treatments. In 2014, 44 trials were activated: 2,693 new patients were visited and among these 538 entered clinical trials.
The Unit, together with other important members of the multidisciplinary team, was asked by ROL (Rete Oncologica Lombarda) to update national guidelines and is also involving in writing the AIOM (Italian Association of Medical Oncology) guidelines for melanoma, kidney and gastric cancer.

HEAD

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PUBLICATIONS
AS FIRST/LAST AUTHOR

234.19
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

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2. Biondani P., Verzoni E., Torri V., Porcu L., Grassi P., Testa I., de Braud F., Procopio G.: Sequential tyrosine kinase inhibitors (TKIs) in metastatic renal cell carcinoma: Results from a large cohort of patients. Anticancer Res 2014; 34: 2395-2398 [IF 1.872]
3. Celio L., de Braud F., Aapro M.: Aprepitant versus dexamethasone for delayed emesis: What is the role of the 5-hydroxytryptamine type 3 receptor antagonist palonosetron? J Clin Oncol 2014; 32: 2185-2186 [IF 17.879]
4. Chiarion-Sileni V., Pigozzo J., Ascierto P.A., Simeone E., Maio M., Calabrò L., Marchetti P., De Galitiis F., Testori A., Ferrucci P.F., Queirolo P., Spagnolo F., Quaglino P., Carnevale Schianca F., Mandal a M., Di Guardo L., Del Vecchio M.: Ipilimumab retreatment in patients with pretreated advanced melanoma: The expanded access programme in Italy. Br J Cancer 2014; 110: 1721-1726 [IF 4.817]
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7. Di Cosimo S., Arpino G., Generali D.: Neo-adjuvant treatment of HER2 and hormone-receptor positive breast cancer - Moving beyond pathological complete response. Breast 2014; 23: 188-192 [IF 2.581]

8. Di Cosimo S., Serpico D., Porcu L., Molino L., Fanetti G., Torri V., de Braud F.: Clinical outcome of HER2-positive breast cancer patients after failure on adjuvant trastuzumab: The potential of the time to relapse. Clin Oncol (R Coll Radiol) 2014; 26: 174 [IF 2.826]
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13. Giannatempo P., Alessi A., Miceli R., Raggi D., Farè E., Nicolai N., Serafini G., Padovano B., Piva L., Biasoni D., Torelli T., Catanzaro M., Stagni S., Maffezzini M., Mariani L., Gianni A.M., Sonpavde G., Salvioni R., Necchi A., Crippa F.: Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. Clin Genitourin Cancer 2014; 12: 433-439 [IF 1.693]
14. Grassi P., Verzoni E., Porcu L., Testa I., Iacovelli R., Torri V., De Braud F., Procopio G.: Targeted therapies in advanced renal cell carcinoma: The role of metastatic sites as a prognostic factor. Future Oncol 2014; 10: 1361-1372 [IF 2.611]
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16. Haspinger E.R., Garassino M.C., Torri V., Cinquini M., De Braud F., Gelsomino F.: Do we really need another epidermal growth factor receptor tyrosine kinase inhibitor in first-line treatment for patients with non-small-cell lung cancer and EGFR mutations? J Clin Oncol 2014; 32: 859-863 [IF 17.879]
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18. Iacovelli R., Pietrantonio F., Farcomeni A., Maggi C., Palazzo A., Ricchini F., De Braud F., Di Bartolomeo M.: Chemotherapy or targeted therapy as second-line treatment of advanced gastric cancer. A systematic review and meta-analysis of published studies. PLoS ONE 2014; 9 [IF 3.534]
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23. Iacovelli R., Verzoni E., Grassi P., Farcomeni A., de Braud F., Procopio G.: Rationale and protoc ol of SOAP: a phase II study to evaluate the efficacy of sorafenib as second-line treatment after pazopanib in patients with advanced renal cell carcinoma. Tumori 2014; 100: e282- e285 [IF 1.09]
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33. Necchi A., Pennati M., Zaffaroni N., Landoni E., Giannatempo P., Raggi D., Schwartz L.H., Morosi C., Crippa F., Farè E., Nicolai N., Lanocita R., Sava T., Sacco C., Messina C., Ortega C., De Braud F.G., Salvioni R., Daidone M.G., Gianni A.M., Mariani L.: Analysis of plasma cytokines and angiogenic factors in patients with pretreated urothelial cancer receiving Pazopanib: The role of circulating interleukin-8 to enhance the prognostic accuracy. Br J Cancer 2014; 110: 26-33 [IF 4.817]
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ADULT MESENCHYMAL TUMOR MEDICAL ONCOLOGY

HEAD

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DATA MANAGER

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The Adult Mesenchymal Tumor Medical Oncology Unit deals with adult patients with sarcomas and peritoneal mesothelioma. It coordinates the Italian Network on Rare Cancers (RTR), a project aimed at distantly sharing cases of adult patients with rare solid cancers to improve quality of care and reduce patient migration. It operates within the institutional multidisciplinary Sarcoma Tumour Board and provides clinical teleconsultations within RTR.
The Unit was involved in updating the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines on soft tissue sarcomas, Gastrointestinal Stromal Tumors (GIST) and bone sarcomas. This took place through a consensus event organized by ESMO involving the European Sarcoma community.
The Unit carries out, or participates in, institutional research projects, national and international clinical trials, both industry-sponsored and investigator-driven. Overall, in 2014 the Unit participated in 37 clinical studies with 80 patients enrolled.
The Unit keeps a strong focus on:

- translational research on prognostic and/or predictive biomarkers in soft tissue sarcomas, gastrointestinal stromal tumors, rare bone tumors (chordoma, giant cell tumor), and malignant peritoneal mesothelioma;
- targeted therapy for soft tissue sarcomas, gastrointestinal stromal tumors, rare bone tumors (chordoma, giant cell tumor, PVNS);
- histology-driven medical therapy of soft tissue sarcomas, both in the neoadjuvant and in advanced setting.

From the clinical point of view, institutional facilities include a 6-bed inpatient ward, a day-hospital area, 3 outpatient rooms.
In 2014, the Unit carried out:

- 4,143 outpatient visits (758 first consultations and 3,385 visits on patients on treatment or follow-up)
- 436 admitted patients
- about 800 new sarcoma cases were clinically shared with other Italian centers within the Italian Network on Rare Cancers.

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7
PUBLICATIONS AS FIRST/LAST AUTHOR

27.613
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

HEAD AND NECK CANCER MEDICAL ONCOLOGY

HEAD

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The Unit has been involved in 36 trials in the following setting:

- Curative treatment (6 trials)
- Recurrent/metastatic disease (7 trials)
- Thyroid cancer (12 trials)
- Non-melanoma skin cancer (2 trials)
- Salivary glands cancer (2 trials)
- Quality of life and supportive care (7 trials)

A total of 128 patients were enrolled in clinical trials during 2014. Two International Consensus Conferences were organized. Both events were supported by the Italian Association of Medical Oncology (AIOM), Radiation Oncology (AIRO) and Head and Neck Oncology (AIOCC):

- May 2014: Best practices in supportive care during chemoradiotherapy for head and neck cancer.
- October 2014: Diagnosis and treatment of salivary gland cancer.

Two perceptorship courses were held (July and December 2014) with a target audience composed of international medical oncologists, surgeons, and radiation oncologists experienced in the management of head and neck cancer patients.

Number of outpatient visits:

- Multidisciplinary first visits: 320
- Multidisciplinary follow-up visits: 962
- First oncological visits: 383
- Oncological out-patient visits during therapy: 1,099, or follow-up: 3,031

Number of inpatients: 205 for a total of 456 hospitalizations per year.
Our future plans are to increase the number of studies in which the Unit is involved. We are very interested in academic studies that include translational research, value based research, supportive care, and cost effectiveness research. Our challenge is to deliver high quality academic research data through fruitful interaction of national and international collaborations. We believe that such an approach will be crucial in applying for appropriate research support.

11
PUBLICATIONS AS FIRST/LAST AUTHOR

49.064
I.F. AS FIRST/LAST AUTHOR

28
H-INDEX HEAD OF UNIT

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4. Bossi P., Orlandi E., Miceli R., Perrone F., Guzzo M., Mariani L., Granata R., Locati L., Fallai C., Cortelazzi B., Pilotti S., Scaramellini G., Gloghini A., Licitra L.: Treatment-related outcome of oropharyngeal cancer patients differentiated by HPV dictated risk profile: A Tertiary Cancer Centre series analysis. Ann Oncol 2014; 25: 694-699 [IF 6.578]
5. De Cecco L., Bossi P., Locati L., Canevari S., Licitra L.: Comprehensive gene expression meta-analysis of head and neck squamous cell carcinoma microarray data defines a robust survival predictor. Ann Oncol 2014; 25: 1628-1635 [IF 6.578]
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MEDICAL DAY HOSPITAL

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ADMINISTRATIVES

Antonella Bifano, Anna Rosa Cabiddu

The Medical Day Hospital is part of the department of Medical Oncology. Our Unit features rooms for outpatient visits, waiting rooms, hospital rooms, oral medication dispensing rooms, and short infusional therapy rooms.
The oncological diseases followed are those of established interest for our Department: breast cancer, gastrointestinal tumors, head/neck carcinomas, malignant melanoma, sarcomas, and neuroendocrine tumors. About 300 patients are seen daily, and, of these, about 100 are undergoing medical treatments.
Short duration therapies (less than 90 minutes) are performed in a large room with 11 dedicated chairs. Another room is dedicated to management of venous catheters; the goal is to minimize the risk of complications related to these devices. There are about 60-65 of these treatments per day. There are 5 hospitalization rooms for a total of 18 beds and 5 chairs. In addition, there is a room dedicated to mini-invasive treatments such as thoracentesis, paracentesis, lumbar puncture, bone marrow, and cutaneous biopsies. Research nurses are also involved in the taking serial blood samples seriated over time. Volunteers from the "Lega Italiana lotta ai Tumori" provide effective support to the Unit. In 2014, the total number of treatments in the Day Hospital unit was 8,126. For short therapies plus catheters, there were 13,831 procedures.
In January 2014, our structure was confirmed as a center of excellence by the European Neuroendocrine Tumors Society demonstrating the importance that we place on diagnosis, management, treatment, follow-up, and implementation of original investigative trials. We have a database on more than 1,650 patients with a diagnosis of neuroendocrine tumor. Several trials, sponsored and spontaneous, are ongoing. Our Institution, in Italy and in Europe, is a landmark in the management of these heterogeneous neoplasms whose incidence is increasing worldwide. Every year 250-270 new cases are cared for at our Institution and collaborative relationships are active with external hospitals.

SELECTED PUBLICATIONS

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3
PUBLICATIONS
AS FIRST/LAST AUTHOR

8.758
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

CARDIOLOGY

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The Cardiology Unit carries out activity mainly concerning cardiac evaluation of patients undergoing general surgery or chemo-radiotherapy for cancer in order to define individual cardiovascular risk and predict the need of monitoring for complications.
Many patients, candidates for surgery and/or medical therapy, are subjected to diagnostic tests and therapies for ischemic heart disease, hypertension, valvular heart disease, arrhythmias, and congestive heart failure before and/or during the course of cancer treatment. Preoperative evaluation of cardiac risk, perioperative assessment and monitoring are performed as shown in the latest International Guidelines. All of the Phase I, II, and III clinical studies carried out require regular cardiologic surveillance to assess the cardiotoxicity of new experimental drugs (monoclonal antibodies, receptor tyrosine kinase inhibitors, BRAF inhibitors, MEK inhibitors).
Clinical research mainly investigates monitoring of cardiovascular toxicity related to antineoplastic treatment. The Unit is involved in numerous clinical trials, national and international, requiring regular, mandatory, cardiologic surveillance assessment, differentiated according to protocols for patients undergoing chemotherapy regimens containing anthracyclines, or treated with new anticancer compounds and monoclonal antibodies. Cardiology is involved in over 150 clinical trials of new drugs in collaboration with other Units of the INT.
In 2014, there were 26,059 (16,362 for inpatients and 9,697 for outpatients) ordinary cardiologic procedures. In addition, 12,070 EKG and 8,832 clinical cardiac examinations, 3,453 Echo-color Doppler tests were performed.
There has been an important and growing involvement of cardiologists in relation to the analysis and evaluations required by study protocols and monitoring of cardiovascular toxic effects of new drugs.

RESPIRATORY PATHOPHYSIOLOGY

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The Respiratory Pathophysiology and Tobacco Control Unit has been involved in several clinical and research activities. We are committed to providing the highest quality of care suffering from all forms of lung diseases. Our areas of expertise cover chronic obstructive pulmonary diseases, tobacco control policies and interventions, cardiopulmonary exercise testing in the pre-operative evaluation of patients admitted to thoracic surgery, as well as the long-term consequences of Hodgkin Lymphoma treatments.
In 2014, we provided more than 100 smoking cessation interventions (integrated pharmacological and psychological support) addressed to inpatients (with a 40% rate of smoking cessation at the first re-evaluation) and 150 to outpatients (with a 25% rate of smoking cessation at one year).
From a public prevention perspective, in the first part of 2014 we assisted the Italian steel firma Marcegaglia in the transition to a smoke-free company by raising the awareness among its workers about the harmful effects of cigarette smoke and how to cope with it.
Since October 2014, our team administers the online antismoking forum of the important Italian newspaper, "Corriere della Sera".
Our recent research interest is focused on electronic cigarettes and their health effects in terms of second-hand exposure. We participate in a clinical research study concerning the physiological consequences of the "rib-like" technique, a semi-rigid tridimensional prosthesis reproducing the shape of native ribs for sarcoma patients. Starting from the end of 2014, the study Crystal for COPD patients is open by our Unit for enrollment.
We aim at providing insights on new tobacco smoking products that heat tobacco rather than burn it.
We have a cooperative project on the impact of smoking on interstitial lung disease and their treatment with the S. Gerardo Hospital of Monza, Milano-Bicocca University, and the S. Giuseppe Hospital of Milan.

SELECTED PUBLICATIONS

1. Ruprecht A.A., De Marco C., Pozzi P., Munarini E., Mazza R., Angellotti G., Turla F., Boffi R.: Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. Tumori 2014; 100: e24-e27 [IF 1.09]

1
PUBLICATIONS AS FIRST/LAST AUTHOR
1.09
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12
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HEMATOLOGY AND PEDIATRIC ONCO-HEMATOLOGY

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HEMATOLOGY AND ALLOGENEIC BONE MARROW TRANSPLANTATION
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SUPPORTIVE CARE IN CANCER
CARLA I. RIPAMONTI

The Department of Hematology and Pediatric Onco-Hematology comprises five clinical divisions: 1) the Hematology Unit, a leader in hematological malignancies care and research. It controls an advanced cell processing laboratory that is dedicated to preparing safe and effective hematologic cells for transplantation and a laboratory devoted to translational research to rapidly turn scientific discoveries into more effective and personalized treatment modalities; 2) the Pediatric Oncology Unit, devoted to the treatment and study of typical infancy, adolescent and young adult solid tumors and hematological malignancies. This Unit focuses on prevention, early diagnosis and management of long-term cancer- and treatment-induced effects. Clinical activities include dedicated medical care, educational and sport programs; 3) the Immunohematology and Transfusion Medicine (SIMT) Unit, responsible for laboratory diagnosis as well as donation, testing, processing, preservation, storage, distribution, and transfusion safety of blood components (a donor center, apheresis center, and HLA typing laboratory are part of this Unit). This Unit is responsible for collecting and processing hematopoietic stem cells and performs the necessary analyses required for bone marrow transplantation procedures; 4) the Supportive Care in Cancer Unit pursues clinical, educational, and research objectives aimed at the prevention assessment, treatment, and study of side effects or toxicity resulting from cancer therapy, as well as the cure of emotional, social, and spiritual patient needs through the complete care of patients starting from diagnosis. The treatments offered are compliant with guidelines of the WHO, MASCC, ESMO, and AIOM; 5) the Clinical Psychology Unit, that supports patients with life-threatening illnesses, along with their families, and is aimed to improve the quality of life and well-being, and relieve mental suffering throughout the course of illness and survivorship.

HEMATOLOGY AND ALLOGENEIC BONE MARROW TRANSPLANTATION

New treatments tailored to overcome aggressiveness and refractory lesions are required. Ongoing clinical and biological studies in the field of multiple myeloma (MM), indolent and aggressive non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), myelodysplastic and myeloproliferative disorders, and graft-versus-host disease (GVHD) are aimed at:

- Evaluating the efficacy of new, targeted therapies alone or in combination with standard chemotherapy to allow individualized treatment options. Massive sequencing technologies will help in identifying genetic lesions/mechanism(s) driving lymphoma aggressiveness and/or chemo-refractoriness and to define new targets for treatment.
- Exploiting the role of potential genes/proteins as diagnostic tools and novel biomarkers for the early recognition/stratification of patients requiring intensified treatment options or those unlikely to respond to standard chemoimmunotherapies.
- Introducing new molecular methods for diagnosis of hematological malignancies. In B cell malignancies, several methods have been developed for the detection of minimal residual disease (MRD). We are applying a next generation sequencing strategy based on the use of Ion Torrent Personal Genome Machine to monitor B cell malignancies and clonal evolution in MM patients. We have introduced and developed molecular tests for detection of mutations with diagnostic impact (BRAF V600E in hairy cell leukemia, MYD88 L265P in Waldenstrom macroglobulinemia, TET2 and IDH mutations in peripheral T cell lymphomas, and JAK2 V617F in myeloproliferative disorders).

Extensive research in our Unit has the clear goal of a rapid translation in the clinical setting by: i) improving the early identification of chemo-refractory/relapsing patients and patients requiring auto- or allo-SCT as first line treatment with novel biomarkers; ii) designing phase 1/2 clinical studies aimed at exploring the clinical activity of rationale combinations of targeted drugs that have been previously tested in in vitro models.

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10
PUBLICATIONS
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37.139
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H-INDEX HEAD OF UNIT

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9. Perrone G., Corradini P.: Autologous Stem Cell Transplantation for T-Cell Lymphomas. Semin Hematol 2014; 51: 59-66 [IF 2.462]

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PEDIATRICS ONCOLOGY

Our activity is based on the treatment and study of tumors typical of infancy, adolescence, and young adult with around 20% of patients over 18 years of age at diagnosis. This Unit is the largest for accrual of solid tumors in Italy. During 2014, 259 new patients were diagnosed and treated. Our clinical activities are managed in both inpatient and outpatient regimens, also involving education and sport continuation. In 2014, around 75 surgical and over 150 radiation treatments were performed for malignant tumors; post-operative courses are cared inside the Unit. It should be underlined that most of the over 80 patients with brain tumors undergo surgery and referred for adjuvant treatment despite the fact that a Neurosurgery Unit is not present at the INT. A total of 32 autologous bone-marrow transplantations were performed for high-risk or relapsed solid tumors.

Other activities of the Unit include:

- In brain tumors, we have ended procedures for the National coordination of the International Society of Pediatric Oncology trials for medulloblastoma and ependymoma. Study of biopsy surrogate serum biomarkers and miRNA profiles in DIPG (Diffuse Intrinsic Pontine Glyoma) is ongoing.
- Continued National coordination for stage 4 and poor prognosis neuroblastoma trial that includes intensive chemotherapy, autologous hemopoietic stem cell transplantation, surgery, radiotherapy, and immunotherapy with anti-GD2.
- As part of our strong involvement in the network ITCC (Innovative Therapies for Children with Cancer), we continue to offer relapsing patients with a number of further line therapies with new drugs that contribute to some clinical success.
- The Youth Project has promoted the creation of a new scientific Italian society: SIAMO (www.progettosiamo.it) aimed towards better care with inclusion in controlled trials and tailored post-treatment return to normal life with fertility, psychology, sport, education and job programs.
- Our Unit is the national coordinator for Wilm's tumor, germ cell tumors, metastatic Ewing sarcoma and soft tissue sarcomas different from rhabdomyosarcoma.

HEAD

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17
PUBLICATIONS
AS FIRST/LAST AUTHOR

31.654
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Chiaravalli S., Guzzo M., Bisogno G., De Pasquale M.D., Migliorati R., De Leonardis F., Collini P., Casanova M., Cecchetto G., Ferrari A.: Salivary gland carcinomas in children and adolescents: the Italian TREP project experience. Pediatr Blood Cancer 2014; 61: 1961-1968 [IF 2.562]
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9. Proserpio T., Ferrari A., Veneroni L., Giacon B., Massimino M., Clerici C.A.: Spiritual aspects of care for adolescents with cancer. Tumori 2014; 100: e130-e135 [IF 1.09]

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13. Spreafico F., Terenziani M., Testa S., Perotti D., Collini P., Piva L., Ardissino G.: Long-term renal outcome in adolescent and young adult patients nephrectomized for unilateral Wilms tumor. Pediatr Blood Cancer 2014; 61: 1136-1137 [IF 2.562]

14. Spreafico F., Terenziani M., Testa S., Perotti D., Collini P., Piva L., Ardissino G.: Response Re: Long-term renal outcome in adolescent and young adult patients nephrectomized for unilateral Wilms tumor. Pediatr Blood Cancer 2014; 61: 1714 [IF 2.562]

15. Spreafico F., Terenziani M., Van Den Heuvel-Eibrink M.M., Pritchard-Jones K., Levitt G., Graf N., Bergeron C., Massimino M.: Why should survivors of childhood renal tumor and others with only one kidney be denied the chance to play contact sports? Expert Rev Anticancer Ther 2014; 14: 363-366 [IF 2.279]

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17. Terenziani M., Spinelli M., Jankovic M., Bardi E., Hjorth L., Haupt R., Michel G., Byrne J.: Practices of pediatric oncology and hematology providers regarding fertility issues: a European survey. Pediatr Blood Cancer 2014; 61: 2054-2058 [IF 2.562]

IMMUNOHEMATOLOGY AND TRANSFUSION MEDICINE (SIMT)

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The Immunohematology and Transfusion Medicine Service (SIMT) provides clinical services to support patients in need of blood component therapy, cellular therapy, and therapeutic apheresis. The Unit has a ISO 9001:2008 Certification and is responsible for handling all aspects of donor recruitment for whole blood products, apheresis products, and the auto-transfusion program collects, for preparing the blood components and cellular therapy products and for blood testing (serology and immunohematology). During 2014, the Unit determined eligibility on 591 potential blood donors; 25% of these candidates were not accepted. The Unit collected a total of 7093 donations of whole blood and 1,077 donations by apheresis, platelet-pheresis, or plasmapheresis.
The Therapeutic Apheresis and Cellular Therapy subunit is responsible for collecting and processing hematopoietic stem cells and performs the necessary diagnostic tests required for bone marrow transplantation procedures. Therapeutic apheresis procedures to treat patients with blood diseases, including photopheresis and plasma exchange procedures, are also performed routinely (433 procedures).

The Unit includes the following specialized laboratories (about 175,000 tests/year):

- Immunohematology, performing analyses for antibody identification, antigenic typing, and hemolytic autoimmune disease
- European Federation of Immunogenetics certified and accredited HLA Laboratory, performing typing of patients and donors (related/unrelated)
- Serology and virology laboratories have introduced new tests such as everolimus and sirolimus and procalcitonin
- 1,830 tests to quantify cytomegalovirus DNA for monitoring virus load during CMV disease in immunocompromised patients

The laboratory also evaluated, in collaboration with the Urology Unit, the possibility to perform the HPV DNA test (with molecular biology technique) in men samples. In particular, it has been optimized for sample collection and DNA extraction to obtained better results.

CLINICAL PSYCHOLOGY

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Claudia Borreani, Psychologist
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SOCIAL WORKER
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The mission of the Unit is to support adult patients facing with cancer. Psychologists look at the entire range of psychosocial issues related to cancer and focus on the patient's internal and external resources. This is accomplished by providing expert clinical intervention based on scientific evidence and aimed at following the patient through the various phases of the disease and its treatment. The Unit is involved in Research and Education in the psycho-oncological field.
Clinical activity includes: individual psychological counseling; short psychotherapies; verbal and psycho-bodily groups; psycho-educational groups; family therapies; psychological assessment. During 2014, 3,000 clinical outpatient and inpatient consultations were carried out.
Several sessions with psycho-educational groups were conducted: a) The Itaca program, which involves patients and their relatives in educational and psychological support group activities; b) Stress management training and relaxation imagery groups; c) psycho-existential groups. "Giocoparola Ambulatory" give a specific support to ill parents in the communication with their children about the disease.
Multidisciplinary clinical projects to evaluate and support cancer patients undergoing liver transplant and to evaluate and support decision making in BRCA1/2 carriers are being carried out in collaboration.
Research activity is oriented on evaluation of subjective impact of cancer and its treatment on psychological, relational, and quality of life dimensions.
During 2014, the following studies were conducted:

- Observational study to assess the impact of aromatase inhibitors on the psychological dimension in breast cancer patients.
- Expectation, experiences, and preferences of patients and clinicians involved in the informed consent process for phase 2 and 3 clinical trials.
- Psychological determinants of preventive choices in BRCA1/2 carriers.

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2. Borreani C., Giordano A., Falautano M., Lugaresi A., Martinelli V., Granella F., Tortorella C., Plasmati I., Radaelli M., Farina D., Dalla Bella E., Bianchi E., Acquarone N., Miccinesi G., Solari A.: Experience of an information aid for newly diagnosed multiple sclerosis patients: A qualitative study on the SIMS-Trial. Health Expect 2014; 17: 36-48 [IF 2.852]
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3
PUBLICATIONS
AS FIRST/LAST AUTHOR

10.038
I.F. AS FIRST/LAST AUTHOR

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SUPPORTIVE CARE IN CANCER

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The Supportive Care in Cancer Unit (SCCU) was established in 2009. The treatments carried out are compliant with the guidelines of the WHO, MASCC, ESMO, and AIOM. We work in integration with INT Units and administer therapies according to the different clinical problems caused by cancer, by anticancer treatments, and/or co-morbidities. All patients are regularly assessed for the presence and intensity of physical and psychological symptoms, and spiritual and social needs. In a separate space of the SCCU the patients have the support of a chaplain and/or social worker and/or psychologists during infusion of medications.
In 2014, there were 5,239 visits, 4,275 infusions of drugs or hydration, 1,065 transfusions of hemoderivatives and 668 IV treatments with bisphosphonates and denosumab. The team consists of 3 physicians, 3 nurses, 2 health technicians, and 8 volunteers trained by the Italian League Against Cancer. The 3 physicians, specialized, respectively, in Medical Oncology and Clinical Pharmacology, in Oncology/Chemotherapy, and in Internal Medicine and also have also a background in Pain Management and Palliative Care. The team works closely with the Chaplain, the psychologists and one social worker and with all the physicians of the different Units.
Research activity is performed in collaboration with both internal and national and international structures, and involves patients on active cancer treatment and follows pharmacological and non-pharmacological pattern of treatment. The Unit collaborates with WHO, ESMO, MASCC, IAHPC, ISPO (Florence), Consorzio Mario Negri Sud (Chieti), Campus Biomedico (Rome), Istituto Scientifico Romagnolo, and the University of Milan and Bologna.
The Unit has set up theoretical and practical training for oncologists, internists, geriatricians, radiotherapists, primary care physicians, and nurses with the aim of diffusing a model of integrated supportive care.

SELECTED PUBLICATIONS

1. Pessi M.A., Zilembo N., Haspinger E.R., Molino L., Di Cosimo S., Garassino M., Ripamonti C.I.: Targeted therapy-induced diarrhea: A review of the literature. Crit Rev Oncol Hematol 2014; 90: 165-179 [IF 4.046]
2. Ripamonti C.I., Bandieri E., Pessi M.A., Maruelli A., Buonaccorso L., Miccinesi G.: The Edmonton Symptom Assessment System (ESAS) as a screening tool for depression and anxiety in non-advanced patients with solid or haematological malignancies on cure or follow-up. Support Care Cancer 2014; 22: 783-793 [IF 2.495]
3. Ripamonti C.I., Bossi P., Santini D., Fallon M.: Pain related to cancer treatments and diagnostic procedures: A no man's land? Ann Oncol 2014; 25: 1097-1106 [IF 6.578]
4. Ripamonti C.I., Prandi C., Costantini M., Perfetti E., Pellegrini F., Visentin M., Garrino L., De Luca A., Pessi M.A., Peruselli C.: The effectiveness of the quality program Pac-IficO to improve pain management in hospitalized cancer patients: A before-after cluster phase II trial. BMC Palliat Care 2014; 13: 15 [IF 1.787]

4
PUBLICATIONS
AS FIRST/LAST AUTHOR

14.906
I.F. AS FIRST/LAST AUTHOR

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ANESTHESIA, INTENSIVE CARE, PAIN THERAPY, AND PALLIATIVE CARE

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CECILIA GAVAZZI

The Department has a key position in the hospital, and collaborates closely with all the other Clinical Departments for the treatment of cancer patients. The most demanding collaboration is certainly the perioperative treatment of surgical patients, but efficacious treatment of pain and symptom relief in the advanced phase of illness are increasingly recognized as a right of patients and quality of life is important as is the duration of life.

Educating students in anesthesia, critical care medicine, palliative care, pain medicine and clinical nutrition in postgraduate and master courses and promoting research in this field is important as is the clinical activity.

CLINICAL ANESTHESIA AND INTENSIVE CARE

Surgery is a key component of modern oncological treatment as anesthesia and perioperative medicine makes surgery possible, safe, and acceptable by patients. The Anesthesia and Perioperative Medicine Service has a key role in Operating Rooms and postoperative care in the Intensive Care Unit (ICU) and wards to support invasive procedures in radiotherapy, interventional radiology, and pediatric imaging as well as endoscopic procedures. The bulk of the activity is in 9-10 operating rooms, scheduled for 70-75 hrs/day with 7-8,000 surgical procedures a year with about 5% urgent operations and 30-35 liver transplants. Improvements in postoperative multimodal analgesia have shown good results, allowing faster mobilization and earlier postoperative recovery. In our outpatient anesthesiology clinic, we also offer counseling and motivation. The Postoperative Pain Service, run by specialized nurses and anesthesiology residents is supervised by a senior anesthesiologist and by a colleague from the Chronic Pain Medicine Unit. About 500 patients are treated with epidural catheters yearly, and between 1,000 and 1,500 with a patient-controlled pump. The new set-up of the **Intensive Care Unit** has permitted remarkable change in treatment modalities and strategies; communication within the staff and between patients/relatives and primary physicians has markedly improved. The clinical anesthesia team (together with the radiologists) is also deeply involved in the venous access program: given the treatment modalities in our institution, many patients need long term vascular accesses; in our units, about 600 central lines as long-term catheter and 1,000 short-term catheters were placed last year and the need is continually expanding.
The training program for residents in the Anesthesia and Intensive Care Program at the University of Milan is established and allows 5-7 young physicians/year to specialize in clinical anesthesia and acute postoperative pain therapy.

6
PUBLICATIONS
AS FIRST/LAST AUTHOR
11.477
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20
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Colombo J., Arena A., Codazzi D., Langer M.: Intra-abdominal candidiasis and probiotics: We know little but it's time to try. Intensive Care Med 2014; 40: 297-298 [IF 5.544]
2. Langer M., Castellari R., Locatelli P., Sini E., Torresani M., Facchini R., Moser R.: An integrated approach to safety-driven and ICT-enabled process reengineering: Methodological advice and a case study. Stud Health Technol Inform 2014; 201: 203-210 [IF 0]
3. Piccioni F., Colombo J., Fumagalli L., Lassola S., Previtali P., Ammatuna M., Langer M.: Inadvertent high central neuraxial block and possible total spinal anaesthesia occurring after nerve stimulation guided thoracic paravertebral block. Anaesth Intensive Care 2014; 42: 270-271 [IF 1.47]
4. Piccioni F., Fumagalli L., Garbagnati F., Di Tolla G., Mazzaferro V., Langer M.: Thoracic paravertebral anesthesia for percutaneous radiofrequency ablation of hepatic tumors. J Clin Anesth 2014; 26: 271-275 [IF 1.21]
5. Piccioni F., Mariani L., Bogno L., Rivetti I., Tramontano G.T., Carbonara M., Ammatuna M., Langer M.: An acceleromyographic train-of-four ratio of 1.0 reliably excludes respiratory muscle weakness after major abdominal surgery: A randomized double-blind study. Can J Anesth 2014; 61: 641-649 [IF 2.495]
6. Previtali P., Fumagalli L., Ammatuna M., Materazzo C., Colombo C., Langer M.: Coronary spasm under combined epidural-general anesthesia. Case report. Exp Clin Cardiol 2014; 20: 1997-1999 [IF 0.758]

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HEALTHCARE ASSISTANTS

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PALLIATIVE CARE, PAIN THERAPY, AND REHABILITATION

The clinical and research mission of the Unit encompasses palliative care and pain management and cancer rehabilitation.

Palliative care and pain management

The palliative care program has a comprehensive clinical and research structure, fully integrated with the primary oncological clinical activities performed in the surgical, radiation therapy, and medical oncology Units. The pain therapy clinic is active 5 days a week and sees about 30 to 40 patients per day (930 new patients, 6,158 follow-up visits, 7,189 multidimensional symptom assessments, and 5,100 therapies in 2014) with the additional availability of palliative care day-hospital admissions (1,072 day-hospital admissions in 2014).
The inpatient hospice facility is based on a 10 bed specialized Unit and offers admission to more complex clinical conditions for symptom control, terminal end-of-life care and respite care. In 2014, 187 patients were admitted. A fully multidisciplinary and multidimensional approach is provided. An inpatient consultation service is offered to liaise with medical and surgical clinical units to improve symptom control and plan care transitions to hospice, or home care. This service saw 470 new patients in 2014. The institutional home care service follows about 150 patients each year with a multiprofessional team approach (two palliative care doctors, 4 nurses and 1 psychologist), offering 24 hr contact with the team.

Cancer rehabilitation

The clinical rehabilitation program outpatient clinic has specific programs for the treatment of pediatric patients undergoing antineoplastic therapy and for multimodal decongestive therapy of lymphedema. In the outpatient clinic, more than 5,300 medical evaluations are performed yearly with about 14,000 physical therapy sessions. Rehabilitation interventions are available for all inpatients of clinical Units of the cancer center. Medical evaluations were done in 449 inpatients in 2014, and rehabilitation therapists provided about 10,500 therapeutic interventions.

HEAD

Augusto T. Caraceni, MD

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NURSES

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ADMINISTRATIVES

Manuela Brusati, Loredana D'Urso, Chiara Vinuzzi

SELECTED PUBLICATIONS

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2. Brunelli C., Kaasa S., Knudsen A.K., Hjermstad M.J., Pigni A., Caraceni A.: Comparisons of patient and physician assessment of pain-related domains in cancer pain classification: Results from a large international multicenter study. J Pain 2014; 15: 59-67 [IF 4.216]
3. Granata R., Bossi P., Bertulli R., Saita L.: Rapid-onset opioids for the treatment of breakthrough cancer pain: Two cases of drug abuse. Pain Med 2014; 15: 758-761 [IF 2.243]

3
PUBLICATIONS
AS FIRST/LAST AUTHOR

12.295
I.F. AS FIRST/LAST AUTHOR

40
H-INDEX HEAD OF UNIT

CLINICAL NUTRITION

HEAD
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Michela Bassano, RD
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Anna Armonti, Franca Filincieri, Carmen Maiorana, Lorena Riva

The major goal of the structure is prevention and treatment of malnutrition. Malnutrition is a well known negative prognostic factor in the final prognosis of cancer patients. Malnutrition reduces tolerance to treatment, increases morbidity and mortality, and deteriorates the quality of life. The structure provides nutrition interventions throughout all the phases of the oncologic course, from diagnosis, surgery, chemotherapy, and radiotherapy to allow the successful completion of planned oncological treatment and preserve an acceptable quality of life. Nutrition therapy is tailored for different cancer types and oncological treatments.
In accordance with European Society of Clinical Nutrition and the Organisation of European Cancer Institutes requirements, nutritional screening is undertaken in all patients with high risk of malnutrition. Patients affected by any form of malnutrition are included in a comprehensive nutrition program which consists of nutritional status monitoring and personalized nutrition therapy, mainly with artificial nutrition, enteral and parenteral, and diet therapy. For patients who need artificial nutrition for a prolonged period, specialized nurses and logistics are organized, and patients are discharged on home artificial nutrition.
In 2014, 224 (115 GI cancers; 41HN; 23 sarcoma; 21 pediatric; 24 other) hospitalized patients were treated with personalized nutrition for a total of 1,823 days of therapy. Furthermore, 447 consultancies and 1305 outpatient visits were performed. Special care has been given in 2014 to nutritional problems in patients with upper GI cancer, in a comprehensive multidisciplinary group and specific algorithm has been developed and implemented. The structure is a major reference center for home artificial nutrition in our region.

DIAGNOSTIC IMAGING AND RADIOTHERAPY

DIRECTOR OF DEPARTMENT
ALFONSO MARCHIANÒ
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RADIATION ONCOLOGY 1
RICCARDO VALDAGNI

RADIATION ONCOLOGY 2
CARLO FALLAI

RADIOLOGY 1 (FUNCTIONAL IMAGING)
PIETRO PANIZZA

RADIOLOGY 2 (DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY)
ALFONSO MARCHIANÒ

NUCLEAR MEDICINE
FLAVIO CRIPPA

MEDICAL PHYSICS
EMANUELE PIGNOLI

The Department is a large multidisciplinary structure comprising different areas of clinical activity and research, where many disciplines work together in very close interaction. The Department is equipped with a large number of high-technology facilities and supports the implementation of biologic imaging and image-guided contouring radiotherapy. The development and study of several specific radiopharmaceuticals has led to the improvement of targeted radiotherapy. These achievements are possible thanks to the strong collaboration of many experts from the fields of physics, biotechnology, biology, radiopharmacy, instrumentation, and medical sciences.

RADIATION ONCOLOGY 1

Radiation Oncology 1 provides irradiation to patients with breast, genitourinary, gastrointestinal, and lung cancers as well as bone and soft tissue sarcomas, lymphomas, and pediatric cancers. Multidisciplinary management represents a priority to deliver high quality therapies.
In close collaboration with the Medical Physics Unit, particular efforts are dedicated to improve new technologies in daily clinical practice, such as IMRT (Intensity Modulated Radiotherapy), VMAT (Volumetric Modulated Arc Therapy), and 3 dimensional conformal radiotherapy, with IGRT (Image Guided Radiation Therapy) in each clinical setting. In 2014, almost 50% of treated patients received irradiation with one of the more innovative and advanced intensity modulated techniques. The Calypso 4D Localization System, a tool that utilizes radiofrequency waves to align the prostate very precisely before and during each treatment session, has been operating since 2012.
In 2014, 86 patients with hematological malignancies were administered radiotherapy. Advanced technologies like PET-CT image co-registration to delineate target volumes and organs at risk, IMRT, VMAT and IGRT techniques for treatments, are routinely applied. These techniques are also used with thoracic malignancies (Non Small Cell Lung Cancer, Small Cell Lung Cancer, thymoma) including Stereotactic Body Radiation Therapy (SBRT).
Radiation Oncology 1 also offered palliative/symptomatic RT to 454 patients with metastatic disease. To limit discomfort to this very fragile subset of patients as much as possible, in April 2014 a dedicated outpatient clinic was activated to offer metastatic patients a specialized fast track start of symptomatic RT. All clinically tested hypofractionated schedules and advanced RT technologies are utilized to optimize treatment and limit the number of accesses to the Unit.
The Unit is extensively involved in clinical research and scientific activity involving radiotherapy of soft tissue sarcomas, and breast, genitourinary, and gastrointestinal cancers as well as radiotherapy in pediatric patients.

HEAD

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Pediatric Radiotherapy

Lorenza Gandola, MD (Director)

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Mariarita Cassese

DATA MANAGER

Laura Andreoli

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1. Bellardita L., Rancati T., Valdagni R.: Editorial Comment to Health-related quality of life after carbon-ion radiotherapy for prostate cancer: A 3-year prospective study. Int J Urol 2014; 21: 375-376 [IF 1.798]
2. Bellardita L., Villa S., Valdagni R.: Living with untreated prostate cancer: Predictors of quality of life. Curr Opin Urol 2014; 24: 311-317 [IF 2.115]
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5
PUBLICATIONS
AS FIRST/LAST AUTHOR

15.091
I.F. AS FIRST/LAST AUTHOR

27
H-INDEX HEAD OF UNIT

RADIATION ONCOLOGY 2

HEAD
Carlo Fallai, MD

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RESEARCH STAFF
Monica Alicia Garcia, MD; Anna Maria Mileo, MD

RADIATION ONCOLOGY TRAINEES
Nicola Alessandro Iacovelli, Brigida Pappalardi

Radiation Oncology 2 has an inpatient section with eight beds for patients needing hospitalization for radiotherapy or radio-chemotherapy procedures, supportive therapy, and interventional manoeuvres. During 2014, there were 315 hospitalizations. Of these, 256 patients underwent radiotherapy procedures.

Radiotherapy of Head and Neck Cancer is an essential part of the activities of the Head and Neck Cancer multidisciplinary group. All patients are subjected to CT simulation, generally with contrast medium, and personalized positioning devices (masks). In 2014, 178 patients affected with head and neck cancer were irradiated curatively or palliatively. In 2013, we began using an innovative radiotherapy technique (Volumetric Arc Therapy - VMAT photons with hadrontherapy boost) in patients with tumors of the paranasal sinuses.

The radiation treatment of gynecologic cancers is also an essential part of our activities. During 2014, 81 patients were treated with curative intent with external beam radiotherapy were irradiated with VMAT. Overall, 145 cycles of concurrent chemotherapy were given.

Brachytherapy for prostate cancer was carried out in collaboration with the multidisciplinary team of the prostate. Patients who do not have limitations (claustrophobia) or contraindications (e.g. femoral prostheses) have carried out a prostate MRI with endorectal coil that can be used as a reference in the subsequent treatment planning. The treatment consists of two sessions of interstitial HDR-BCT (High-Dose Rate Brachytherapy) under continuous ultrasound guidance. Twelve procedures were performed in 2014.

Palliative RT/stereotactic brain RT Besides palliation of primary tumors, 191 additional palliative treatments were performed during 2014. In particular, 153 treatments were made for patients suffering from cerebral metastases. In 2014, there was an increase in the use of stereotactic radiotherapy of the brain. This can offer the patient focused radiation therapy, limited to the site of metastases.

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2
PUBLICATIONS
AS FIRST/LAST AUTHOR

7.468
I.F. AS FIRST/LAST AUTHOR

12
H-INDEX HEAD OF UNIT

RADIOLOGY 1 (FUNCTIONAL IMAGING)

The Unit includes traditional radiology (chest and bones X-rays), breast imaging, and MRI. In 2014, the Unit performed about 29,000 X-ray examinations, 12,000 MRI scans, and 28,000 breast imaging examinations, including 800 breast MRI and 900 interventional breast procedures.
Breast imaging has all the diagnostic and interventional tools needed in an advanced comprehensive cancer center, where patients are referred from other centers. The Unit has 2 FFDM (Full Field Digital Mammography) units equipped with breast tomosynthesis, 3 breast ultrasound units, 1 stereotactic table, 2 MRI 1.5 T units with breast coils, and a VABB system (Vacuum Assisted Breast Biopsy) for percutaneous image-guided biopsies. Specific attention has been devoted to breast MRI in high risk patients and BRCA mutation carriers, within the surveillance program, and for pre-operative staging of cancer. Interventional examinations consist of pre-operative localization of non-palpable lesions and assessment of breast masses or microcalcifications by core-needle biopsies or vacuum-assisted biopsies with ultrasonographic, stereotactic, or MRI guidance. These interventions are a crucial part of a multidisciplinary approach to provide the optimal assistance for surgical planning.
The Unit is continuously improving and working in this issue with ongoing collaboration with the Radiotherapy Unit for treatment planning for uterine cancer with a research feasibility study. Furthermore, response to treatment is under investigation for breast cancer and oropharyngeal squamous cell carcinoma. The Unit is involved in several multicenter ongoing MRI studies; fields of scientific interest are: pediatric MRI, focused on neuro-oncology, soft tissue sarcomas, oro-nasopharyngeal carcinoma, and colorectal cancer. The Unit has a number of ongoing collaborations at the national and international levels, many of which involve breast and prostate cancer and is in charge of writing the national breast imaging guidelines for Seno-network.

HEAD

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Daniele Vergnaghi, MD (Head)

Radiology and Magnetic Resonance GI Trac

Davide Scaramuzza, MD (Head)

Pediatric Magnetic Resonance

Paolo Potepan, MD (Head)

Breast Imaging Unit

Gianfranco Scaperrotta, MD (Head)

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RADIOLOGY 2 (DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY)

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Diagnostic oncology and interventional-oriented radiology represent the core activity of the Unit. Inpatients and outpatients undergo diagnostic work-up that includes the different steps of patient management: primary cancer diagnosis, staging, follow-up and monitoring after surgery, chemotherapy and radiotherapy. Two CT scanners are available, both with fast multislice scanning capacity. About 23,000 diagnostic examinations per year and a substantial number of interventional radiologic procedures are carried out. The lung cancer screening program (bioMILD) with "low dose" spiral CT continued in 2014. We performed about 2,000 low-dose spiral CT, and are currently testing a system of computer-aided detection of pulmonary nodules. A total of 16,000 ultrasound examinations were carried out.

Interventional radiology activities include long-term venous central catheter placement, embolization, and chemoembolization for regional cancer treatment. Intralesional radiofrequency ablation based-methods, such as the chemo-interventional procedures consisting in loco-regional drug delivery for malignancies of the liver, head and neck, pelvis and limbs, are successfully performed.

In the biliary field, definitive jaundice palliation with drainages or stents, curative dilatation of cicatricial stenoses, drainage of fistulas, transluminal biopsies were performed. In the gastrointestinal field, in addition to treatment of complications (transluminal drainage of fluid collections, dilatation of cicatricial stenoses) interventional radiology played a basic role in nutritional support (percutaneous gastrostomy, positioning of feeding tubes, stenting of inoperable stenoses). In the gastrointestinal diagnostic field, examinations of functional disorders represent a relevant part of the activity.

During 2014, over 1,200 vascular and non-vascular interventional procedures, over 500 long-term venous central catheters, and over 1,100 percutaneous biopsies in various body districts were performed.

SELECTED PUBLICATIONS

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2. Spreafico C., Maccauro M., Mazzaferro V., Chiesa C.: The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization (TARE). Eur J Nucl Med Mol Imaging 2014; 41: 634-638 [IF 5.217]

2
PUBLICATIONS
AS FIRST/LAST AUTHOR

8.109
I.F. AS FIRST/LAST AUTHOR

23
H-INDEX HEAD OF UNIT

NUCLEAR MEDICINE

HEAD

Flavio Crippa, MD

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ADMINISTRATIVE

Rosangela Ghilardi

The Nuclear Medicine Unit is fully-inclusive, including integrated sections, where various nuclear medicine procedures for imaging and therapy are performed in adult and pediatric cancer patients. For nuclear medicine therapies, patients can be hospitalized in isolated and protected rooms inside the Metabolic Therapy and Endocrinology Unit. An endocrine outpatient clinic is available. The main technical equipment of the Department are: one 17 MeV cyclotron, 2 radiochemistry laboratories for production of beta- and gamma-emitter radiopharmaceuticals, 1 bone densitometry scan, 2 stand-alone gamma cameras, 1 state-of-the-art SPECT/CT equipped with an innovative reconstruction software conceived to be quantitative, 2 PET/CT scanners installed in the PET Unit of the Department. A laboratory equipped with a micro-PET system for pre-clinical imaging of small animals tumor models is available.

In 2014, the clinical activity was as follows: about 5,500 conventional scintigraphic procedures, 1,700 bone densitometry scans, and 5,600 PET/CT scans. About 400 nuclear medicine treatments with appropriate radiopharmaceuticals were performed in patients affected by thyroid cancer (33% of treatments) and other type of malignancies including neuroendocrine tumors, lymphomas, malignant neuroectodermal tumors, primary liver cancer, and bone metastases; 3,500 outpatient clinical examinations were performed.

The main clinical research activities involved:

- SPECT and PET diagnostic procedures to study tumor function and metabolism;
- brain C-11 methionine PET/CT examination in glioma patients;
- radiolabelled oncotropic tracers as a prognostic index of tumors;
- new methodologic approaches to visualize metastatic lymph nodes;
- treatment of hepatocarcinomas by intra-arterial radioembolization with Y-90 microspheres;
- treatment of NET by association of somatostatin analogues labeled with dual radioisotopes (Y-90 and Lu-177);
- optimization of radiometabolic therapy by developing different dosimetric methods.

4
PUBLICATIONS
AS FIRST/LAST AUTHOR

17.69
I.F. AS FIRST/LAST AUTHOR

25
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Chiesa C., Lambert B., Maccauro M., Ezziddin S., Ahmadzadehfar H., Dieudonne A., Cremonesi M., Konijnenberg M., Lassmann M., Pettinato C., Strigari L., Vanderlinden B., Crippa F., Flamen P., Garin E.: Pretreatment dosimetry in HCC radioembolization with 90Y glass microspheres cannot be invalidated with a bare visual evaluation of 99mTc-MAA uptake of colorectal metastases treated with resin microspheres. J Nucl Med 2014; 55: 1215-1216 [IF 5.563]

2. Giannatempo P., Alessi A., Miceli R., Raggi D., Farè E., Nicolai N., Serafini G., Padovano B., Piva L., Biasoni D., Torelli T., Catanzaro M., Stagni S., Maffezzini M., Mariani L., Gianni A.M., Sonpavde G., Salvioni R., Necchi A., Crippa F.: Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. Clin Genitourin Cancer 2014; 12: 433-439 [IF 1.693]

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4. Spreafico C., Maccauro M., Mazzaferro V., Chiesa C.: The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization (TARE). Eur J Nucl Med Mol Imaging 2014; 41: 634-638 [IF 5.217]

MEDICAL PHYSICS

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During 2014, the clinical activities of the Medical Physics Unit in favor of the two complex structures of radiotherapy mainly consisted in the study, planning, and optimization of radiation treatments for new patients. A total of 2,291 patients were treated of which: 67 were treated by brachytherapy and 2,224 by external beam radiotherapy. Many of these treatments required the delivery of different dose levels to different target volumes, so that the radiation treatment normally had to be divided into different phases. Every single phase required a specific treatment plan and the doses of different phases were then summated, thus allowing evaluation of the dose distribution of overall treatment.

A mandatory activity for the Medical Physics Unit is to participate in quality assurance programs for both radiotherapy and all radiological equipment. A lab is active to manage dosimetry, film-badge and thermoluminescent (TL) dosimeters, for controlling personnel exposed to ionizing radiation. In the 2014, our lab processed more than 8,200 films and 1,450 TL dosimeters. The service also provides support to specific dosimetric questions in radiation therapy, for in vivo dosimetry, or in some diagnostic checks on X-ray equipment. In 2014, the unit assessed all artificial optical radiation sources available at the Institute to quantify the risks arising from the different sources: more than 37 types of sources were evaluated, ranging from ultraviolet lamps to operating theater lights.

Clinical research and scientific activities involve the following:

- Preliminary study to implement adaptive radiotherapy
- MR-guided brachytherapy
- In vivo dosimetry in brachytherapy
- Manage intrafraction motion in radiotherapy of prostate cancer
- Radiation dose levels and neurocognitive damage in pediatric patients
- Study of natural fluorescence spectroscopy of human blood plasma for colorectal cancer
- Dose in digital mammography
- Optimization of CT dose for pediatric patients
- Optimization of image quality in brain CT exam

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2. Carrara M, Tenconi C, Rossi G, Guilizzoni R, Borroni M, Cerrotta A, Fallai C, Gambarini G, Vedda A, Pignoli E. Temperature dependence of a Ce3+ doped SiO2 radioluminescent dosimeter for in vivo dose measurements in HDR brachytherapy. Radiat Meas 2014; 71:324-328 [I.F. 1.14]
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4
PUBLICATIONS
AS FIRST/LAST AUTHOR

8.326
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

PATHOLOGY AND LABORATORY MEDICINE

DIRECTOR OF DEPARTMENT
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giuseppe.pelosi@istitutotumori.mi.it

ANATOMIC PATHOLOGY 1
MARIA LUISA CARCANGIU

ANATOMIC PATHOLOGY 2
GIUSEPPE PELOSI

LABORATORY MEDICINE
DANIELE MORELLI

The mission of the Department is to provide accurate diagnoses and information of prognostic and therapeutic value to clinicians. The activities of Surgical Pathology, Molecular Pathology, Cytopathology and Autopsy Pathology are carried out in the two Anatomic Pathology Units, while an extensive activity of laboratory tests and microbiological investigations is carried out at the Laboratory Medicine Unit, all based on state-of-the-art techniques and quality certification (ISO9001;2008, until 2017).

ANATOMIC PATHOLOGY 1, 2 AND LABORATORY MEDICINE

Extensive pheno-genotyping and assessment of predictive and/or prognostic factors are integrant parts of diagnosis and research activities aiming at the best clinical management of the patients, as well as at developing diverse research lines in the field of human oncology.

The Department of Pathology includes four functional Units (Dermatopathology and Cytopathology; Hematopathology; Soft Tissue Bone Pediatric and Childhood Pathology; Urological, Male Genital Tract and Adulthood Pathology) and is organized for diagnosis and research on the basis of the criterion of organ disease with different specialists Pathologists in the different fields of human cancers. Besides a diagnostic laboratory supplied with the most updated equipment for standard histological and cytological investigations, the Department of Pathology includes two functional sections of immunohistochemistry and molecular pathology supplied with automatized instruments that are able to offer extensive immunophenotyping and molecular characterization of tumors tissues by using a large array of monoclonal antibodies, fluorescence and bright-field in situ hybridization, cytofluorimetry, real-time PCR, direct sequencing and next generation sequencing techniques. The two Units of Anatomic Pathology, during 2014, performed many thousands of histological, cytological and molecular diagnoses (surgical specimens: 10,078; biopsy samples: 9,990; examinations for second opinion: 3,224; papanicolaou tests: 15,903; cytological samples: 2,652; bone marrow smears: 179; molecular assays: 8,498), to witness the great relevance of them to the clinical management of patients.

The Department is also engaged in the Institutional human frozen tumor tissue collection for banking, a project aimed at the creation of an extensive raising of human tissues that is not restricted to a specific organ or disease type but cover most human cancers, as well as in a telepathology project involving several Italian cancer institutes.

The Department also belongs to the education network of the Postgraduate Medical School in Pathology of the University of Milan School of Medicine.

HEAD ANATOMIC PATHOLOGY 1

Maria Luisa Carcangiu, MD

Urological, Male Genital Tract and Adulthood Pathology Unit

Maurizio Colecchia, MD

HEAD ANATOMIC PATHOLOGY 2

Giuseppe Pelosi, MD

Hematopathology Unit

Antonello D. Cabras, MD

Soft Tissue Bone Pediatric and Childhood Pathology Unit

Paola Collini, MD

Dermatopatology and Cytopathology Unit

Gabrina Tragni, MD

CLINICAL RESEARCH STAFF

Antonella Aiello, Biol Sci D; Marta Barisella, MD; Antonello D. Cabras, MD; Paola Collini, MD; Maurizio Colecchia, MD; Alessandra Fabbri, MD; Annunziata Gloghini, Biol Sci D; Massimo Milione, MD; Biagio Paolini, MD; Alessandro Pellegrinelli, MD; Federica Perrone, Biol Sci D; Pasquale Quattrone, MD; Carla Riva, Biol Sci D; Mario Ruggeri, Biol Sci D; Angelica Sonzogni, MD; Elena Tamborini, Biol Sci D; Adele Testi, Biol Sci D; Barbara Valeri, MD

RESEARCH STAFF

Manuela Bimbatti, MD; Giorgia Leone, MD; Alessio Pellegrinelli, MD; Ester Antelmi, Biol Sci D; Adele Busico, Biol Sci D; Elena De Paoli, Biol Sci D; Ambra Gualeni, Biol Sci D; Benedetta Picciani, Biol Sci D; Giulio Settanni, Biol Sci D; Francesca Testa, Biol Sci D; Laura Vittoria, Biol Sci D; Chiara Volpi, Biol Sci D

Personnel involved in specific research activities

Silvana Pilotti, MD (responsible for some GIST and chordoma research projects)

TECHNICIANS

Maria Grazia Bonora; Renata Borchini; Rita A. Carminati; Giovanni Centonze; Luca Cesana; Alessandra Chinosi; Marilena Colantuono; Silvia Colombo; Daniela De Bari; Francesca Dominoni (Chief-Technician); Alessandra Elli; Maria Grazia Facciorusso; Elena Fomiatti; Angelo Gaito; Daniela Galbiati; Morena Gobbo; Rosangela Intorre; Teresa Labella; Matteo Marcuzzo; Alessia Mietta; Marzia Mietta; Loretta Missiato; Maria Luisa Moiraghi; Margherita Mondini; Paola Murè; Marta Orsenigo; Desirè Parimbelli; Katia Ponzoni; Silvia Redaelli; Consiglia Sgura

ADMINISTRATIVES

Patrizia Cangioli; Margherita Cariglia; Cosima Ciccarese; Maria Teresa Codecasa; Maria Cristina Di Bartolomeo; Roberto Ferrari; Maria Morelli; Alda Tosi; Enrica Colzani

HEALTHCARE ASSISTANTS

Paolo Castioni; Massimo Festa; Paola Tonielli; Anna Urbano

FELLOWS

Antonino Belfiore, Biol Sci D; Fabio Bozzi, Biol Sci D; Tiziana Negri, Biol Sci; D; Gian Paolo Dagrada, Biol Sci D; Silvia Brich, Biol Sci D; Elena Conca, Biol Sci D; Barbara Cortelazzi, Biol Sci D; Rosalin Dolores Spagnuolo, Biol Sci D

In 2014 the **Laboratory Medicine Unit** carried out about two millions of tests, which have been conducted using high-quality standards to assure the best reliability of results, in turn continuously monitored inside national and international External Quality Assessment (EQA) projects. Laboratory Medicine Unit performs biological tests and microbiological investigations that contribute to the diagnosis, prognosis and monitoring of oncologic patients submitted to conventional and experimental therapies inside clinical trials.

LABORATORY MEDICINE

Daniele Morelli, Biol Sci D (Head)

CLINICAL RESEARCH STAFF

Mariachiara Bonini, Biol Sci D; Eutilia Conte, Biol Sci D; Antonio Mastroianni, Biol Sci D; Roberta Rossi, Biol Sci D; Loredana Simoni, MD; Giovanna Viola, Biol Sci D

TECHNICIANS

Giuseppina Ballabio, Rosella Bonfanti, Chiara Brusati, Maria R. Carati, Maria R. Cattaneo, Maria V. Corengia, Carlo Maggi, Roberta Marchetti, Valerio Motta, Giovanni Nido, Giuseppa Perrucci, Pia S. M. Picco, Marco Ranzani, Nicola Salvatore, Federica Sozzani

ADMINISTRATIVE

Santa Zingone

24
PUBLICATIONS
AS FIRST/LAST AUTHOR

69.029
I.F. AS FIRST/LAST AUTHOR

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SELECTED PUBLICATIONS

1. Bozzi F., Manenti G., Conca E., Stacchiotti S., Messina A., Dagrada G., Gronchi A., Panizza P., Pierotti M.A., Tamborini E., Pilotti S.: Development of transplantable human chordoma xenograft for preclinical assessment of novel therapeutic strategies. Neuro-Oncology 2014; 16: 72-80 [IF 5.286]
2. Carbone A., Gloghini A.: CD75: A B-cell marker which should not be forgotten in lymphocyte predominant Hodgkin lymphoma. Am J Hematol 2014; 89: 449 [IF 3.477]
3. Carbone A., Gloghini A.: Emerging issues after the recognition of in situ follicular lymphoma. Leuk Lymphoma 2014; 55: 482-490 [IF 2.605]
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5. Carbone A., Tripodo C., Carlo-Stella C., Santoro A., Gloghini A.: The role of inflammation in Lymphoma. Adv Exp Med Biol 2014; 816: 315-333 [IF 2.012]
6. Colecchia M.: Observations on the paper "sclerosing sertoli cell tumor of the testis: A clinicopathologic study of 20 cases" by Kao et al. Am J Surg Pathol 2014; 38: 1160 [IF 4.592]
7. Collini P., et al.: Tall cell variant of papillary thyroid carcinoma in children: Report of three cases with long-term follow-up from a single institution. Int J Surg Pathol 2014; 22: 499-504 [IF 0.961]
8. De Cecco L.D., Negri T., Brich S., Mauro V., Bozzi F., Dagrada G., Disciglio V., Sanfilippo R., Gronchi A., Maurizio D'Incalci, Casali P.G., Canevari S., Pierotti M.A., Pilotti S.: Identification of a gene expression driven progression pathway in Myxoid liposarcoma. Oncotarget 2014; 5: 5965-5977 [IF 6.627]
9. Di Bernardo A., Mussetti A., Aiello A., De Paoli E., Cabras A.: Alternate clonal dominance in richter transformation presenting as extranodal diffuse large B-cell lymphoma and synchronous classic hodgkin lymphoma. Am J Clin Pathol 2014; 142: 227-232 [IF 3.005]
10. Fellegara G., Gabba S., Dorji T., De Luca G., Colecchia M.: Observations on Aron et al's "utility of a triple antibody cocktail intraurothelial neoplasm-3 (IUN-3 CK20/CD44s/p53) and α-methylacyl-CoA racemase (AMACR) in the distinction of urothelial carcinoma in situ (CIS) and reactive urothelial atypia". Am J Surg Pathol 2014; 38: 1013-1015 [IF 4.592]
11. Gloghini A., Carbone A.: Primary central nervous system lymphoma. J Neurosci Rural Pract 2014; 6: 2-3 [IF 0]
12. Gloghini A., et al.: Primary effusion lymphoma: Secretome analysis reveals novel candidate biomarkers with potential pathogenetic significance. Am J Pathol 2014; 184: 618-630 [IF 4.602]
13. Locati L.D., Perrone F., Cortelazzi B., Imbimbo M., Bossi P., Potepan P., Civelli E., Rinaldi G., Quattrone P., Licitra L., Pilotti S.: Activity of abiraterone in rechallenging two AR-expressing salivary gland adenocarcinomas, resistant to androgen-deprivation therapy. Cancer Biol Ther 2014; 15: 678-682 [IF 3.63]
14. Milione M., et al.: Ewing sarcoma of the small bowel: A study of seven cases, including one with the uncommonly reported EWSR1-FEV translocation.Histopathology 2014; 64: 1014-1026 [IF 3.301]
15. Milione M., Pilotti S., Pelosi G.: Is the pathologist indispensable in gastrointestinal stromal tumors and neuroendocrine tumors? J OncoPath 2014; 2: 9-31 [IF 0]
16. Milione M., Pilotti S., Pelosi G.: Is the pathologist indispensable in gastrointestinal stromal tumors and neuroendocrine tumors? J OncoPath 2014; 2: 9-31 [IF 0]
17. Pelosi G., et al.: Controversial issues and new discoveries in lung neuroendocrine tumors. Diagn Histopathol (Oxf) 2014; 20: 392-397 [IF 0]
18. Pelosi G., et al.: Does immunohistochemistry affect response to therapy and survival of inoperable non-small cell lung carcinoma patients? A survey of 145 stage III-IV consecutive cases. Int J Surg Pathol 2014; 22: 136-148 [IF 0.961]
19. Pelosi G., et al.: Unraveling tumor grading and genomic landscape in lung neuroendocrine tumors. Endocr Pathol 2014; 25: 151-164 [IF 1.644]
20. Pelosi G., Rindi G., Travis W.D., Papotti M.: Ki-67 antigen in lung neuroendocrine tumors: Unraveling a role in clinical practice. J Thorac Oncol 2014; 9: 273-284 [IF 5.8]
21. Perrone F., et al.: Circulating free DNA in a screening program for early colorectal cancer detection. Tumori 2014; 100: 115-121 [IF 1.09]
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23. Perrone F., et al.: Frequent mutation and nuclear localization of β-catenin in sertoli cell tumors of the testis. Am J Surg Pathol 2014; 38: 66-71 [IF 4.592]
24. Rossi G., Mengoli M.C., Cavazza A., Nicoli D., Barbareschi M., Cantaloni C., Papotti M., Tironi A., Graziano P., Paci M., Stefani A., Migaldi M., Sartori G., Pelosi G.: Large cell carcinoma of the lung: Clinically oriented classification integrating immunohistochemistry and molecular biology. Virchows Arch 2014; 464: 61-68 [IF 2.56]

EXPERIMENTAL ONCOLOGY AND MOLECULAR MEDICINE

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BIOMARKERS
MARIA GRAZIA DAIDONE

MOLECULAR IMMUNOLOGY
MARIO P. COLOMBO

MOLECULAR PHARMACOLOGY
NADIA ZAFFARONI

TUMOR GENOMICS
GABRIELLA SOZZI

IMMUNOBIOLOGY OF HUMAN TUMORS
ANDREA ANICHINI

IMMUNOTHERAPY OF HUMAN TUMORS
LICIA RIVOLTINI

MOLECULAR MECHANISMS
MARIA ANGELA GRECO

MOLECULAR MECHANISMS OF CELL CYCLE CONTROL
DOMENICO DELIA

MOLECULAR THERAPIES
DELIA MEZZANZANICA

MOLECULAR TARGETING
ELDA TAGLIABUE

AIRC START UP UNIT
MARILENA V. IORIO

This Department includes 10 Research Units and one AIRC-awarded start-up Unit dedicated to preclinical investigations. Its primary goal is to serve as an important conduit through which new discoveries are applied to cancer diagnosis, prognosis, and treatment.

The activity of the Research Units is addressed:

- to identify and validate biomolecular features associated with tumor development and progression as diagnostic, prognostic, and treatment response/resistance markers, and as molecular targets to develop new treatment approaches;
- to investigate the tumor microenvironment and extracellular matrix at a molecular and functional level;
- to elucidate the interactions between tumor cells and the immune system;

with the final aims of:

- developing highly sensitive tests (which utilize a panel of novel biomolecular markers) for a possible clinical application;
- preclinical testing of novel drug combinations, and development of novel therapeutic agents;
- identifying novel therapeutic strategies based on immunomodulation, and to develop vaccination strategies, also taking advantage of the acquired competence in developing new generation recombinant antibodies.

Such studies involve multidisciplinary approaches, statistical and bioinformatic methodologies, and integration among the different high-throughput and high-resolution techniques and functional tests. Investigations are carried out using different preclinical experimental models and validated on large series of human biospecimens, taking advantage of the Institutional Biobank.

The Department supports investigators with state-of-the-art core facilities, with shared instrumentation, dedicated trained specialists, and also with the collaboration of experts from the different Research Units. The following core facilities are available.

Immunohistochemistry. Technical Specialists: Lorena Ventura and Lucia Gioiosa

Cell imaging facility. Technical Specialist: Patrizia Casalini, Biol Sci D

Flow cytometry and cell sorting. Technical Specialist: Gabriella Abolafio, Ivan Muradore

Microbiology. Technical Specialist: Maria Teresa Radice

Cytogenetics and molecular cytogenetics. Specialist: Patrizia Gasparini, Biol Sci D

Proteomics/mass spectrometry laboratory. Italia Bongarzone, Biol Sci D (Senior Researcher); Luca Varinelli, Biotech Med D; Technical specialists: Maida De Bortoli, Elena Taverna

Functional genomics and Bioinformatics (FGB). Silvana Canevari, Biol Sci D (Senior Researcher); Marina Bagnoli, Biol Sci D; Vera Cappelletti, Biol Sci D; Loris De Cecco, Biol Sci D; Marco Giannoccaro, Biotech D; Rosaria Orlandi, Biol Sci D; Marialuisa Sensi, Biol Sci D; Maurizio Callari, Biotech D, Bioinformatician; Gaetano De Feo, Biol Sci D; Matteo Dugo, Biotech D, Bioinformatician; Patrizia Pinciroli, Biol Sci D and Technical Specialists: Edoardo Marchesi, Donata Penso)
The activities of the FGB are conducted using the following instruments: QIAcube for nucleic acid purification; Agilent Bioanalyzer, Nanodrop, Qubit for quantity and quality control of nucleic acids; Illumina and Agilent platforms for microarray analysis of mRNA expression, miRNA and lncRNA expression, ChIP-on-chip, DNA methylation, CGH and CNV, SNPs; Quantstudio 12K for quantitative real-time PCR; automated liquid handling MultiProbe II; Next Generation Sequencing SOLiD™ 5500xl Wildfire and 3130 Sequencer for Sanger Sequencing; dedicated servers, work-stations, and up-to-date software, hardware and web-based databases. The research group comprises full time personnel involved in wet analyses and personnel dedicating part of their institutional activity to computational analysis using wet and in silico data. The FGB performs: study design; RNA and DNA extraction and quality controls; all the labeling and hybridization methodologies required for high quality analysis; data processing and statistical analysis. Full computational analyses are performed using open-source software and dedicated licenses. Identification and bio-functional interpretation of promising biomarkers are based on differential expression analysis, pathway analysis with over-representation or gene set enrichment approaches (GO and GSEA), and integration of different kinds of data. The FGB also provides certification of identity of cell lines adhering to ATCC guidelines and sample processing on a 3130 capillary genetic analyzer.

Laboratory animal facility

Biospecimen repository - BioBank (Silvia Veneroni, Biol Sci D and Technical Specialists: Antonio Scavo, Francesco Pastore, Gloria Morandi, Lucilla Ciorba): see Research Programs, page 66.

Molecular Genetics of Cancer Unit at IFOM: Manuela Gariboldi, Biol Sci D, PhD (Senior Researcher); Viktorija Sokolova, Biol SciD, PhD; Susanna Zanutto, Biotech Sci D; Maria Valeria Majorana, Biol Sci D (PhD Student)

Administratives: Simona Galuzzi; Claudia Miranda, Biol Sci D; Luisa Rivetta; Daniela Silva
Technician: Loredana Cleris
Laboratory Management Team: Enrico Ronchi, Domenico Di Fazio, Angelo Labori, Salvatore Venturino
Supporting Personnel: Antonietta Calcagno, Linda Cimaglia, Angelo Farina, Giuseppina Liguori, Agata Mancuso, Luisa Mona, David Penni, Gisella Rivadossi, Giovanna Ripoli, Maria Cristina Ripoli, Carlo Salandra, Claudio Santagostini, Massimiliano Scaranello

In 2014, the services supplied by DOSMM were certified to implement and maintain a Quality Management System which fulfills the requirements of ISO 9001:2008 standards.

BIOMARKERS

HEAD

Maria Grazia Daidone, Biol Sci D, PhD

RESEARCH STAFF

Vera Cappelletti, Biol Sci D; Silvia Veneroni, Biol Sci D; Raffaella Villa, Biol Sci D

RESEARCH ASSOCIATE

Valentina Appierto, Biol Sci D, PhD;

POSTDOCTORAL AND RESEARCH FELLOWS

Valentina Angeloni, Ind Biotech D, PhD; Maurizio Callari, Med Biotech D, PhD; Francesca D'Aiuto, Biostatistics D; Giuseppe Merlino, Med Biotech D; Valeria Musella, Med Biotech D, PhD; Carolina Reduzzi, Biol Sci D; Paola Tiberio, Ind Biotech D

PHD STUDENT

Emanuela Fina, Biol Sci D

TECHNICIANS

Elena Cavadini; Cinzia De Marco, Patrizia Miodini, Gloria Morandi, Rosita Motta

ADMINISTRATIVE

Laura Zanesi

Research in this Unit is aimed at identifying and validating cancer-related and actionable biomarkers relevant for cancer progression and treatment response, using molecular and cell biology approaches, high-throughput techniques, and bioinformatic tools. Studies are mainly focused on solid tumors to investigate: a) transcriptomic and genomic profiles on critical samples (formalin-fixed paraffin-embedded [FFPE] material, and/or circulating tumor cells [CTC] and tumor-initiating cells [TIC]); b) nucleic acids (microRNAs and tumor DNA) as blood-derived biomarkers that are potentially useful for early detection and risk assessment through non-invasive approaches. To develop sensitive and specific tests for clinical application, particular efforts are spent to understand pre-analytical and analytical confounders for circulating biomarkers, with the development of a simple, robust, sensitive, cost-effective, spectrophotometrically-based system to identify hemolyzed plasma/serum specimens. In addition, in order to obtain more consistent results in downstream analyses on FFPE samples (which represent an invaluable tissue source for biomarkers development, validation and routine implementation), we developed an appropriate sample and data processing that can significantly improve the reliability of gene expression data using the standard Affymetrix platform.

We have extensively characterized breast cancer with these techniques, and identified a new possible therapeutic strategy that could make aggressive breast cancers responsive to standard treatments. We have also shown that monitoring miR-181a/b expression may be helpful in tailoring more effective treatments based on PARP1 inhibition. In a large case series we have validates a signature of a differentially expressed (DE) metagene that is associated with distant metastases beyond classical risk factors. Further studies are ongoing to investigate the role of myeloid-derived suppressor cell recruitment as possible 'effectors' of the negative prognostic role IFN-metagenes.

SELECTED PUBLICATIONS

1. Appierto V., Callari M., Cavadini E., Morelli D., Daidone M.G., Tiberio P.: A lipemia-independent NanoDrop®-based score to identify hemolysis in plasma and serum samples. Bioanalysis 2014; 6: 1215-1226 [IF 3.027]
2. Callari M., Lembo A., Bianchini G., Musella V., Cappelletti V.G., Gianni L., Daidone M.G., Provero P.: Accurate data processing improves the reliability of affymetrix gene expression profiles from FFPE samples. PLoS ONE 2014; 9: e86511 [IF 3.534]
3. Callari M., Musella V., Di Buduo E., Sensi M., Miodini P., Dugo M., Orlandi R., Agresti R., Paolini B., Carcangiu M.L., Cappelletti V., Daidone M.G.: Subtype-dependent prognostic relevance of an interferon-induced pathway metagene in node-negative breast cancer. Mol Oncol 2014; 8: 1278-1289 [IF 5.935]

3
PUBLICATIONS
AS FIRST/LAST AUTHOR

12.496
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

MOLECULAR IMMUNOLOGY

HEAD

Mario Paolo Colombo, Biol Sci D

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Claudia Chiodoni, Biol Sci D, PhD; Silvia Miotti, Biol Sci D

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Sabina Sangaletti, Biol Sci D, PhD

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TECHNICIANS

Ivano Arioli, Claudia Bassani, Laura Botti, Barbara Cappetti, Renata Ferri, Mariella Parenza, Paola Portararo, Chiara Ratti

ADMINISTRATIVE

Ester Grande

The extracellular matrix is viewed as a meshwork of molecules that form a structural scaffold for growing tissues. Proteins belonging to the matrix are not merely bystanders, but living integrators in cellular processes. We have studied SPARC by looking at its function in bone marrow and secondary lymphoid organs (spleen and lymph nodes). SPARC is ubiquitous, almost silent, and expressed in case of danger, tissue repair, and in tissues under continuous remodeling, like cancer. The normal continuous supply of white and red blood cells from the bone marrow can be altered by infections or cancer occurring at distant sites. Under such circumstances SPARC is produced by mesenchymal cells; we have shown that its overproduction can cause myelofibrosis whereas its absence myeloproliferation, which can become uncontrolled. This latter case depends on SPARC controlling the deposition of collagen fibers. Collagen can press a brake existing on white blood cells, including granulocytes, thus inhibiting their function. In lymph nodes exposed to infection or in condition of autoimmunity, lack of SPARC leads to reduced and disorganized collagen and therefore different regions of lymph node, normally functionally separated, mix together also allowing granulocytes, which no longer sense the brake signal, to interact with B lymphocytes promoting their proliferation and transformation to lymphoma.

We have also found that SPARC regulates the different phases of normal B cell lymphopoiesis both in bone marrow and secondary lymphoid organs (SLO). Defective lymphopoiesis beginning at level of BM B-cell precursors occurs in case of SPARC deficiency. Splenic lymphopoiesis is affected by the lack of SPARC from stroma resulting in impoverished $CD93^{+}$ T1 immature B-cell fraction. We showed that this cell fraction reside in collagen-IV rich areas at the edge of the highly vascularized red pulp, a front-line in BM-SLO trafficking. The infiltration of SLO lymphoid niches by myeloid cells is emerging as a relevant event in the loss of lymphopoietic homeostasis.

SELECTED PUBLICATIONS

1. Colombo M.P., Prendergast G.C.: Editors' viewpoint - Response. Cancer Res 2014; 74: 635 [IF 9.284]
2. Sangaletti S., Tripodo C., Portararo P., Dugo M., Vitali C., Botti L., Guarnotta C., Cappetti B., Gulino A., Torselli I., Casalini P., Chiodoni C., Colombo M.P.: Stromal niche communalities underscore the contribution of the matricellular protein SPARC to B-cell development and lymphoid malignancies. Oncoimmunology 2014; 3: e28989 [IF 6.283]
3. Sangaletti S., Tripodo C., Sandri S., Torselli I., Vitali C., Ratti C., Botti L., Burocchi A., Porcasi R., Tomirotti A., Colombo M.P., Chiodoni C.: Osteopontin shapes immunosuppression in the metastatic niche. Cancer Res 2014; 74: 4706-4719 [IF 9.284]
4. Sangaletti S., Tripodo C., Vitali C., Portararo P., Guarnotta C., Casalini P., Cappetti B., Miotti S., Pinciroli P., Fuligni F., Fais F., Piccaluga P.P., Colombo M.P.: Defective stromal remodeling and neutrophil extracellular traps in lymphoid tissues favor the transition from autoimmunity to lymphomas. Cancer Discov 2014; 4: 110-129 [IF 15.929]

4
PUBLICATIONS
AS FIRST/LAST AUTHOR

40.78
I.F. AS FIRST/LAST AUTHOR

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MOLECULAR PHARMACOLOGY

Our research focuses on the following major areas:
Novel therapeutic targets. These studies use biophysical and molecular analyses as well as global gene expression analysis to identify novel therapeutic targets. Future studies will focus on alternative lengthening of telomere and the heparanase/heparin sulfate axis.
XPO1/CRM1. These studies have suggested that selective blockade of XPO1/CRM1-dependent nuclear export could represent a completely novel approach for the treatment of advanced prostrate cancer. The relevance of XPO1/CRM1 as a novel therapeutic target will be studied in preclinical models of diffuse malignant peritoneal mesothelioma (DMPM), a lethal disease with limited therapeutic options.
Rational design of novel drug combinations and identification of companion diagnostics. These investigations will provide the molecular bases for rational drug combinations to be exploited in the clinical setting and to suggest relevant biomarkers for patient selection. Future studies are planned to test the Ret inhibitor-cisplatin combinatory approach in preclinical models of medullary thyroid cancer using tyrosine kinase inhibitors.
Exploitation of molecular alterations associated with tumor drug resistance to improve the efficacy of treatment. The studies are aimed at identifying deregulated signaling pathways playing a role in inherent and acquired tumor treatment resistance and suitable for specific inhibition with pharmacological and/or genetic tools.
Identification and validation of microRNAs as novel therapeutic targets and biomarkers. These studies have characterized miRNA expression profiles associated with activation of tumor-surrounding stroma and acquisition of the capability to drive transformation and enhance tumor dissemination.
Optimization of drug/radiation combinations. We will try to achieve restoration of the expression of genes inhibiting the metastatic behavior of tumor cells and modulation of factors implicated in drug resistance by HDAC inhibitors.

HEAD

Nadia Zaffaroni, Biol Sci D, PhD

RESEARCH STAFF

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PHD STUDENTS

Valentina Profumo, Biol Sci D; Rihan El Bezawy, Biotech Sci D

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ADMINISTRATIVE

Laura Zanesi

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PUBLICATIONS
AS FIRST/LAST AUTHOR

68.61
I.F. AS FIRST/LAST AUTHOR

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H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

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3. Folini M.: Targeting telomere maintenance mechanisms in cancer therapy. Curr Pharm Des 2014; 20: 6359-6360 [IF 3.288]
4. Gandellini P., Giannoni E., Casamichele A., Taddei M.L., Callari M., Piovan C., Valdagni R., Pierotti M.A., Zaffaroni N., Chiarugi P.: MiR-205 hinders the malignant interplay between prostate cancer cells and associated fibroblasts. Antioxid Redox Signal 2014; 20: 1045-1059 [IF 7.667]
5. Gandellini P., Rancati T., Valdagni R., Zaffaroni N.: miRNAs in tumor radiation response: by standers or participants? Trends Mol Med 2014; 20: 529-539 [IF 10.11]
6. Gatti L., Cossa G., Tinelli S., Carenini N., Arrighetti N., Pennati M., Cominetti D., De Cesare M., Zunino F., Zaffaroni N., Perego P.: Improved apoptotic cell death in drug-resistant non-small-cell lung cancer cells by tumor necrosis factor-related apoptosis-inducing ligand-based treatments. J Pharmacol Exp Ther 2014; 348: 360-371 [IF 3.855]
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9. Lopergolo A., Nicolini V., Favini E., Bo L.D., Tortoreto M., Cominetti D., Folini M., Perego P., Castiglioni V., Scanziani E., Borrello M.G., Zaffaroni N., Cassinelli G., Lanzi C.: Synergistic cooperation between sunitinib and cisplatin promotes apoptotic cell death in human medullary thyroid cancer. J Clin Endocrinol Metab 2014; 99: 498-509 [IF 6.31]
10. Pennati M., Lopergolo A., Profumo V., De Cesare M., Sbarra S., Valdagni R., Zaffaroni N., Gandellini P., Folini M.: MiR-205 impairs the autophagic flux and enhances cisplatin cytotoxicity in castration-resistant prostate cancer cells. Biochem Pharmacol 2014; 87: 579-597 [IF 4.65]
11. Santambrogio F., Gandellini P., Cimino Reale G., Zaffaroni N., Folini M.: MicroRNA-dependent regulation of telomere maintenance mechanisms: A field as much unexplored as potentially promising. Curr Pharm Des 2014; 20: 6404-6421 [IF 3.288]
12. Stacchiotti S., Tortoreto M., Baldi G.G., Grignani G., Toss A., Badalamenti G., Cominetti D., Morosi C., Dei Tos A.P., Festinese F., Fumagalli E., Provenzano S., Gronchi A., Pennacchioli E., Negri T., Dagrada G.P., Spagnuolo R.D., Pilotti S., Casali P.G., Zaffaroni N.: Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour. Eur J Cancer 2014; 50: 3021-3028 [IF 4.819]

TUMOR GENOMICS

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Roberto Caserini, Davide Conte, Federica Facchinetti, Mavis Mensah
ADMINISTRATIVE
Cristina Zanini

Our research activity is centered on all aspects of lung cancer with the aim of making an impact on a disease that represents a major healthcare burden in terms of morbidity and mortality. We use an integrated approach that combines cellular and molecular biology, biochemistry, and pharmacology to gain new insights in the pathogenesis of lung cancer and on novel ways to provide early diagnosis and novel treatment options. The goal of our translational studies is the implementation of highly sensitive molecular tests that could be used within screening programs to improve both detection and clinical management of lung cancers.

Major research projects:

miRNAs: sensors and players of lung carcinogenesis. We have completed an extended retrospective validation of a miRNA signature classifier (MSC) in plasma samples of 1000 cases and controls subjects enrolled in the MILD trial.
The bioMILD trial (www.biomild.org), a truly innovative study testing the efficacy of a combined molecular and imaging approach, where blood miRNAs and LDCT are both applied at baseline screening, which determines the intensity and modality of subsequent investigations.
Development of novel pre-clinical experimental models. We have recently developed in vivo lung cancer xenograft models by directly implanting fragments of the patient's tumor in the flank of immunocompromised mice.
Stromal cells as accomplices of lung carcinogenesis. We have demonstrated that cross-talk between stroma and cancer cells can dictate the composition of the extracellular matrix.
Isolation and characterization of Cancer Stem Cell (CSC) in lung cancer. We identified a specific subset of lung metastatic $CD133^{+}CXCR4^{+}$ CSC modulated by the tumor microenvironment and associated with poor prognosis.
Molecular cytogenetics. These studies have shown an association of ALK protein expression with gene copy number gain and significant correlation between positive-ALK IHC, metastasis, and worse overall survival in pediatric rhabdomyosarcoma patients.

SELECTED PUBLICATIONS

1. Fortunato O., Boeri M., Moro M., Verri C., Mensah M., Conte D., Caleca L., Roz L., Pastorino U., Sozzi G.: Mir-660 is downregulated in lung cancer patients and its replacement inhibits lung tumorigenesis by targeting MDM2-p53 interaction. Cell Death Dis 2014; 5: e1564 [IF 5.177]
2. Fortunato O., Boeri M., Verri C., Conte D., Mensah M., Suatoni P., Pastorino U., Sozzi G.: Assessment of circulating micrornas in plasma of lung cancer patients. Molecules 2014; 19: 3038-3054 [IF 2.095]
3. Fortunato O., Boeri M., Verri C., Moro M., Sozzi G.: Therapeutic use of microRNAs in lung cancer. Biomed Res Int 2014; 2014: 756975 [IF 0]
4. Sozzi G., Boeri M., Rossi M., Verri C., Suatoni P., Bravi F., Roz L., Conte D., Grassi M., Sverzellati N., Marchiano A., Negri E., La Vecchia C., Pastorino U.: Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study. J Clin Oncol 2014; 32: 768-773 [IF 17.879]
5. Sozzi G., Boeri M.: Potential biomarkers for lung cancer screening. Transl Lung Cancer Res 2014; 3: 139-148 [IF 0]

5
PUBLICATIONS
AS FIRST/LAST AUTHOR
25.151
I.F. AS FIRST/LAST AUTHOR
47
H-INDEX HEAD OF UNIT

IMMUNOBIOLOGY OF HUMAN TUMORS

HEAD

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Throughout 2014 the research activity of this Unit has focused mainly on immunology, targeted therapy, and biology of cutaneous melanoma and other tumors. The main goals are to: a) improve understanding of how the innate and adaptive arms of the immune response contribute to naturally occurring tumor immunity and to decipher the mechanism of action of immune checkpoint blockade therapy; b) provide proof of principle evidence for more effective approaches to target therapy of different tumors; c) characterize the biological role of genes and molecules overexpressed in melanoma to identify new potential therapeutic targets and prognostic biomarkers.

The salient results to date include:

- Identification of a new subset of highly cytotoxic NK cells that is enriched in tumor-invaded lymph nodes of melanoma patients.
- Characterization of pre- and post-therapy neoplastic lesions from several non-responding patients treated with anti-CTLA4 antibody to understand the mechanism of resistance.
- Identification of selective enrichment for recently activated and functional T cells at the tumor site in NSCLC, which provide further rationale for treatment of NSCLC patients with anti-PD-1 monoclonal antibodies.
- Identification of molecular markers that may allow to predict which tumors may show primary/intrinsic resistance to BRAF inhibition
- Assessment of the potential efficacy of combinatorial approaches to target therapy in melanoma, where we combined small molecule inhibitors with a biological molecule known for its selective anti-tumor activity (TRAIL).
- Definition of the role of the SEMA6A gene, belonging to the semaphorin-plexin ligand-receptor pathway, in BRAF-mutant melanoma cells, suggesting that it may represent a novel potential therapeutic target.
- New classification of melanoma into discrete subsets based on profiling for gangliosides.

SELECTED PUBLICATIONS

1. Grazia G., Vegetti C., Benigni F., Penna I., Perotti V., Tassi E., Bersani I., Nicolini G., Canevari S., Carlo-Stella C., Gianni A.M., Mortarini R., Anichini A.: Synergistic anti-tumor activity and inhibition of angiogenesis by cotargeting of oncogenic and death receptor pathways in human melanoma. Cell Death Dis 2014; 5: e1434 [IF 5.177]

1
PUBLICATIONS
AS FIRST/LAST AUTHOR

5.177
I.F. AS FIRST/LAST AUTHOR

41
H-INDEX HEAD OF UNIT

IMMUNOTHERAPY OF HUMAN TUMORS

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DATA MANAGER

Paola Frati, Biotech D

RESEARCH NURSE

Felicetta Giardino

ADMINISTRATIVE

Grazia Convertino

The interest of the Unit is focused on evaluating the interactions taking place between the immune system and tumor cells in cancer patients. The aim is to identify pathways involved in tumor progression that can be targeted by therapeutic intervention or exploited for prognostic purposes. In tight collaboration with the clinicians, we study biological samples obtained from the tumor site, lymph nodes, or peripheral blood to achieve these goals. Our studies are focused on three major areas.

Dissection of the molecular mechanisms underlying tumor immune escape and resistance to therapy through study of:

- Exosomes in cancer-related myeloid conditioning
- CCL2 and miRNA in BRAF resistance
- CD30 in T cell anergy and suppression
- LAG-3 and plasmacytoid dendritic cells in melanoma

Immunological aspects in the response to targeted therapy of sarcoma patients. Identify immune-related prognostic factors for patients selection and therapeutic planning

- Circulating Myeloid Index Score in melanoma
- MDSC-associated miRNA signature in plasma exosomes as prognostic biomarker for melanoma patients

Investigation of novel micro/macroenvironment-modulating strategies to tilt the balance of tumor immunity in cancer patients

- TRAIL-exosomes for the delivery of pro-apoptotic stimuli to tumor microenvironment
- pH regulators in hepatocellular carcinoma
- Immunomodulatory effect of drugs inhibiting pH regulators: the Adesom2 trial

Our interest is to gain further insights into the mechanisms underlying cancer-mediated myeloid conditioning and MDSC generation, defining the potential involvement of bone marrow precursors, dissecting the differentiation patterns involved, and identifying antagonizing strategies based on selective antagomirs. We will be extending our studies on the prognostic sentinel node gene expression and miRNA signature, validating it in an independent dataset and investigating at preclinical level the functional implications of identified immune pathways such as those mediated by CD30.

8
PUBLICATIONS
AS FIRST/LAST AUTHOR

37.591
I.F. AS FIRST/LAST AUTHOR

55
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Camisaschi C., De Filippo A., Beretta V., Vergani B., Villa A., Vergani E., Santinami M., Cabras A., Arienti F., Triebel F., Rodolfo M., Rivoltini L., Castelli C.: Alternative activation of human plasmacytoid DCs in vitro and in melanoma lesions: Involvement of LAG-3. J Invest Dermatol 2014; 134: 1893-1902 [IF 6.372]
2. Camisaschi C., Tazzari M., Rivoltini L., Castelli C.: Monitoring the frequency and function of regulatory T cells and summary of the approaches currently used to inhibit regulatory T cells in cancer patients. Methods Mol Biol 2014; 1139: 201-221 [IF 0]
3. Camisaschi C., Vallacchi V., Castelli C., Rivoltini L., Rodolfo M.: Immune cells in the melanoma microenvironment hold information for prediction of the risk of recurrence and response to treatment. Expert Rev Mol Diagn 2014; 14: 643-646 [IF 4.27]
4. Frigerio S., Disciglio V., Manoukian S., Peissel B.G., Della Torre G., Maurichi A., Collini P., Pasini B., Gotti G., Ferrari A., Rivoltini L., Massimino M., Rodolfo M.: A large de novo 9p21.3 deletion in a girl affected by astrocytoma and multiple melanoma. BMC Med Genet 2014; 15: 59 [IF 2.45]
5. Gomez-Lira M., Ferronato S., Malerba G., Santinami M., Maurichi A., Sangalli A., Turco A., Perego P., Rodolfo M.: Association of promoter polymorphism -765G>C in the PTGS2 gene with malignant melanoma in Italian patients and its correlation to gene expression in dermal fibroblasts. Exp Dermatol 2014; 23: 766-768 [IF 4.115]
6. Rodolfo M., Castelli C., Rivoltini L.: Immune response markers in sentinel nodes may predict melanoma progression. Oncoimmunology 2014; 3: e28498 [IF 6.283]
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8. Vallacchi V., Vergani E., Camisaschi C., Deho P., Cabras A., Sensi M., De Cecco L., Bassani N., Ambrogi F., Carbone A., Crippa F., Vergani B., Frati P., Arienti F., Patuzzo R., Villa A., Biganzoli E., Canevari S., Santinami M., Castelli C., Rivoltini L., Rodolfo M.: Transcriptional profiling of melanoma sentinel nodes identify patients with poor outcome and reveal an association of CD30+ T lymphocytes with progression. Cancer Res 2014; 74: 130-140 [IF 9.284]

MOLECULAR MECHANISMS

HEAD

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The Unit is involved in studies aimed at identification of the molecular mechanisms contributing to pathogenesis of thyroid carcinoma. Ongoing studies focus on i) papillary thyroid carcinoma (PTC), arising from thyroid follicular epithelium and ii) medullary thyroid carcinoma (MTC) from parafollicular C cells. The goal is identification of markers for early detection, prognosis, follow-up, and novel therapeutic targets. We employ several approaches including: high-throughput analyses; generation of in vitro models of thyroid carcinogenesis using tumor derived cell lines and primary thyrocytes; functional, mRNA, and microRNA studies; characterization of thyroid tumor case collections.

During 2014, we have progressed in several projects:
Identification of thyroid tumor cell vulnerability. We identified 13 genes whose inhibition interferes with tumor, but not normal thyroid cell viability.
Oncogene-induced senescence (OIS). We demonstrated that OIS may restrain the thyroid epithelial tumor progression, and that thyrocytes undergoing OIS model in vitro the early thyroid tumour stages.
microRNA in PTC. We identified miR-199a-3p as a novel tumor suppressor miRNA in PTC.
Next generation sequencing of PTC. A project aimed at definition of the genetic landscape of PTC employing next generation sequencing technologies is ongoing.
Crosstalk between thyroid tumor cells and macrophages. Characterization of the interaction between tumor microenvironment components, in particular macrophages and thyroid tumor cells representative of early and late tumor stages has been initiated.
Functional characterization of NTRK1 mutations. These results have excluded a role for NTRK1 mutations in melanoma.
Functional characterization of the RET-G691S non-synonymous polymorphism in MTC. Expression/penetrance studies in two RET-S891A FMTC families suggest that analysis of this polymorphism can contribute to clinical and follow-up management.
Identification of specific tumor and plasma miRNA profiles of metastatic MTC patients. We obtained circulating miRNA profiles from MTC patients before and after vandetanib treatment to identify predictive markers.

6
PUBLICATIONS
AS FIRST/LAST AUTHOR

31.812
I.F. AS FIRST/LAST AUTHOR

34
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Cremona M., Espina V., Caccia D., Veneroni S., Colecchia M., Pierobon M., Deng J., Mueller C., Procopio G., Lanzi C., Daidone M.G., Cho W.C.S., Petricoin E.F., Liotta L., Bongarzone I.: Stratification of clear cell renal cell carcinoma by signaling pathway analysis. Expert Rev Proteomics 2014; 11: 237-249 [IF 3.542]
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3. Minna E., Romeo P., De Cecco L., Dugo M., Cassinelli G., Pilotti S., Degl'Innocenti D., Lanzi C., Casalini P., Pierotti M.A., Greco A., Borrello M.G.: miR-199a-3p displays tumor suppressor functions in papillary thyroid carcinoma. Oncotarget 2014; 5: 2513-2528 [IF 6.627]
4. Miranda C., Mazzoni M., Sensi M., Pierotti M.A., Greco A.: Functional characterization of NTRK1 mutations identified in melanoma. Genes Chromosom Cancer 2014; 53: 875-880 [IF 3.836]
5. Orlandi R., De Bortoli M., Ciniselli C.M., Vaghi E., Caccia D., Garrisi V., Pizzamiglio S., Veneroni S., Bonini C., Agresti R., Daidone M.G., Morelli D., Camaschella C., Verderio P., Bongarzone I.: Hepcidin and ferritin blood level as noninvasive tools for predicting breast cancer. Ann Oncol 2014; 25: 352-357 [IF 6.578]
6. Vizioli M.G., Santos J., Pilotti S., Mazzoni M., Anania M.C., Miranda C., Pagliardini S., Pierotti M.A., Gil J., Greco A.: Oncogenic RAS-induced senescence in human primary thyrocytes: Molecular effectors and inflammatory secretome involved. Oncotarget 2014; 5: 8270-8283 [IF 6.627]

MOLECULAR MECHANISMS OF CELL CYCLE CONTROL

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This research unit is involved in two main projects:

Analysis and dissection of the ATM-dependent pathway in DNA damage response (DDR) and genomic stability in tumor cells and in cancer-predisposing neurodegenerative syndrome.

We have identified CCAR2 (previously known as DBC1 or KIAA1967) as a target of ATM, being phosphorylated by this kinase on Thr454 in DDR. Our studies show that CCAR2 is required for repair of heterochromatic DNA lesions. Loss of the DDR protein ATM predisposes to neurodegeneration, as seen in the ataxia-telangiectasia (A-T) syndrome. We have shown that ATM deficiency suppresses the response to and repair of DNA breaks, and enhances Top1-cc accumulation.

Development of pro-apoptotic SMAC-mimetic (SMs) compounds targeting the BIR3 domain of the inhibitor of apoptosis XIAP, frequently upregulated in tumors.

SMs constitute a class of compounds that target the inhibitor of apoptosis proteins (IAPs) and enhance the cytotoxic activity of a number of drugs. We are currently working on cIAP1/Snai2 mechanistic interplay to determine its role in the anti-metastatic activity of SM83. Unexpectedly, we found that SM83 greatly enhances the cytotoxic activity of camptothecin in premalignant models of human epithelial cells expressing KRAS G13D. Analysis of colorectal cancer lines bearing knock-in and knock-out mutations of KRAS G13D showed that the sensitivity to SM83/CPT treatment is independent of KRAS status. This led us to speculate that other survival pathways are counteracting the potential pro-apoptotic effect of mutant KRAS. Indeed, inhibition of PI3K/AKT sensitizes cancer cells to treatment, especially in presence of mutated KRAS. Our work suggests that pharmacological inhibition of pathways triggered by oncogenes may inhibit the expression of oncogene-stimulated pro-apoptotic proteins. The efficacy of treatment might be increased by combining traditional chemotherapy with targeted therapy towards specific pathways such as the one controlled by AKT.

SELECTED PUBLICATIONS

1. Buscemi G., Ricci C., Zannini L., Fontanella E., Plevani P., Delia D.: Bimodal regulation of p21waf1 protein as function of DNA damage levels. Cell Cycle 2014; 13: 2901-2912 [IF 5.006]
2. Carlessi L., Fusar Poli E., Bechi G., Mantegazza M., Pascucci B., Narciso L., Dogliotti E., Sala C., Verpelli C., Lecis D., Delia D.: Functional and molecular defects of hiPSC-derived neurons from patients with ATM deficiency. Cell Death Dis 2014; 5: 1342 [IF 5.177]
3. Magni M., Ruscica V., Buscemi G., Kim J.E., Nachimuthu B.T., Fontanella E., Delia D., Zannini L.: Chk2 and REGgamma-dependent DBC1 regulation in DNA damage induced apoptosis. Nucleic Acids Res 2014; 42: 13150-13160 [IF 8.808]
4. Zannini L., Delia D., Buscemi G.: CHK2 kinase in the DNA damage response and beyond. J Mol Cell Biol 2014; 6: 442-457 [IF 8.432]

4
PUBLICATIONS AS FIRST/LAST AUTHOR
27.423
I.F. AS FIRST/LAST AUTHOR
43
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MOLECULAR THERAPIES

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Silvia Portincasa

The Unit of Molecular Therapies is involved in translational research primarily dedicated to respond to the major clinical needs related to ovarian cancer. Unmet clinical needs related to this disease are: late diagnosis, rapid progression, frequent disease relapse, and development of chemoresistance.

The activity is organized into the below lines of research:

Molecular basis of tumor growth and progression. This research will provide the basis for designing new approaches for early detection of ovarian cancer and allow more rational design of new therapeutic strategies that include target-specific drugs and peptidomimetic ligands able to inhibit cell-cell and cell-ECM adhesion.

Identification and validation of new prognostic/predictive markers of early relapse and chemo-resistance and identification of new therapeutic targets. The overall aim is definition of new prognostic and predictive markers that take into account tumor biology and heterogeneity and help in identifying patients with increased risk of disease recurrence.

Exome sequencing: integration with genomic and epi-genomic profiles to decipher mechanisms of chemoresistance. The integration of multiple and multi-layered "omics" data resources is expected to contribute to the identification of main prognostic/predictive biomarkers and in deciphering their functional relevance. The overall integration of these molecular layers is expected to allow identification of patient subtypes that could benefit from both stratification and tailoring of treatment.

Development, preclinical, and clinical validation of antibody-based reagents for diagnostic and therapeutic use. In this area, the aim is the preparation, characterization and optimization of antibody-based reagents using antibody engineering to better respond to clinical needs. We are focused on monoclonal antibodies or antibody fragments directed against the alpha folate receptor.

In addition to ovarian cancer, other tumors (prostate cancer, melanoma, lymphoma and thyroid cancer) are studied.

SELECTED PUBLICATIONS

1. Granata A., Nicoletti R., Tinaglia V., De Cecco L., Pisanu M.E., Ricci A., Podo F., Canevari S., Iorio E., Bagnoli M., Mezzanzanica D.: Choline kinase-alpha by regulating cell aggressiveness and drug sensitivity is a potential druggable target for ovarian cancer. Br J Cancer 2014; 110: 330-340 [IF 4.817]

1
PUBLICATIONS AS FIRST/LAST AUTHOR

4.817
I.F. AS FIRST/LAST AUTHOR

23
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MOLECULAR TARGETING UNIT

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We aim to gain insight into the molecular pathways relevant for the progression and response to therapy of breast carcinomas, especially those with HER2 overexpression and triple-negative (TN) features. During 2014, we demonstrated that TN tumors, defined as based on the absence of HER2 and hormone receptor expression, have the ability to form vascular-like channels in vitro and to generate blood lacunae lined by tumor cells in vivo. This feature is associated with poor outcome and PDGFR β - and FGFR2-mediated pathways, identified as relevant in mediating this characteristic, potentially represent valid targets for a specific therapy of this breast cancer subgroup.

In light of the need to identify prognostic factors in T1 HER2-positive tumors routinely treated with trastuzumab-based adjuvant therapy, we found that nodal status, tumor grade, ER^- and PgR-expression showed a raw association with disease-free survival and patients who were both ER-negative and lymph node-positive (ER^-/N^+) associated with the highest risk of relapse.
Concerning the identification of a robust predictor marker of trastuzumab benefit, we uncovered the relevance of a splice isoform of the HER2 receptor which lacks exon 16 (Δ16HER2) in susceptibility of HER2-positive breast tumors to trastuzumab treatment. Patients expressing high pSRC or an activated "Δ16HER2 metagene" were found to derive the greatest benefit from trastuzumab treatment.
In relation to tumor microenvironment, we identified a subgroup of breast carcinomas (ECM3) showing a homogeneous gene pattern, consisting of 58 genes encoding 43 structural ECM proteins. Multivariate analysis of distant metastasis-free survival in untreated breast tumor patients revealed a significant interaction between ECM3 and histological grade with a highly significant association between ECM3 and worse survival probability only in grade III tumors. ECM3 is also predictive of resistance to chemotherapy treatment.

SELECTED PUBLICATIONS

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2. Castagnoli L., Iezzi M., Ghedini G.C., Ciravolo V., Marzano G., Lamolinara A., Zappasodi R., Gasparini P., Campiglio M., Amici A., Chiodoni C., Palladini A., Lollini P.L., Triulzi T., Menard S., Nanni P., Tagliabue E., Pupa S.M.: Activated d16HER2 homodimers and src kinase mediate optimal efficacy for trastuzumab. Cancer Res 2014; 74: 6248-6259 [IF 9.284]
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7
PUBLICATIONS
AS FIRST/LAST AUTHOR

41.575
I.F. AS FIRST/LAST AUTHOR

43
H-INDEX HEAD OF UNIT

AIRC START UP UNIT

HEAD
Marilena V. Iorio, Biotech Sci D, PhD
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POSTDOCTORAL FELLOW
Ilaria Plantamura, Biol Sci D, PhD
PHD STUDENT
Elvira D'Ippolito, Biotech Sci D

The goal of the Start Up Unit is the identification and study of microRNAs involved in the most important pathways activated in human breast cancer, with the aim to better define the role of these small but powerful molecules in this neoplasia, and to provide the experimental bases for their possible use as targets or tools in specific therapies.
Several studies have demonstrated that microRNAs, a class of small non-coding RNAs able to regulate gene expression at the post-transcriptional level, are involved human cancer. Our group (Iorio MV et al., 2005) described the first breast cancer-specific microRNA profile, identifying a list of microRNAs able to classify tumors and normal tissues with an accuracy of 100%, and signatures associated to specific biopathological features. Breast cancer is a complex and heterogeneous disease, where survival and proliferation of a cancerous cell might depend on the activation of different pathways. In addition to breast tumors depending on ER activation or HER2 overexpression, the third major subgroup of breast cancer includes the so-called Triple Negative Breast Cancer (TNBC), which are negative for ER, PgR, and HER2 expression. Very aggressive from a clinical point of view, they are characterized by an undifferentiated phenotype and lack specific markers for an effective targeted therapy. These tumors still represent a relatively unknown area in breast cancer biology. MicroRNAs could both provide the missing information to explain the behavior of this class of breast carcinoma, and represent possible tools or targets for a specific therapy. The goal of our project is the identification and the study of microRNAs involved in the most important pathways activated in human breast cancer, with the aim to better define the role of these small but powerful molecules in this neoplasia, and to provide the experimental bases for their possible use as targets or tools of specific therapies. The most recent results of this study include the description, in collaboration with Dr. Tagliabue, of PDGFRbeta-related vascular mimicry properties of TNBC (Plantamura I et al., 2014); the discovery of two microRNAs exerting an opposite role on this phenomenon (D'Ippolito E, Plantamura I et al, manuscript in preparation); the description of a striking effect of genetic loss of miR-205 on normal mammary gland development and proliferation, and preliminary data on the effects of miR-205 KO in HER2-mediated tumorigenesis through crossing with MMTV-neu transgenic mice (Piovan C et al., manuscript in preparation); in addition to preliminary data on miR-205 and responsiveness to trastuzumab in $HER2^{+}$ breast cancer.

SELECTED PUBLICATIONS

1. Plantamura I., Casalini P., Dugnani E., Sasso M., D'Ippolito E., Tortoreto M., Cacciatore M., Guarnotta C., Ghirelli C., Barajon I., Bianchi F., Triulzi T., Agresti R., Balsari A., Campiglio M., Tripodo C., Iorio M., Tagliabue E.: PDGFR β and FGFR2 mediate endothelial cell differentiation capability of triple negative breast carcinoma cells. Mol Oncol 2014; 8: 968-981 [IF 5.935]

1
PUBLICATIONS
AS FIRST/LAST AUTHOR
5.935
I.F. AS FIRST/LAST AUTHOR
19
H-INDEX HEAD OF UNIT

PREVENTIVE AND PREDICTIVE MEDICINE

DIRECTOR OF DEPARTMENT
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EPIDEMIOLOGY AND PREVENTION
VITTORIO KROGH

ANALYTICAL EPIDEMIOLOGY AND HEALTH IMPACT
MILENA SANT

EVALUATIVE EPIDEMIOLOGY
GEMMA GATTA

ENVIRONMENTAL EPIDEMIOLOGY
PAOLO CONTIERO

CANCER REGISTRY
GIOVANNA TAGLIABUE

MEDICAL GENETICS
SIRANOUSH MANOUKIAN

HEREDITARY DIGESTIVE TRACT TUMORS
LUCIO BERTARIO *(Until July 2014)*
GIUSEPPE PELOSI *(Interim from August 2014)*

MOLECULAR BASES OF GENETIC RISK AND GENETIC TESTING
PAOLO RADICE

GENETIC EPIDEMIOLOGY AND PHARMACOGENOMICS
TOMMASO A. DRAGANI

The Department focuses primarily on epidemiological and translational research. This comprises knowledge of lifestyle and genetic risk factors in order to take preventive action (i.e. from prediction to prevention), and knowledge of inequalities in cancer prevention and treatment in order to take corrective actions. The research relies on extensive interaction between researchers in the fields of basic experimental science, epidemiology, genetics, and clinical medicine.

EPIDEMIOLOGY AND PREVENTION

HEAD

Vittorio Krogh, MD, MSc

RESEARCH STAFF

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TECHNICIANS

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CONSULTANT

Franco Berrino

The Epidemiology and Prevention Unit is involved in large prospective and intervention studies on the association between diet, hormones, nutrition, lifestyle, genetic factors, and cancer risk.

The main results published in 2014 involved a wide variety of tumors and showed new potential risk factors:

- renal cell carcinoma: red and processed meat consumption in women but not in men;
- head, neck and esophageal cancer: elevated circulating levels of homocysteine for developing squamous cell carcinoma;
- thyroid carcinoma: high thyroglobulin levels precede by up to 8 years the detection of thyroid carcinoma;
- lung cancer: biomarkers of tryptophan metabolism;
- hepatocellular carcinoma: increased SHBG levels;
- gastric cancer: four variants in AB0 for diffuse-type gastric cancer;
- colorectal cancer: high dietary glycemic index and high carbohydrate intake; elevated plasma total and LDL-cholesterol;
- breast cancer: high saturated fat for ER(+)PR(+) and HER2(-) cancer; adult weight gain, especially for cancers diagnosed before age 50; higher premenopausal circulating levels of testosterone, but not of estradiol or progesterone;
- endometrial and cervical cancer: smoking for cervical intraepithelial neoplasia of grade 3, carcinoma in situ and invasive cervical cancer; HPV16E6 seropositivity is the strongest marker to predict invasive cervical cancer;
- cancer of unknown primary site: smoking and waist circumference.

The Unit is also involved in many clinical trials:
ORDET, one of the first prospective European studies on the role of hORmones and Diet in the Etiology of breast Tumor.
TPM, a prospective study designed to evaluate the prognostic role of androgens and related endocrine - metabolic factors in breast cancer.
COS, a randomized controlled trial of diet and physical activity in BRCA mutation carriers.
TEVERE (Diana-4), a blinded randomized controlled trial of diet and metformin for primary prevention of breast cancer.
MeMeMe, a randomized controlled trial of diet and metformin for primary prevention of age-related chronic diseases (ArCD).
DIANA-5, a multicentric randomized controlled trial of the effectiveness of a diet based on Mediterranean and macrobiotic recipes and principles, associated with moderate physical activity, in reducing additional breast cancer events in women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu.

8
PUBLICATIONS
AS FIRST/LAST AUTHOR

31.369
I.F. AS FIRST/LAST AUTHOR

59
H-INDEX HEAD OF UNIT

SELECTED PUBLICATIONS

1. Agnoli C., Grioni S., Sieri S., Sacerdote C., Vineis P., Tumino R., Giurdanella M.C., Pala V., Mattiello A., Chiodini P., Iacoviello L., De Curtis A., Cattaneo L., van Duijnhoven F.J.B., Panico S., Krogh V.: Colorectal cancer risk and dyslipidemia: A case-cohort study nested in an Italian multicentre cohort. Cancer Epidemiol 2014; 38: 144-151 [IF 2.558]

2. Berrino F., Villarini A., Traina A., Bonanni B., Panico S., Mano M.P., Mercandino A., Galasso R., Barbero M., Simeoni M., Bassi M.C., Consolaro E., Johansson H., Zarcone M., Bruno E., Gargano G., Venturelli E., Pasanisi P.: Metabolic syndrome and breast cancer prognosis. Breast Cancer Res Treat 2014; 147: 159-165 [IF 4.198]

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7. Pasanisi P., Bruno E., Manoukian S., Berrino F.: A randomized controlled trial of diet and physical activity in BRCA mutation carriers. Fam Cancer 2014; 13: 181-187 [IF 1.618]

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ANALYTICAL EPIDEMIOLOGY AND HEALTH IMPACT

HEAD

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RESEARCH STAFF

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TECHNICIANS

Camilla Amati, Simone Bonfarnuzzo, Ilaria Cavallo, Agata Cifalà, Francesco Funaro, Chiara Margutti, Stefania Saltarelli, Alberto Turco

The main research activity is focused on the investigation of cancer outcomes and survival across regions and groups of patients, in Europe and Italy, through collection, centralization, and analyses of data in population cancer registries and hospital-based sets of patients.
The Unit was involved in the following projects:

EUROCARE. The largest European database on survival and care of over 10 million cancer patients is monitoring cancer patient survival in Europe for over 20 years.

High resolution (HR) studies. Compare patterns of cancer care across areas, between groups of patients and over time. Presently, a total of 12,469 cases are available.

European Partnership Action Against Cancer (EPAAC). EPAAC involved most EU member states and cancer organizations, and was organized in 9 Working Groups each focusing on a different cancer domain.

CANCON. CANCON will produce a guide covering best practices and recommendations to governments on screening, primary care, integrated care, and rehabilitation.

Institutional Breast Cancer Registry. INT is establishing cancer center-based clinical registries for oncological pathologies to allow researchers and clinicians to quickly identify cases of interest, with access to a predefined set of demographic, clinical, and biological variables.

Risk for hematological malignancy mortality. Investigated risk for mortality of hematological malignancy in potential high-risk zones near an Italian petrochemical refinery. A significant increase in death risk was found among women.

Out-of-pocket costs in Italy. From lists of prevalent cases in 2013, a random sample of 600 persons was extracted who were interviewed and information on costs for doctor's appointment, medical examinations, drugs, and travels.

Website 'I tumori in Italia'. The project coordinated by INT and ISS aims to provide epidemiological information on cancer in Italy. The website includes incidence, prevalence and mortality estimates for seven major neoplasms at the national and regional level from 1970 to 2015.

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2. Micheli A., Meneghini E., Mariottini M., Baldini M., Baili P., Di Salvo F., Sant M.: Risk of death for hematological malignancies for residents close to an Italian petrochemical refinery: a population-based case-control study. Cancer Causes Control 2014; 25: 1635-1644 [IF 2.961]
3. Minicozzi P., Bouvier A.M., Faivre J., Sant M.: Management of rectal cancers in relation to treatment guidelines: A population-based study comparing Italian and French patients. Dig Liver Dis 2014; 46: 645-651 [IF 2.889]
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5. Sant M., Minicozzi P., Mounier M., Anderson L.A., Brenner H., Holleczek B., Marcos-Gragera R., Maynadi й M., Monnereau A., Osca-Gelis G., Visser O., De Angelis R., Baili P., Berrino F., Foschi R., Gatta G., Trama A., EUROCARE-5 Working Group.: Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: Results of EUROCARE-5, a population-based study. Lancet Oncol 2014; 15: 931-942 [IF 24.725]

5
PUBLICATIONS AS FIRST/LAST AUTHOR

34.124
I.F. AS FIRST/LAST AUTHOR

35
H-INDEX HEAD OF UNIT

EVALUATIVE EPIDEMIOLOGY

HEAD
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ADMINISTRATIVES
Rossana Berruti, Lucia Buratti

The main activities of the Unit involve the following:

Rare tumors: creation of an information network
Due to their low frequency, rare cancers pose particular challenges such as late or incorrect diagnosis, lack of access to appropriate therapies and clinical expertise, limited information about the disease and a scarcity of clinical trials. In responses to these challenges, Rare Cancers Europe (RCE) has launched a Call to Action that urges policymakers and stakeholders to give priority to rare cancers.
A new rare cancers project (RARECAREnet) has been undertaken. The overall goal is to serve as the reference source of information on rare cancers in Europe and contribute to ameliorate diagnosis and treatment of rare cancers, foster research on rare cancers, support the establishment of CoE and empower patients.

Childhood cancers
According to EUROCARE-5, there are still survival disparities between countries and European regions, but with few exceptions, survival was lowest in Eastern Europe. Several reasons might explain persisting inequalities. The lack of healthcare resources is probably most important, especially in countries with limited drug supply, lack of specialized centers with multidisciplinary teams, delayed diagnosis and treatment, poor management of treatment and drug toxicity. Many of these aspects will be studied in the Horizon 2020 project 'PICORET' supported by the European Society for Paediatric Oncology (SIOPE).

Prostate cancers
In Italy, as in other Western countries, prostate cancer incidence is reducing after a dramatic increase. Mortality remained stable or slightly increased and is now slightly decreasing. The reason for this is explained by the diffusion of the prostate-specific antigen test started in the early 1990s and ultrasound-guided biopsy and needle biopsies. With high-resolution studies founded on population based cancer registries data and sophisticated statistical model 'cured models', we can try to understand the extent of the true improvement of treatment.

SELECTED PUBLICATIONS

1. Gatta G., Botta L., Rossi S., Aareleid T., Bielska-Lasota M., Clavel J., Dimitrova N., Jakab Z., Kaatsch P., Lacour B., Mallone S., Marcos-Gragera R., Minicozzi P., S б nchez-P й rez M.-J., Sant M., Santaquilani M., Stiller C., Tavilla A., Trama A., Visser O., Peris-Bonet R., and EUROCARE Working Group, Baili P., Berrino F., Contiero P., Tagliabue G.: Childhood cancer survival in Europe 1999-2007: Results of EUROCARE-5-a population-based study. Lancet Oncol 2014; 15: 35-47 [IF 24.725]
2. Oddone E., Modonesi C., Gatta G.: Occupational exposures and colorectal cancers: A quantitative overview of epidemiological evidence. World J Gastroenterol 2014; 20: 12431-12444 [IF 2.433]

2
PUBLICATIONS
AS FIRST/LAST AUTHOR
27.158
I.F. AS FIRST/LAST AUTHOR
48
H-INDEX HEAD OF UNIT

ENVIRONMENTAL EPIDEMIOLOGY

HEAD
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RESEARCH STAFF
Martina Bertoldi, PhD; Alessandro Borgini, PhD; Alessandra Scaburri, PhD; Maria E. Sanoja Gonzalez, PhD
DATA MANAGER
Alessandro Cau
ADMINISTRATIVE
Immacolata Favia

The Unit was founded with the aim of monitoring and analyzing the effects of exposure to environmental agents on the development of cancers and prognoses for such cancers, and to characterize geographic areas in terms of environmental risk factors that influence the incidence of, and prognosis for, these diseases. A further objective is to monitor public health initiatives to protect health and prevent disease, and validate that such initiatives are effective and uniformly distributed across the area of application. Changes are suggested as necessary to ensure equity of access to both preventive measures and treatments.
Studies are carried out on cohorts from the population-based Lombardy Cancer Registry, which is a vey complete and has high quality data. Many of these studies involve collaboration with partners of the Open Registry Network, thereby exploiting a population of 3,800,000 individuals in which 30,000 new cancer cases per year are diagnosed.
To study birth defects and adverse reproductive outcomes, a similar approach is used, selecting cohorts from the Lombardy Birth Defects Registry. The Unit is also investigating the prevalence of factors that affect prognosis for a disease after it has been diagnosed. For example, the effect of fasting glucose levels or comorbidities on prognosis in women diagnosed with breast cancer, performed on an observational cohort from cancer registries.

The above-mentioned research projects are population-based, sustainable epidemiological studies, and have the important characteristic that they make use of electronic information sources collected routinely for administrative or clinical purposes. These sources comprise hospital discharge records, pathology reports, death certificates, outpatient consultation databases, and drug prescription databases.

However, indiscriminate use of these information sources, without a clear scientific objective and without systematic data quality checking, risks producing biased results. The Unit, working with the Cancer Registry Unit, is therefore leading partner in collaborative studies involving the Open Registry Network to develop more secure methods and systems to identify adverse health events from routinely collected electronic information sources.

CANCER REGISTRY

HEAD
Giovanna Tagliabue, MD, PhD
RESEARCH STAFF
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DATA MANAGER
Tiziana Codazzi
ADMINISTRATIVE
Anna Maghini

The Cancer Registry Unit manages several registries, as listed below.

The Open Registry information system and the Open Registry Network
Open Registry is a system used to generate and manage cancer registry data. Open Registry was designed and built by Lombardy Cancer Registry staff who are also working on further development of the system, and who participate in research projects involving analysis of data produced by cancer registries involved in the Open Registry Network, which facilitates speedy transfer of scientific results and collection of electronic data.

The Lombardy Birth Defects Registry
The Lombardy Birth Defects Registry was developed at INT to study relationships between adverse reproductive outcomes and cancer and cancer treatments in women of fertile age. The population-based birth defects registry has now been collecting birth defects for 12 years and had archived over 15,000 cases. The Birth Defects Registry is a member of the Italian National Birth Defects Registries Network, managed by the Italian Superior Health Institute (ISS). Registration has now been extended to include all low-weight and preterm births, spontaneous miscarriages, and ectopic deliveries.

Lombardy Cancer Registry Province of Varese (LCR)
The LCR is longest-established Italian cancer registry, working for over 30 years, with over 168,000 cancer cases registered. Using routinely-available electronic data sources, all patients are followed over time for disease recurrence, other cancer and other disease diagnoses, use of prescribed drugs, and the provision of all other medical or health services. The innovative scientific collaboration developed between a division dedicated to research and an institution concerned with public health has made it possible to carry out projects that answer important scientific questions and are also relevant to public health.

MEDICAL GENETICS

HEAD
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Caterina Spina

The Medical Genetics Unit provides genetic counseling for hereditary cancer syndromes. Hereditary tumors represent only a minority of all cancers and not all causative genes have been identified. Although genetic evaluation is now part of the good clinical practice for some type of cancer, genetic counseling and testing should actually be offered only to patients/families that are suspected to have increased risk and only when a benefit from a thorough assessment of their genetic risk of cancer is expected.
The main focus of the Unit is the study of Hereditary Breast and Ovarian Cancer syndrome (HBOC), but other rare inherited predispositions to cancer are also investigated although representing only a small fraction of the Unit activity. During 2014, more than 900 new families asked for genetic evaluation. To rationalize access to genetic counseling and testing and to guarantee a high level of appropriateness and effectiveness, all requests underwent a first clinical evaluation in order to better select patients who may really benefit from risk assessment. Only eligible patients fulfilling INT selection criteria underwent genetic counseling.
Since the beginning of the activity 5802 genetic counseling for HBOC were completed; during last year 327 first genetic counselings were performed. Another emerging cause of rapid testing are clinical trials on PARP inhibitor therapy in BRCA1/BRCA2 carriers or high grade serous carcinoma. During the period of activity, 1,960 strictly eligible index cases were tested, 558 carried a mutation in BRCA1/BRCA2 genes, corresponding to a detection rate of 28.5% for deleterious mutations (plus 4.7% variants of unknown significance). When less stringent criteria were used (borderline eligibility) the overall detection rate in 2,568 index cases decreased, but was still of 23.7% for deleterious mutations (plus 5.2% variants of unknown significance). These values are among the highest reported in national/international literature, proving the effectiveness of INT testing selection criteria.

HEREDITARY DIGESTIVE TRACT TUMORS

HEAD

Lucio Bertario, MD *(until July 2014)*

Giuseppe Pelosi, MD *(Interim from August 2014)*

CLINICAL RESEARCH STAFF

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ADMINISTRATIVES

Mariangela Diceglie, Ornella Galuppo

The Unit of Hereditary Digestive Tract Tumors is devoted to the counseling, molecular testing, and clinical management of individuals with genetic predisposition to major hereditary syndromes of the gastrointestinal tract, including Lynch syndrome, Familial Adenomatous Polyposis (FAP) and its attenuated variant Peutz-Jeghers syndrome, juvenile polyposis and hereditary gastric cancer. Individuals receiving genetic counseling and the relevant families at risk of developing related cancer are offered molecular testing for specific genetic alterations. During 2014, about 370 individuals were screened for germline mutations in cancer predisposing genes, such as MLH1, MSH2, and MSH6 for Lynch syndrome; APC and MUTYH for FAP and attenuated FAP; STK11 for Peutz-Jeghers syndrome; PTEN for Cowden syndrome; CDH1 for hereditary gastric cancer; and TP53 for Li-Fraumeni Syndrome.

The Unit has been involved in the identification of gastrointestinal hereditary tumors in at-risk subjects, in the study of hereditary predisposition to estimate the risk of cancer, and in studies on chemoprevention of colorectal cancer.

SELECTED PUBLICATIONS

1. Vitellaro M., Sala P., Signoroni S., Radice P., Fortuzzi S., Civelli E.M., Ballardini G., Kleiman D.A., Morrissey K.P., Bertario L.: Risk of desmoid tumours after open and laparoscopic colectomy in patients with familial adenomatous polyposis. Br J Surg 2014; 101: 558-565 [IF 5.21]

1
PUBLICATIONS
AS FIRST/LAST AUTHOR

5.21
I.F. AS FIRST/LAST AUTHOR

38
H-INDEX HEAD OF UNIT

MOLECULAR BASES OF GENETIC RISK AND GENETIC TESTING

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PHD STUDENT
Sara Ciceri, Med Biotech D
TECHNICIAN
Patrizia Mondini
ADMINISTRATIVE
Silvia Grassi

The research activities of this unit are focused on the identification and characterization of the genetic elements associated with hereditary predisposition to cancer and with cancer progression. Our studies are mainly focused on familial breast carcinoma and Wilm's tumor (WT).
Main achievements of 2014:

- We characterized two germline mutations that appear to be present in high risk breast/ovarian cancer families originating from the province of Bergamo at frequencies approximately 10 times higher than those observed in high risk families from other areas of Italy. The identification of pathogenic founder mutations in cancer predisposing genes is important to improve risk assessment, since it may provide specific targets resulting in cost-effective genetic testing.
- We participated in a large-scale international study that, for the first time, provided robust estimates of the risk of breast cancer in carriers of germline mutations of the PALB2 gene. This study indicated that loss-of-function mutations in PALB2 are an important cause of hereditary breast cancer, and support the notion that the screening for such mutations should be considered in clinical practice for women with evidence of inherited predisposition to breast cancer who test negative for BRCA1 and BRCA2 alterations.
- A relevant fraction of pathogenic mutations in the BRCA1 gene, which confer markedly increased risk of breast and ovarian cancer, affect mRNA splicing, leading to the synthesis of non-functional or unstable protein products. Overall, our data suggest a model of alternative splicing in which most non-mutually exclusive events are randomly combined into individual mRNA molecules to produce hundreds of different BRCA1 isoforms.
- In WT, several clinical, histological, and genetic parameters are being proposed for risk stratification of WT patients. Our findings suggest that the gene signature associated with naive primary relapsing tumors could be exploited as a potential prognostic factor.

SELECTED PUBLICATIONS

1. Caleca L., Putignano A.L., Colombo M., Congregati C., Sarkar M., Magliery T.J., Ripamonti C.B., Foglia C., Peissel B.G., Zaffaroni D., Manoukian S., Tondini C., Barile M., Pensotti V., Bernard L., Papi L., Radice P.: Characterization of an Italian founder mutation in the RING-finger domain of BRCA1. PLoS ONE 2014; 9: e86924 [IF 3.534]
2. Catucci I., Peterlongo P., Ciceri S., Colombo M., Pasquini G., Barile M., Bonanni B., Verderio P., Pizzamiglio S., Foglia C., Falanga A., Marchetti M., Galastri L., Bianchi T., Corna C., Ravagnani F., Bernard L., Fortuzzi S., Sardella D., Scuvera G., Peissel B., Manoukian S., Tondini C., Radice P.: PALB2 sequencing in Italian familial breast cancer cases reveals a high-risk mutation recurrent in the province of Bergamo. Genet Med 2014; 16: 688-694 [IF 6.435]
3. Colombo M., Blok M.J., Whiley P., Santamarina M., Gutierrez-Enriquez S., Romero A., Garre P., Becker A., Smith L.D., De Vecchi G., Brandao R.D., Tserpelis D., Brown M., Blanco A., Bonache S., Menendez M., Houdayer C., Foglia C., Fackenthal J.D., Baralle D., Wappenschmidt B., Diaz-Rubio E., Caldes T., Walker L., Diez O., Vega A., Spurdle A.B., Radice P., De La Hoya M.: Comprehensive annotation of splice junctions supports pervasive alternative splicing at the BRCA1 locus: A report from the ENIGMA consortium. Hum Mol Genet 2014; 23: 3666-3680 [IF 6.677]

3
PUBLICATIONS
AS FIRST/LAST AUTHOR

16.646
I.F. AS FIRST/LAST AUTHOR

40
H-INDEX HEAD OF UNIT

GENETIC EPIDEMIOLOGY AND PHARMACOGENOMICS

HEAD
Tommaso A. Dragani, Pharm Sci D, PhD
RESEARCH STAFF
Giacomo Manenti, Pharm Sci D, PhD
RESEARCH ASSOCIATES
Francesca Colombo, Biotech D; Sara Noci, Biol Sci D, PhD
RESEARCH FELLOW
Chiara E. Cotroneo, Vet Biotech D
PHD STUDENTS
Alice Dassano, Vet Biotech D, MSc; Giulia Pintarelli, Biol Sci D
TECHNICIAN
Angela Pettinicchio
ADMINISTRATIVE
Silvia Portincasa

During 2014, we published the results of studies that identified genetic markers and candidate genes associated with survival of lung cancer patients. In particular, we analyzed existing genotype and clinical data from UK-resident patients with lung adenocarcinoma, identifying candidate Single Nucleotide Polymorphisms (SNPs) that associated with survival; we then genotyped these candidate SNPs in a series of 748 patients from Italy who were genetically compatible with the UK series based on principal component analysis. Four SNPs were confirmed as having a hazard ratio indicating the same direction of effect in the two series and $p < 0.05$ with a Cox proportional hazard model adjusted for age, sex and clinical stage. The strongest association was provided by rs2107561, an intronic SNP of PTPRG, protein tyrosine phosphatase, receptor type G. PTPRG mRNA levels in samples of lung adenocarcinoma were 40% of those observed in non-involved lung tissue from the same patients. PTPRG overexpression significantly inhibited the clonogenicity of A549 lung carcinoma cells and anchorage-independent growth of the NCI-H460 large cell lung cancer line. The four germline variants represent promising candidates that may help predict clinical outcome. In addition, the PTPRG locus may have a role in tumor progression.

In an experimental model of genetic predisposition to lung tumorigenesis, we characterized the role of the Pulmonary adenoma susceptibility 1 (Pas1) locus as an expression quantitative trait locus (QTL). In both tumor lung tissue and its normal counterpart, the expression of Kras-4A, one of the two alternatively spliced Kras transcripts, was linked to genotype at the Pas1 locus. In contrast, expression of the second Kras isoform (Kras-4B) was not influenced by genotype at this locus. Overall, Pas1 is an expression QTL, suggesting that Pas1 modulates susceptibility to lung tumorigenesis through control of Kras isoform levels.

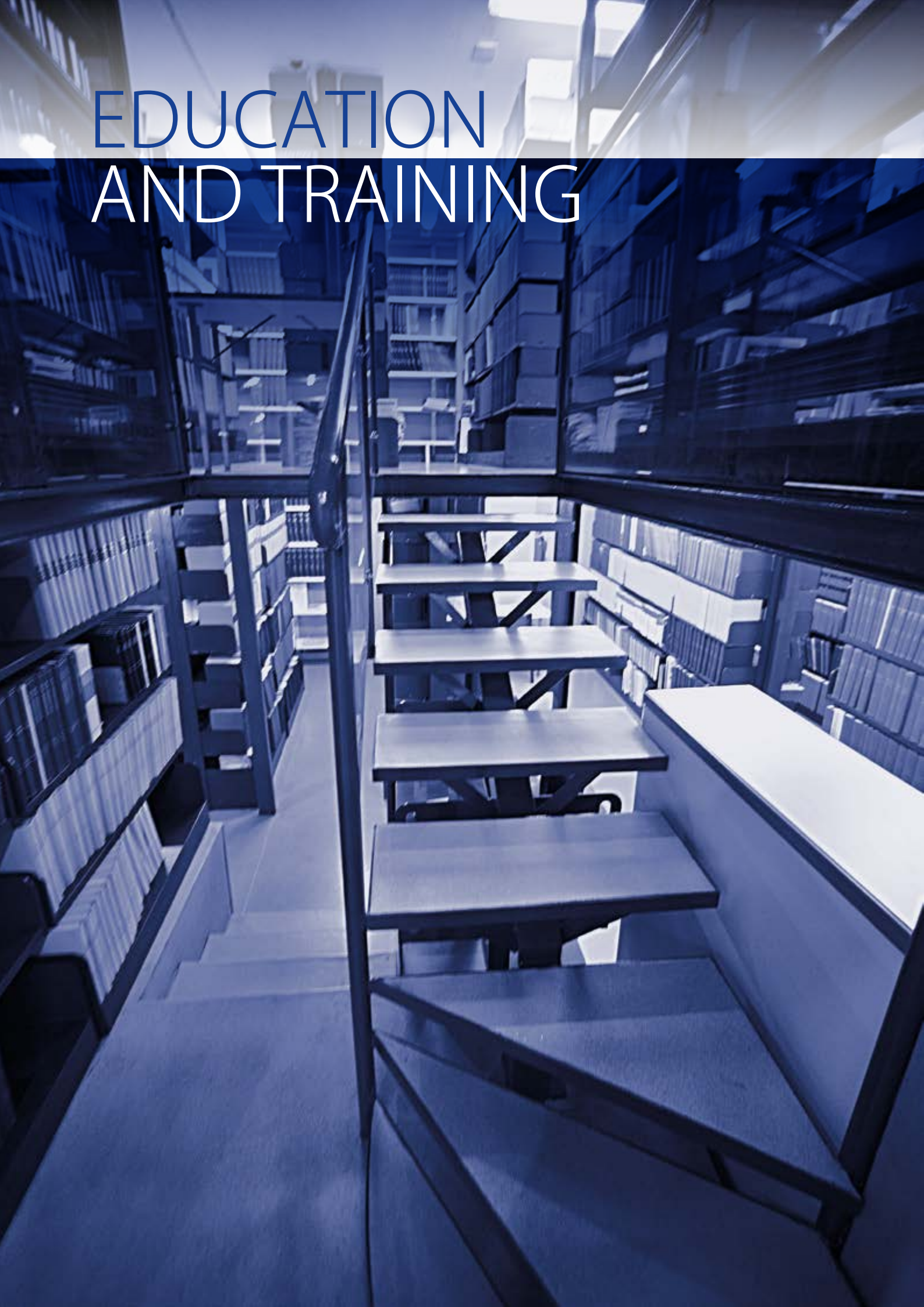
SELECTED PUBLICATIONS

1. Dassano A., Colombo F., Trincucci G., Frullanti E., Galvan A., Pettinicchio A., De Cecco L., Borrego A., Martinez Ibanez O.C., Dragani T.A., Manenti G.: Mouse Pulmonary Adenoma Susceptibility 1 Locus Is an Expression QTL Modulating Kras-4A. Plos Genet 2014; 10: e1004307 [IF 8.167]

2. Dassano A., Mancuso M., Giardullo P., De Cecco L., Ciuffreda P., Santaniello E., Saran A., Dragani T.A., Colombo F.: N6-isopentenyladenosine and analogs activate the NRF2-mediated antioxidant response. Redox Biol 2014; 2: 580-589 [IF 0]

2
PUBLICATIONS AS FIRST/LAST AUTHOR
8.167
I.F. AS FIRST/LAST AUTHOR
33
H-INDEX HEAD OF UNIT

EDUCATION AND TRAINING



EDUCATION AND TRAINING

INT is strongly committed to educating future scientists and clinicians and is directly engaged in quality education and training. INT offers a wide range of educational activities for clinical and experimental researchers at different stages of their professional careers.
PhD studentships, postdoctoral research fellowships, graduate student training, medical residency training, psychology, and social work training, as well as continuing medical education are all included in the portfolio of educational opportunities offered to staff and external participants.
Invited lectures, seminars and workshops in a variety of research disciplines related to cancer are regularly arranged. Participants in education and training programs are encouraged to attend interdepartmental journal clubs, clinical case discussions, and grand rounds as well as other multidisciplinary activities aimed to create cross-specialty knowledge.

ACADEMIC PROGRAMS

INT provides education and training at various levels, including undergraduate, graduate as well as postgraduate medical and biotechnology students, physicians, nursing students, and nurses. On the basis of formal agreements with the University of Milan, INT hosts the Chairs of Medical Oncology (Prof Alessandro M. Gianni, till October 2014), Hematology (Prof Paolo Corradini, Coordinator of the Experimental Hematology Doctoral Program at the University of Milan), Medical Statistics and Biometry (Prof Adriano Decarli), Anesthesiology (Prof Martin Langer), and Pathology (Prof Giuseppe Pelosi). A number of staff members have joint appointments as professors at the University of Milan. INT hosts the Postgraduate School in Oncology, the Postgraduate Medical School in Pathology, and the 3-year degree in Nursing Sciences of the University of Milan. Additionally, INT participates in the degree in Biotechnology and Molecular Medicine in Oncology, as well as in two PhD programs at the University of Milan (Hematology and Medical Biotechnology). Every year INT offers a range of highly specialized Master Courses.

DOCTORAL (PhD) TRAINING PROGRAM

As an Affiliated Research Center of the Open University, Milton Keynes, UK, INT offers a PhD Program in Life and Biomolecular Sciences. The program is regularly monitored to ensure that it meets the requirements of the Quality Assurance Agency (QAA) for Higher Education Code of Practice. INT provides direct support for these training positions and offers fellowships/ grants to European Community postgraduate students holding a degree in Medicine, Biological Sciences or Pharmacy. Students are involved in several activities, including courses, generic skills training, journal club meetings, and seminars.

OPEN UNIVERSITY PhD STUDENTS AND THEIR RESEARCH TOPICS

MARIANNA SASSO	BIOMARKERS OF AGGRESSIVE PHENOTYPE IN TRIPLE NEGATIVE BREAST CANCER
ALICE RIGONI	MAST CELLS AT THE INTERFACE BETWEEN EXTERNAL CHALLENGES AND IMMUNE REGULATION IN COLITIS AND COLORECTAL CANCER
DAVIDE BERNAREGGI	CONVERSION OF AFRA FAB INTO A FULLY HUMAN MONOCLONAL ANTIBODY DIRECTED AGAINST A FOLATE RECEPTOR: IN VITRO AND IN VIVO STUDIES
DANIELE LECIS	INHIBITORS OF APOPTOSIS PROTEINS (IAPS) AS TARGETS FOR ANTI-CANCER TREATMENT
ILARIA TORSELLI	THE INFLUENCE OF TUMOR MICROENVIRONMENT ON OSTEOSARCOMA
GAIA GHEDINI	ROLE OF Δ 16HER2 SPLICE VARIANT IN RESPONSE TO DRUG TARGETING HER2 RECEPTOR
SARA CICERI	MOLECULAR CHARACTERISATION OF WILMS TUMOR
ALICE DASSANO	EXPRESSION NETWORKS AND EFFECTORS OF GENETIC SUSCEPTIBILITY TO LUNG CANCER IN MICE
ELVIRA D'IPPOLITO	THE ROLE OF MICRORNAS IN TRIPLE NEGATIVE BREAST CANCER

EMANUELA FINA	BIOLOGICAL AND CLINICAL SIGNIFICANCE OF CIRCULATING TUMOR CELLS IN BREAST CANCER
OLGA KUCHUK	INTERFERENCE OF pH REGULATORS AS AN IMMUNOMODULATING THERAPEUTIC STRATEGY FOR LIVER CANCER
EMANUELA MINNA	miRNA DEREGULATION IN THYROID CARCINOGENESIS: IN VITRO MODELS TO STUDY MOLECULAR MECHANISMS AND FUNCTIONAL EFFECTS
VALENTINA PROFUMO	THE ROLE OF MICRORNAS IN TRIPLE NEGATIVE BREAST CANCER
ANDREA TOMIROTTI	IDENTIFICATION OF EARLY BIOMARKERS OF NEOPLASTIC TRANSFORMATION IN MOUSE MODELS OF BREAST AND PROSTATE CARCINOGENESIS
VALERIA MAIORANA	ANALYSIS OF IN VITRO AND IN VIVO EFFECTS OF METFORMIN ALONE OR IN COMBINED TREATMENTS IN COLORECTAL CANCER
MARTINA MAGNI	FUNCTIONAL CHARACTERIZATION OF THE HUMAN PROTEIN DELETED IN BREAST CANCER 1 (DBC1) INVOLVEMENT IN THE DNA DAMAGE RESPONSE
MATTEO DUGO	DISSECTING MELANOMA HETEROGENEITY BY INTEGRATIVE GENOMIC ANALYSIS FOR TAILORED ANTI-CANCER THERAPY
LORENZO CASTAGNOLI	ROLE OF Δ16HER2 SPLICE VARIANT IN BREAST CANCER STEM CELLS
NADIA CASTIONI	ROLE OF SPARC AND MAST CELLS IN NON-HODGKIN B CELL LYMPHOMAS
ELENA CETTI	IDENTIFICATION AND CHARACTERIZATION OF POTENTIAL NOVEL TARGETS IN THYROID CARCINOMA: EVIDENCE OF NON-ONCOGENE ADDICTION UNVEILING TUMOR CELL VULNERABILITIES
ROBERTA NICOLETTI	THE ROLE OF mi RNAS IN REGULATING DRUGS SENSITIVITY AND CELLULAR PLASTICITY IN OVARIAN CANCER: MECHANISMS EVALUATION AND CELLULAR DELIVERY THROUGH RETARGETED NANOPARTICLES
TIZIANA TRIULZI	IDENTIFICATION OF MARKERS TO PREDICT BENEFIT FROM TRASTUZUMAB TREATMENT
RIHAN EL BEZAWI	THE ROLE OF MICRO-RNAS IN THE RADIATION RESPONSE OF HUMAN PROSTATE CANCER
MARIA TERESA MAJORINI	INVESTIGATING THE ROLE OF THE INHIBITOR OF APOPTOSIS PROTEINS(IAPS) IN METASTASIS FORMATION

In addition to the students enrolled in the Open University Program, INT hosts PhD students from diverse institutional and disciplinary backgrounds, mainly registered in PhD Courses with Italian Universities:
The Preventive and Predictive Medicine Department hosts PhD Students enrolled in the School of Biomedical, Clinical and Experimental Sciences, UNIMI: Laura Angelici, Claudio Barberi, Marco Centola, Chiara Ciniselli, Maria Filomeno, Michele Garugno, Maria Ghazanfar, Teresa Greco, Elena Landoni, Alessandra Lugo, Elisabetta Marzo, Monica Pandolfi, Delphine Praud, Tiziana Rosso, Maria Giovanna Scarale.
Attending the Hematology and Pediatric Onco-Hematology Department is Sara Rizzitano (Experimental Medicine and Medical Biotechnologies).
The Surgery Department hosts PhD Students from the UNIMI PhD Program in Physiopathological Sciences: Andrea Billé (fellowship granted by the Fondazione Adele e Bruno Onlus).
The Palliative Care, Pain Therapy, and Rehabilitation Unit hosts Cinzia Brunelli, a PhD student registered in a Program in Palliative Care at the Norwegian University of Science and Technology (Trondheim).
The Department of Experimental Oncology and Molecular Medicine hosts the following PhD students: Katia Rea, Alessandro Satta, (all registered with the UNIMI PhD School in Biological and Molecular Sciences), Annalisa Conti, Giulia Grazia (School of Clinical and Experimental Biomedical Sciences, UNIMI).

MASTERS

• Academic Master in Epidemiology. This is a joint appointment with the University of Turin, ISI Foundation, and INT Unit of Epidemiology and Prevention.
• Master in Rectal Surgery. The Master Rectal Surgery for medical doctors offered by INT and ARECO (Association for the European Research in Surgical Oncology).
• Academic Course in Oncologic Lymphology. The course is designed for physicians and students graduating in lymphology and oncologic lymphology. The Unit of Palliative Care, Pain Therapy, and Rehabilitation is the scientific coordinator and is in charge of educational activities, referred to the Medical Faculty of the University of Milan.
• Master in Medical Statistics and Statistical Methods for Epidemiological Research. MSSME is aimed for graduate with Medicine, Biological Sciences, Physics or Statistics degree. Postgraduate course in biostatistics are also

provided. Postgraduate students are often directly involved in research projects coordinated by MSBB members. The Master Program has been temporarily suspended in AA 2014-2015.

OTHER COURSES

The Pathology Department is involved in the training programs of the Postgraduate Medical Schools of Pathology, Endocrinology, and Respiratory Medicine (University of Milan) and of the Soft Tissue Pathology, Postgraduate School of Pathology.

The Anesthesia Department is involved in the training program and residency of the Postgraduate School for Anesthesia and Intensive Care, hosting a number of residents/students and organizing part of teaching in the program of the Postgraduate Course of the Medical School, University of Milan. Residents in Anesthesia and Intensive Care, Cardiology, Nutritional Support (University of Milan and Milano-Bicocca) work within all the Units of the Department.

Within the Surgery Department, the Unit of Colorectal Surgery is affiliated with the General Surgery Residency Programs of the Milano-Bicocca and Pavia Universities; the Unit of Gastrointestinal and Hepatopancreatobiliary Surgery and Liver Transplantation, chosen for clinical fellowships by many visiting clinicians and surgeons every year, is a training center for the University of Milan and has been for over 10 years a training centre for the School for Italian Surgeons "ACOI", where various of the surgeons from this Unit are involved as teachers.

The Gynecologic Oncology Unit is chosen for clinical fellowships by many visiting surgeons from Italy and abroad every year. It also organizes a biennial international meeting and a gynecologic oncology course with more than 50 participants three times a year.

The Otolaryngology Surgery Unit has close links with the University of Milan, and is involved in postgraduate teaching and supervision of junior medical staff. Thanks to a collaboration with the Human Morphology Department of the University of Milan (where a surgeon from the Unit is engaged as a teacher) every year a live surgery session is organized for postgraduate students. A renewed collaboration with the Otorhinolaryngoiatric School of Specialization of the University of Milan have been discussed in 2014.

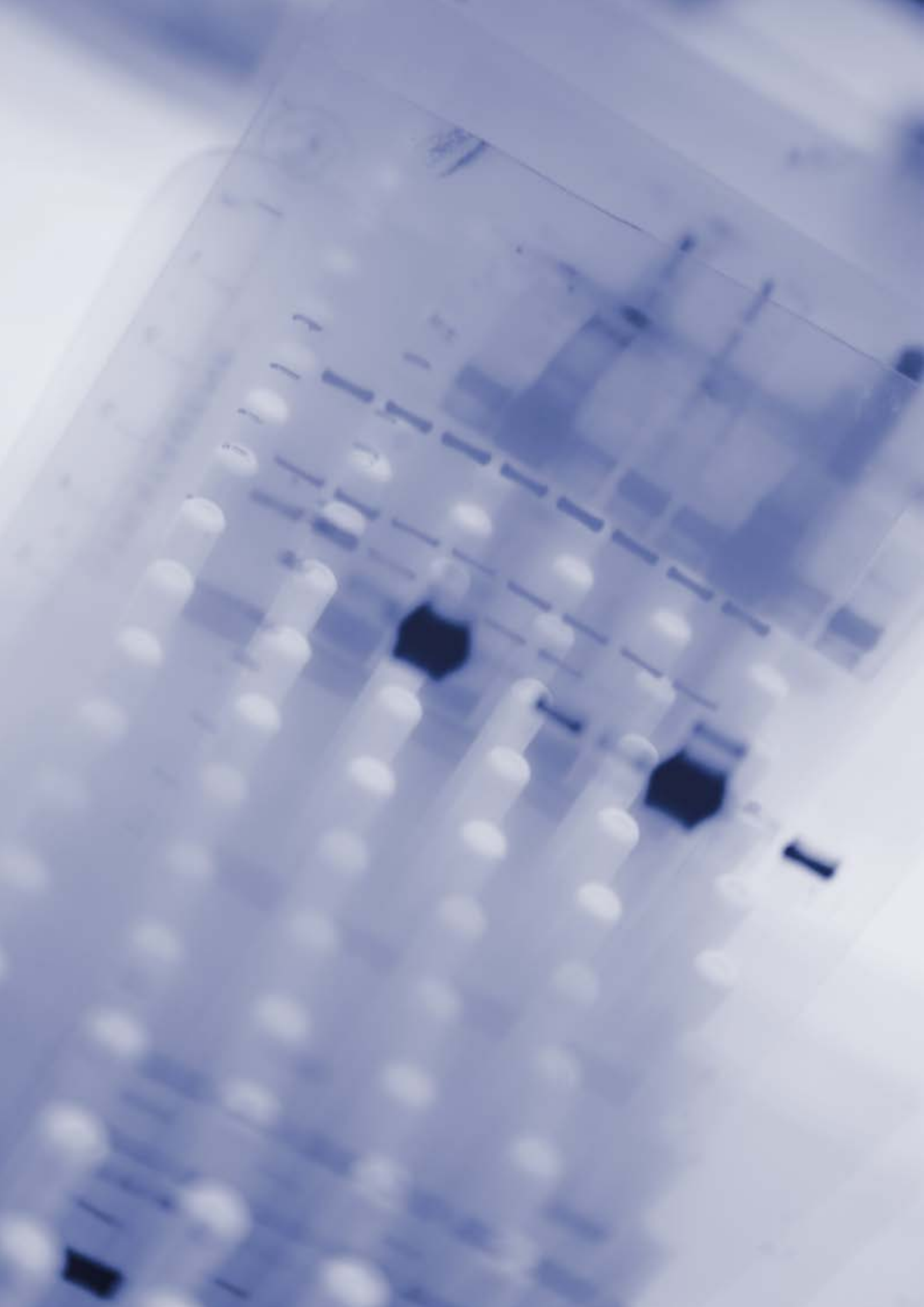
The Thoracic Surgery Unit collaborates with the General Surgery and Thoracic Surgery School of Specialization of the University of Milan, hosting students for practical training.

Several postgraduate students attend the Melanoma and Sarcoma Unit that actively collaborates with several medical universities in Italy and Europe.

The Medical Staff of the Diagnostic Imaging and Radiotherapy Departments is involved in educational activities cooperating with the University of Milan and Milan-Bicocca in the Radiology, Radiotherapy, and Medical Oncology Specialization Schools, in the Clinical Application of Nuclear Medicine of the Nuclear Medicine School of Specialization. The Radiotherapy Unit also provides tutoring of radiography and radiation technician students.

CONTINUING MEDICAL EDUCATION PROGRAM (ECM)

The educational and training program promotes professional, cultural and human growth of INT employees. During 2014, the INT ECM Provider has proposed 181 events in the main areas (clinical governance, on the job learning, risks prevention, and emergency management, etc.) of ECM-CPD (151 were accredited), attracting the interest and the participation of resident and visiting health professionals. In particular, the educational initiatives included in the Business Formation Plan (BFP) have achieved a total amount of about 30,000 formative credits, involving nearly 4,000 individuals.



PUBLICATIONS

N°	Authors	Title	Journal	Impact Factor
1	Abarshi E., Rietjens J., Caraceni A., Payne S., Deliens L., Van Den Block L.	Towards a standardised approach for evaluating guidelines and guidance documents on palliative sedation: Study protocol.	BMC Palliat Care 2014; 13:34	1.787
2	Abarshi E.A., Papavasiliou E.S., Preston N., Brown J., Payne S., Caraceni A., EURO IMPACT	The complexity of nurses' attitudes and practice of sedation at the end of life: a systematic literature review.	J Pain Symptom Manage 2014; 47:915-925.e11	2.737
3	Abbas S., Linseisen J., Rohrmann S., Beulens J.W., Buijsse B., Amiano P., Ardanaz E., Balkau B., Boeing H., Clavel-Chapelon F., Fagherazzi G., Franks P.W., Gavrila D., Grioni S., Kaaks R., Key T.J., Khaw K.T., Kuhn T., Mattiello A., Molina-Montes E., et al.	Dietary vitamin D intake and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition: the EPIC-InterAct study.	Eur J Clin Nutr 2014; 68:196-202	2.95
4	Abuli A., Bujanda L., Munoz J., Buch S., Schafmayer C., Valeria Maiorana M., Veneroni S., van Wezel T., Liu T., Westers H., Esteban-Jurado C., Ocana T., Pique J.M., Andreu M., Jover R., Carracedo A., Xicola R.M., Llor X., Castells A., Dunlop M., Hofstra R., et al.	The MLH1c.1852-1853delinsGC (p.K618A) variant in colorectal cancer: Genetic association study in 18,723 individuals.	PLoS One 2014; 9:e95022	3.534
5	Agarwal D., Pineda S., Michailidou K., Herranz J., Pita G., Moreno L.T., Alonso M.R., Dennis J., Wang Q., Bolla M.K., Meyer K.B., Menéndez-Rodríguez P., Hardisson D., Mendiola M., González-Neira A., Lindblom A., Margolin S., Radice P., Manoukian S., et al.	FGF receptor genes and breast cancer susceptibility: Results from the Breast Cancer Association Consortium.	Br J Cancer 2014; 110:1088-1100	4.817
6	Agnoli C., Grioni S., Sieri S., Sacerdote C., Vineis P., Tumino R., Giurdanella M.C., Pala V., Mattiello A., Chiodini P., Iacoviello L., De Curtis A., Cattaneo L., van Duijnhoven F.J.B., Panico S., Krogh V.	Colorectal cancer risk and dyslipidemia: A case-cohort study nested in an Italian multicentre cohort.	Cancer Epidemiol 2014; 38:144-151	2.558
7	Agorreta J., Hu J., Liu D., Delia D., Turley H., Ferguson D.J., Iborra F., Pajares M.J., Larrayoz M., Zudaire I., Pio R., Montuenga L.M., Harris A.L., Gatter K., Pezzella F.	TRAP1 regulates proliferation, mitochondrial function, and has prognostic significance in NSCLC.	Mol Cancer Res 2014; 12:660-669	4.502
8	Agresti R., Crippa F., Sandri M., Martelli G., Tagliabue E., Alessi A., Pellitteri C., Maccauro M., Maugeri I., Padovano B., Rampa M., Moscaroli A., Ferraris C., Carcangiu M.L., Bianchi G.V., Greco M., Bombardieri E.	Different biological and prognostic breast cancer populations identified by FDG-PET in sentinel node-positive patients: Results and clinical implications after eight-years follow-up.	Breast 2014; 23:334-340	2.581
9	Agresti R., Martelli G., Sandri M., Tagliabue E., Carcangiu M.L., Maugeri I., Pellitteri C., Ferraris C., Capri G., Moliterni A., Bianchi G.V., Mariani G., Trecate G., Lozza L., Langer M., Rampa M., Gennaro M., Greco M., Menard S., Pierotti M.A.	Axillary lymph node dissection versus no dissection in patients with T1N0 breast cancer: A randomized clinical trial (INT09/98).	Cancer 2014; 120:885-893	4.901
10	Agustoni F., Platania M., Vitali M., Zilembo N., Haspinger E., Sinno V., Gallucci R., de Braud F., Garassino M.C.	Emerging toxicities in the treatment of non-small cell lung cancer: Ocular disorders.	Cancer Treat Rev 2014; 40:197-203	6.466
11	Ahmed R.K., Poiret T., Ambati A., Rane L., Remberger M., Omazic B., Vudattu N.K., Winiarski J., Ernberg I., Axelsson-Robertson R., Magalhaes I., Castelli C., Ringden O., Maeurer M.	TCR+CD4-CD8- T cells in antigen-specific MHC class I-restricted T-cell responses after allogeneic hematopoietic stem cell transplantation.	J Immunother 2014; 37:416-425	3.354
12	Ahrens W., Moreno L.A., Marild S., Molnar D., Siani A., De Henauw S., Bohmann J., Gunther K., Hadjigeorgiou C., Iacoviello L., Lissner L., Veidebaum T., Pohlabeln H., Pigeot I., IDEFICS consortium, Krogh V.	Metabolic syndrome in young children: definitions and results of the IDEFICS study.	Int J Obes (Lond) 2014; 38 Suppl 2:S4-14	5.386
13	Ahrens W., Pigeot I., Pohlabeln H., De Henauw S., Lissner L., Molnar D., Moreno L.A., Tornaritis M., Veidebaum T., Siani A., IDEFICS consortium, Krogh V.	Prevalence of overweight and obesity in European children below the age of 10.	Int J Obes (Lond) 2014; 38 Suppl 2:S99-107	5.386

N°	Authors	Title	Journal	Impact Factor
14	Aleksandrova K., Boeing H., Nöthlings U., Jenab M., Fedirko V., Kaaks R., Lukanova A., Trichopoulou A., Trichopoulos D., Boffetta P., Trepo E., Westhpal S., Duarte-Salles T., Stepien M., Overvad K., Tjønneland A., Halkjær J., Boutron-Ruault M.-C., Agnoli C., et al.	Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer.	Hepatology 2014; 60:858-871	11.19
15	Aleksandrova K., Drogan D., Boeing H., Jenab M., Bas Bueno-de-Mesquita H., Jansen E., van Duijnhoven F.J., Rinaldi S., Fedirko V., Romieu I., Kaaks R., Riboli E., Gunter M.J., Romaguera D., Westhpal S., Overvad K., Tjonneland A., Halkjaer J., Agnoli C., et al.	Adiposity, mediating biomarkers and risk of colon cancer in the European prospective investigation into cancer and nutrition study.	Int J Cancer 2014; 134:612-621	5.007
16	Aleksandrova K., Jenab M., Bueno-de-Mesquita H.B., Fedirko V., Kaaks R., Lukanova A., van Duijnhoven F.J., Jansen E., Rinaldi S., Romieu I., Ferrari P., Murphy N., Gunter M.J., Riboli E., Westhpal S., Overvad K., Tjonneland A., Halkjaer J., Agnoli C., et al.	Biomarker patterns of inflammatory and metabolic pathways are associated with risk of colorectal cancer: Results from the European Prospective Investigation into Cancer and Nutrition (EPIC).	Eur J Epidemiol 2014; 29:261-275	5.147
17	Aleksandrova K., Pischon T., Jenab M., Bueno-de-Mesquita H.B., Fedirko V., Norat T., Romaguera D., Knüppel S., Boutron-Ruault M.-C., Dossus L., Dartois L., Kaaks R., Li K., Tjønneland A., Overvad K., Quirós J.R., Buckland G., Sánchez M.J., Krogh V., et al.	Combined impact of healthy lifestyle factors on colorectal cancer: A large European cohort study.	BMC Med 2014; 12:168	7.276
18	Ali A.M., Schmidt M.K., Bolla M.K., Wang Q., Gago-Dominguez M., Castelao J.E., Carracedo A., Garzon V.M., Bojesen S.E., Nordestgaard B.G., Flyger H., Chang-Claude J., Vrieling A., Rudolph A., Seibold P., Nevanlinna H., Muranen T.A., Krogh V., et al.	Alcohol consumption and survival after a breast cancer diagnosis: A literature-based meta-analysis and collaborative analysis of data for 29,239 cases.	Cancer Epidemiol Biomarkers Prev 2014; 23:934-945	4.324
19	Ali T.H., Pisanti S., Ciaglia E., Mortarini R., Anichini A., Garofalo C., Tallerico R., Santinami M., Gulletta E., Ietto C., Galgani M., Matarese G., Bifulco M., Ferrone S., Colucci F., Moretta A., Karre K., Carbone E.	Enrichment of CD56(dim)KIR + CD57 + highly cytotoxic NK cells in tumour-infiltrated lymph nodes of melanoma patients.	Nat Commun 2014; 5:5639	10.742
20	Alterio D., Ciardo D., Preda L., Argenone A., Caspiani O., Micera R., Ruo Redda M.G., Russi E.G., Bianchi E., Orlandi E., Bacigalupo A., Busetto M., Cante D., Deantonio L., De Sanctis V., Franco P., Lastrucci L., Marucci L., Merlotti A., Molteni M., Pajar F., et al.	Contouring of the Pharyngeal Superior Constrictor Muscle (PSCM). A cooperative study of the Italian Association of Radiation Oncology (AIRO) Head and Neck Group.	Radiother Oncol 2014; 112:337-342	4.857
21	Ambrogi F., Biganzoli E., Boracchi P.	Model-based estimation of measures of association for time-to-event outcomes.	BMC Med Res Methodol 2014; 14:97	2.168
22	Ambrogi F., Fornili M., Boracchi P., Trerotola M., Relli V., Simeone P., La Sorda R., Lattanzio R., Querzoli P., Pedriali M., Piantelli M., Biganzoli E., Alberti S.	Trop-2 is a determinant of breast cancer survival.	PLoS One 2014; 9:e96993	3.534
23	Ambrogi F., Trevisi L., Martelli G., Boracchi P.	Is breast cancer curable: A study of long-term crude cumulative incidence.	Tumori 2014; 100:406-414	1.09
24	Anantharaman D., Gheit T., Waterboer T., Halec G., Carreira C., Abedi-Ardekani B., McKay-Chopin S., Zaridze D., Mukeria A., Szeszenia-Dabrowska N., Lissowska J., Mates D., Janout V., Foretova L., Bencko V., Rudnai P., Fabianova E., Krogh V., et al.	No causal association identified for human papillomavirus infections in lung cancer.	Cancer Res 2014; 74:3525-3534	9.284
25	Anastasia A., Carlo-Stella C., Corradini P., Salvi F., Rusconi C., Pulsoni A., Hohaus S., Pregno P., Viviani S., Brusamolino E., Luminari S., Giordano L., Santoro A.	Bendamustine for Hodgkin lymphoma patients failing autologous or autologous and allogeneic stem cell transplantation: A retrospective study of the Fondazione Italiana Linfomi.	Br J Haematol 2014; 166:140-142	4.959
26	Andreassen Jaatun E.A., Hjermstad M.J., Gundersen O.E., Oldervoll L., Kaasa S., Haugen D.F., Caraceni A.	Development and testing of a computerized pain body map in patients with advanced cancer.	J Pain Symptom Manage 2014; 47:45-56	2.737

N°	Authors	Title	Journal	Impact Factor
27	Angelico M., Nardi A., Romagnoli R., Marianelli T., Corradini S.G., Tandoi F., Gavrila C., Salizzoni M., Pinna A.D., Cillo U., Gridelli B., De Carlis L.G., Colledan M., Mazzaferro V., Regalia E., Sposito C., Liver Match Study Investigators	A Bayesian methodology to improve prediction of early graft loss after liver transplantation derived from the liver match study.	Dig Liver Dis 2014; 46:340-347	2.889
28	Antoniou A.C., Casadei S., Heikkinen T., Barrowdale D., Pylkäs K., Roberts J., Lee A., Subramanian D., De Leeneer K., Fostira F., Tomiak E., Neuhausen S.L., Teo Z.L., Khan S., Aittomäki K., Moilanen J.S., Turnbull C., Seal S., Radice P., Manoukian S.	Breast-cancer risk in families with mutations in PALB2.	N Engl J Med 2014; 371:497-506	54.42
29	Appierto V., Callari M., Cavadini E., Morelli D., Daidone M.G., Tiberio P.	A lipemia-independent NanoDrop®-based score to identify hemolysis in plasma and serum samples.	Bioanalysis 2014; 6:1215-1226	3.027
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611	Verderio P., Bottelli S., Ciniselli C.M., Pierotti M.A., Gariboldi M., Pizzamiglio S.	NqA: An R-based algorithm for the normalization and analysis of microRNA quantitative real-time polymerase chain reaction data.	Anal Biochem 2014; 461:7-9	2.305
612	Vermorken J.B., Psyrri A., Mesía R., Peyrade F., Beier F., De Blas B., Celik I., Licitra L.	Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: Retrospective analysis of the phase iii extreme trial.	Ann Oncol 2014; 25:801-807	6.578
613	Verzoni E., Grassi P., Testa I., Iacovelli R., Biondani P., Garanzini E., de Braud F., Procopio G.	Targeted treatments in advanced renal cell carcinoma: Focus on Axitinib.	Pharmgenomics Pers Med 2014; 7:107-116	0
614	Verzoni E., Pusceddu S., Buzzoni R., Garanzini E., Damato A., Biondani P., Testa I., Grassi P., Bajetta E., de Braud F., Procopio G.	Safety profile and treatment response of everolimus in different solid tumors: An observational study.	Future Oncol 2014; 10:1611-1617	2.611
615	Villani A., Malfatto G., Compare A., Dalla Rosa F., Bellardita L., Branzi G., Molinari E., Parati G.	Clinical and psychological telemonitoring and telecare of high risk heart failure patients.	J Telemed Telecare 2014; 20:468-475	1.736

N°	Authors	Title	Journal	Impact Factor
616	Viprey V.F., Gregory W.M., Corrias M.V., Tchirkov A., Swerts K., Vicha A., Dallorso S., Brock P., Luksch R., Valteau-Couanet D., Papadakis V., Laureys G., Pearson A.D., Ladenstein R., Burchill S.A.	Neuroblastoma mRNAs predict outcome in children with stage 4 neuroblastoma: A European HR-NBL1/SIOPEN study.	J Clin Oncol 2014; 32:1074-1083	17.879
617	Virgone C., Cecchetto G., Alaggio R., Ferrari A., Bisogno G., Conte M., Inserra A., Fagnani A.M., Indolfi P., Salfi N., Dall'igna P.	Appendiceal neuroendocrine tumours in childhood: Italian TREP project.	J Pediatr Gastroenterol Nutr 2014; 58:333-338	2.873
618	Vitale A., Volk M.L., De Feo T.M., Burra P., Frigo A.C., Ramirez Morales R., De Carlis L., Belli L., Colledan M., Fagiuoli S., Rossi G., Andorno E., Baccarani U., Regalia E., Vivarelli M., Donataccio M., Cillo U.	A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list.	J Hepatol 2014; 60:290-297	10.401
619	Vitellaro M., Sala P., Signoroni S., Radice P., Fortuzzi S., Civelli E.M., Ballardini G., Kleiman D.A., Morrissey K.P., Bertario L.	Risk of desmoid tumours after open and laparoscopic colectomy in patients with familial adenomatous polyposis.	Br J Surg 2014; 101:558-565	5.21
620	Vizioli M.G., Santos J., Pilotti S., Mazzoni M., Anania M.C., Miranda C., Pagliardini S., Pierotti M.A., Gil J., Greco A.	Oncogenic RAS-induced senescence in human primary thyrocytes: Molecular effectors and inflammatory secretome involved.	Oncotarget 2014; 5:8270-8283	6.627
621	Voigt W., Hoellthaler J., Magnani T., Corrao V., Valdagni R.	Act on oncology' as a new comprehensive approach to assess prostate cancer centres - Method description and results of a pilot study.	PLoS One 2014; 9:e106743	3.534
622	Walrand S., Hesse M., Chiesa C., Lhommel R., Jamar F.	The low hepatic toxicity per gray of 90Y glass microspheres is linked to their transport in the arterial tree favoring a nonuniform trapping as observed in posttherapy PET imaging.	J Nucl Med 2014; 55:135-140	5.563
623	Wang Z., Zhu B., Zhang M., Parikh H., Jia J., Chung C.C., Sampson J.N., Hoskins J.W., Hutchinson A., Burdette L., Ibrahim A., Hautman C., Raj P.S., Abnet C.C., Adjei A.A., Ahlbom A., Albanes D., Allen N.E., Krogh V., Sieri S., et al.	Imputation and subset-based association analysis across different cancer types identifies multiple independent risk loci in the TERT-CLPTM1L region on chromosome 5p15.33.	Hum Mol Genet 2014; 23:6616-6633	6.677
624	West C., Azria D., Chang-Claude J., Davidson S., Lambin P., Rosenstein B., De Ruysscher D., Talbot C., Thierens H., Valdagni R., Vega A., Yuille M.	The REQUITE Project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors.	Clin Oncol (R Coll Radiol) 2014; 26:739-742	2.826
625	West E., Costantini M., Pasman H.R., Onwuteaka-Philipsen B., EURO IMPACT, Caraceni A.	A comparison of drugs and procedures of care in the Italian hospice and hospital settings: the final three days of life for cancer patients.	BMC Health Serv Res 2014; 14:496	1.659
626	Whiley P.J., De La Hoya M., Thomassen M., Becker A., Brandão R., Pedersen I.S., Montagna M., Menéndez M., Quiles F., Gutiérrez-Enríquez S., Leeneer K.D., Tenés A., Montalban G., Tserpelis D., Yoshimatsu T., Tirapo C., Colombo M., De Vecchi G., Radice P., et al.	Comparison of mRNA splicing assay protocols across multiple laboratories: Recommendations for best practice in standardized clinical testing.	Clin Chem 2014; 60:341-352	7.768
627	Wiernikowski J.T., MacLeod S., Working Group on Essential Medicines of the Pediatric Oncology in Developing Countries committee of SIOP, Casanova M.	Regulatory and logistical issues influencing access to antineoplastic and supportive care medications for children with cancer in developing countries.	Pediatr Blood Cancer 2014; 61:1513-1517	2.562
628	Wolpin B.M., Rizzato C., Kraft P., Kooperberg C., Petersen G.M., Wang Z., Arslan A.A., Beane-Freeman L., Bracci P.M., Buring J., Canzian F., Duell E.J., Gallinger S., Giles G.G., Goodman G.E., Goodman P.J., Jacobs E.J., Kamineni A., Klein A.P., Krogh V., et al.	Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer.	Nat Genet 2014; 46:994-1000	29.648
629	Wynne C., Lazzari E., Smith S., McCarthy E.M., Ni Gabhann J., Kallal L.E., Higgs R., Greco A., Cryan S.A., Biron C.A., Jefferies C.A.	TRIM68 negatively regulates IFN-beta production by degrading TRK fused gene, a novel driver of IFN-beta downstream of anti-viral detection systems.	PLoS One 2014; 9:e101503	3.534

N°	Authors	Title	Journal	Impact Factor
630	Zamora-Ros R., Forouhi N.G., Sharp S.J., Gonzalez C.A., Buijsse B., Guevara M., van der Schouw Y.T., Amiano P., Boeing H., Bredsdorff L., Fagherazzi G., Feskens E.J., Franks P.W., Grioni S., Katzke V., Key T.J., Khaw K.T., Kuhn T., Masala G., Mattiello A., et al.	Dietary intakes of individual flavanols and flavonols are inversely associated with incident type 2 diabetes in European populations.	J Nutr 2014; 144:335-343	4.227
631	Zamora-Ros R., Lujan-Barroso L., Bueno-de-Mesquita H.B., Dik V.K., Boeing H., Steffen A., Tjonneland A., Olsen A., Bech B.H., Overvad K., Boutron-Ruault M.C., Racine A., Fagherazzi G., Kuhn T., Katzke V., Trichopoulou A., Lagiou P., Grioni S., et al.	Tea and coffee consumption and risk of esophageal cancer: The European prospective investigation into cancer and nutrition study.	Int J Cancer 2014; 135:1470-1479	5.007
632	Zamora-Ros R., Sacerdote C., Ricceri F., Weiderpass E., Roswall N., Buckland G., St-Jules D.E., Overvad K., Kyrø C., Fagherazzi G., Kvaskoff M., Severi G., Chang-Claude J., Kaaks R., Nöthlings U., Trichopoulou A., Naska A., Trichopoulos D., Palli D., Grioni S., et al.	Flavonoid and lignan intake in relation to bladder cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.	Br J Cancer 2014; 111:1870-1880	4.817
633	Zannella S., Testi M.A., Cattoretti G., Pelosi G., Zucchini N.	Peritoneal malignant mesothelioma metastatic to supraclavicular lymph nodes.	Int J Surg Pathol 2014; 22:552-554	0.961
634	Zannini L., Delia D., Buscemi G.	CHK2 kinase in the DNA damage response and beyond.	J Mol Cell Biol 2014; 6:442-457	8.432
635	Zanutto S., Pizzamiglio S., Ghilotti M., Bertan C., Ravagnani F., Perrone F., Leo E., Pilotti S., Verderio P., Gariboldi M., Pierotti M.A.	Circulating miR-378 in plasma: A reliable, haemolysis-independent biomarker for colorectal cancer.	Br J Cancer 2014; 110:1001-1007	4.817
636	Zappasodi R., Cavanè A., Iorio M.V., Tortoreto M., Guarnotta C., Ruggiero G., Piovan C., Magni M., Zaffaroni N., Tagliabue E., Croce C.M., Zunino F., Gianni A.M., Di Nicola M.	Pleiotropic antitumor effects of the pan-HDAC inhibitor ITF2357 against c-Myc-overexpressing human B-cell non-Hodgkin lymphomas.	Int J Cancer 2014; 135:2034-2045	5.007
637	Zhang H., Korenkova V., Sjoback R., Svec D., Bjorkman J., Kruhoffer M., Verderio P., Pizzamiglio S., Ciniselli C.M., Wyrich R., Oelmueller U., Kubista M., Lindahl T., Lonneborg A., Rian E.	Biomarkers for monitoring pre-analytical quality variation of mRNA in blood samples.	PLoS One 2014; 9:e111644	3.534
638	Zuccolotto G., Fracasso G., Merlo A., Montagner I.M., Rondina M., Bobisse S., Figini M., Cingarlini S., Colombatti M., Zanovello P., Rosato A.	PSMA-specific CAR-engineered T cells eradicate disseminated prostate cancer in preclinical models.	PLoS One 2014; 9:e109427	3.534

ONGOING PROJECTS SUPPORTED BY CHARITIES, INTERNATIONAL AND NATIONAL ORGANIZATIONS

Association for International Cancer Research (AICR) - UK

- Matricellular SPARC in bone marrow failure and lymphomas

"Bianca Garavaglia" Association

- Research activity in pediatric tumors

Association for Italian Cancer Research (AIRC)

- 213Bi-DOTATATE as agent for peptide receptor alpha therapy: preclinical and clinical evaluation
- Agonists and antagonists of Toll-like Receptor 9 in oncological experimental models
- Cadherin-associated signalling pathways in ovarian cancer
- Cell therapy with TRAIL-armed, genetically engineered or phenotypically redirected, effectors (AIRC 5x1000)
- Changes in weight and inflammation markers in relation to breast cancer risk: a nested case-control study
- Circulating miRNAs to predict outcome and to guide treatment of breast cancer patients on preoperative systemic therapy
- Contribution of fibroblasts to stem cell niche in lung cancer
- Diagnostic and therapeutic potential of microRNAs in Lung Cancer
- Distant metastases in early breast cancer: links with activation of inflammatory and immune response genes
- Drug Resistence in Sarcoma Targeted Treatments
- Early innovative diagnostic procedures of lung cancer progression
- Effects of high Intra-abdominal pressure on tissue diffusion and pharmacokinectics of cisplatin during HIPEC
- Efficacy of thermal treatment for respiratory airways in heavy smokers
- Evaluation of biomarkers to predict treatment response in relapsed myeloma
- Extracellular Matrix-Mast cells interplay molds nascent tumor microenvironment
- From regional node to systemic immunity suppression in melanoma metastatic progression
- Hepcidin: clinical utility as a diagnostic tool and potential therapeutic target in breast cancer
- Hypercoagulation screening as an innovative tool for risk assessment, early diagnosis and prognosis in cancer (AIRC 5x1000)
- Identification and validation of miRNAs as novel biomarkers and therapeutic targets in peritoneal mesothelioma
- Identification of expression networks as effectors of genetic susceptibility to lung cancer in mice
- Identification of a molecular predictor of response to Cetuximab based on a phase II trial in recurrent/metastatic HNSCC
- Identifying new molecular pathways and predictor biomarkers of GVHD after allogeneic-HSCT
- Innovative approach for discovery and development of promising targeted agents in head and neck cancer
- Integrative genomic analysis of intrahepatic cholangiocarcinoma: implication for clinical management
- Involvement of microRNAs in breast cancer driving pathways: from biology to possible therapies

- Lifestyle and Breast Cancer Recurrences: The DIANA-5 Trial
- MicroRNAs in papillary thyroid carcinoma: pathways involved and possible therapeutic targets
- Modulating the inflammatory phenotype of cutaneous melanoma
- Novel approaches for the assessment of the functional effects of unclassified variants in BRCA genes
- Overcoming Anti-Angiogenic Therapy Resistance in Selected Sarcomas
- Pediatric malignant glioma: progress starting from the worst case scenario of diffuse intrinsic pontine glioma
- Plasma microRNA profiling as first line screening test for lung cancer detection: a prospective study
- Regulation of myeloid cells homeostasis by ECM proteins: implication for autoimmunity and myeloid malignancies
- Retrospective and prospective study of late radiation damages after focal radiotherapy for childhood brain tumors
- Role of acidity in tumor immunity
- Role of chemotherapy in Trastuzumab cytotoxic activity
- Role of Δ-16-HER2-splice variant in response to biodrugs targeting HER2 receptor
- Role of germline and somatic DNA change in modulating the survival of patients with lung adenocarcinoma
- Role of miRNAs in the control of prostate cancer metastases
- Role of oncogene induced senescence and non oncogene addition in thyroid carcinogenesis
- Statistical tools for prognosis and prediction in cancer: assessments and application to a sarcoma case series
- Targeting of ALK kinase activity in neuroblastoma and rhabdomyosarcoma
- The ovarian cancer cholinic phenotype: exploring possible theragnostic windows
- Therapeutic pathology: the receptor tyrosin kinase model
- Therapeutic targeting of pathways leading to generation of TGFb+myeloid suppressor cells in melanoma patients
- Toremifene in desmoid tumor: prospective clinical trial and identification of potential molecular targets
- Towards improved targeted therapies of melanoma by phosphoproteomics and RTK profiling
- Tumor-microenvironment related changes as new tools for early detection and assessment of high-risk disease (AIRC 5x1000)
- Understanding the biological basis of chemorefractoriness in peripheral T-cell Lymphoma to develop novel treatments
- Validation of HSP105 as novel biotarget in human non-Hodgkin lymphomas
- Wound-healing and vasculogenic mimicry as players of early relapse in triple negative breast carcinomas

Compagnia di San Paolo and CARIPLO Foundation

- EUROCARE - high resolution collection of clinical data and statistical analysis for the interpretation of the prognostic disparities in Italy

CARIPLO Foundation

- Contribution of T-memory stem cells to successful immune-recovery in humans following bone marrow transplantation
- Disease recurrence in epithelial ovarian cancer: deciphering miRNA-driven regulatory networks related to drug sensitivity/cellular plasticity and exploring nanomaterial-based targeted delivery of identified key molecules for therapeutic purposes
- Role of Tumor Microenvironment in Thyroid Carcinogenesis Onset and Progression: Thyroid Cell Cross-Talk with Macrophages
- Targeting pro-survival features of tumor cells by novel inhibitors of the AKT kinase

"Guido Berlucchi" Foundation

- Identification of schemes for integrated treatment of lung carcinoma in preclinical models

"Italo Monzino" Foundation

- Identification and validation of novel therapeutic targets and biomarkers in prostate cancer
- PRIAS - Hormonal and genetic characterization of patients in active surveillance
- PROCABIO - Personalized treatment of prostate cancer using biomarkers

"Luogo di Vita e di Incontro" (LU.V.I.) Foundation

- European study on symptoms in palliative care

Italian League Against Cancer (LILT)

- DARE - Women at ereditary risk
- Psicological determinants and impact of the choice of preventive strategies in two distinct population: healthy women/women with breast cancer, bearer of BRCA 1 and 2 mutation

Telethon

- Determinants of neurodegeneration in Ataxia Telangiectasia

The Harry J Lloyd Charitable Trust - USA

- Study of microRNA related to myeloid derived suppressor cells in early melanoma patients

National Cancer Institute (NCI) - USA

- Identifying non-coding RNAs for early detection and prevention of lung cancer

Desmoid Tumor Research Foundation

- High throughput genome study to identify predictors of aggressiveness in patients with sporadic desmoid tumor who undergo a wait and see approach

European Union

- BENCH-CAN - Benchmarking comprehensive cancer care that provides interdisciplinary treatment for patients, and yield examples of best practice in comprehensive cancer care
- BERTA - Berberine new derivatives as antitumor agents for cancer therapy
- (BIO RARE) K-RAS mutations and DNA repair function in NSCLC
- CANCON - European guide on quality improvement in comprehensive cancer control

- EPAAC - European Partnership for Action Against Cancer
- EPIC-CVD - Individualised CVD risk assessment: tailoring targeted and cost-effective approaches to Europe's diverse populations
- EurocanPlatform - A European platform for translational cancer research
- EUROSARC - European clinical trials in rare sarcomas within an integrated translational trial network
- ExPo-r-NeT - European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment
- HSCT and JAK-STAT - HSCT and Jak-Stat-role and modulation of jak and stat signaling in graft rejection and graft versus host disease
- IACT - Immunostimolatory Agonist Antibodies for Cancer Therapy
- I.Family - Determinants of eating behavoiur in european children, adolescents and their parents
- IMMUNOCAN - Toward enhancing activities of European institutions in the FDUSCC-IM cancer research joint institute in China
- MEMEME - Randomized controlled trial of metformin and dietary restriction to prevent age-related morbid events in people with metabolic syndrome
- RARECARENet - Rare cancers information network
- REQUITE - Validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality-of-life in cancer survivors

Health Ministry - ITALY

- A multicenter randomized trial of contrast-enhanced MR imaging as a breast cancer screening tool in addition to mammography and ultrasonography in women at intermediate risk: feasibility and short-term results
- A randomized controlled trial of diet and physical activity in BRCA mutation carriers
- Activity of Imatinib and Everolimus in advanced chordoma patients progressing on Imatinib
- Allergic components in experimental multiple sclerosis: novel targets for immune intervention
- Cerebrospinal fluid proteome from Central Nervous System pediatric tumours: patient related pattern
- Comparisons of population-based indicators in oncology
- Deleted in BRCA1, a new player in the DNA damage response
- "Early detection and treatment of recurrent, chemotherapy-resistant ovarian cancer stem cells by CPE peptide complexed superparamagnetic iron-oxide nanoparticles (CPE-SPIONs)"
- Evaluation of reproductive risk in areas at high environmental pression
- Extending comprehensive cancer center expertise in patient education: the power of partnership with patient representatives
- Identification and functional validation of microRNA biomarkers in lung cancer
- IGF-I isoforms and breast cancer
- IL-6-related inflammation signatures as a predictive marker of recurrence in liver cancer patients
- Imatinib for the treatment of plexiform neurofibromas in NFI patients
- Interaction framework between patient advocacy groups and cancer centers on sarcomas, as a model for rare cancers
- Involvement of microRNAs in triple negative breast cancer: from biology to possible therapeutic applications
- National network for the promotion of the understanding of molecular phenomena, the optimization of diagnostic and prototype clinical interventios for malignant pleural mesothelioma
- Neoadjuvant targeted agents followed by surgery in squamous cell carcinoma of head and neck: detection of promising agents through identification of molecular and imaging parameters to predict treatment activity and/or resistance
- Peritoneal mesothelioma: optimize outcomes by the integration of new prognostic factors and potential therapeutic targets in a individualized treatment based on molecular characterization and chemosensitivity profile on primary cultures

- Plasma microRNA profiling as first line screening test for lung cancer detection: a prospective study
- Potentiating clinical and immunological effects of chemotherapy by neutralizing acidic pH at tumor site: a phase II randomized study in melanoma patients
- Preoperative TPF chemotherapy in locally advanced resectable oral cavity squamous cell cancer in order to improve pathological complete response rate: a phase II study
- Role of delta16HER2 splice variant in tumor progression and in response to biodrugs targeting HER2 receptor
- Role of nutrients involved in one-carbon metabolism in the development of different molecular subtypes of breast cancer in the ORDET
- Safety, traceability and reliability of collection, processing and transplantation of haematopoietic stem cells (HSCs) and therapeutic cells (TCs): integrated procedures and tools to support operations, clinical care and banking
- Tailored accreditation model for comprehensive cancer centers: validation through the applicability of the experimental OECI-based model to the ACC Network of Cancer IRCCS
- Tailored beta-catenin mutational approach in extraabdominal sporadic desmoid tumor patients
- The role of early systematic best palliative care versus on request palliative care consultation during standard oncologic treatment for patients with advanced gastric or pancreatic cancer: a randomized, controlled, multicenter trial

Italian Citizens "5x1000" to Fondazione IRCCS Istituto Nazionale dei Tumori

- Caloric restriction: metabolism and cancer
- External stereotactic high-dose fraction radiotherapy for prostate cancer
- Innovative and interdisciplinary projects through funding genomics and transcriptomics analysis (NGS)
- Multidisciplinary approach for early diagnosis of colorectal carcinoma using molecular signatures
- New technological frontiers for molecular diagnostics and preclinical research
- Prospective evaluation of plasma levels of inflammation markers in radiation therapy of prostate cancer and correlation with acute and late rectal toxicity
- The hereditary breast and ovarian cancer: clinical and molecular characterization
- The institutional biobank
- To invest in young people: the PhD resource in the educational tenure track of the international biomedical research
- Translating the results of scientific research and innovative therapies giving support to no-profit phase I trials
- Realizzazione del registro clinico per il tumore della mammella
- Studio EPIC-Italia

University and Research Ministry (MIUR) - ITALY

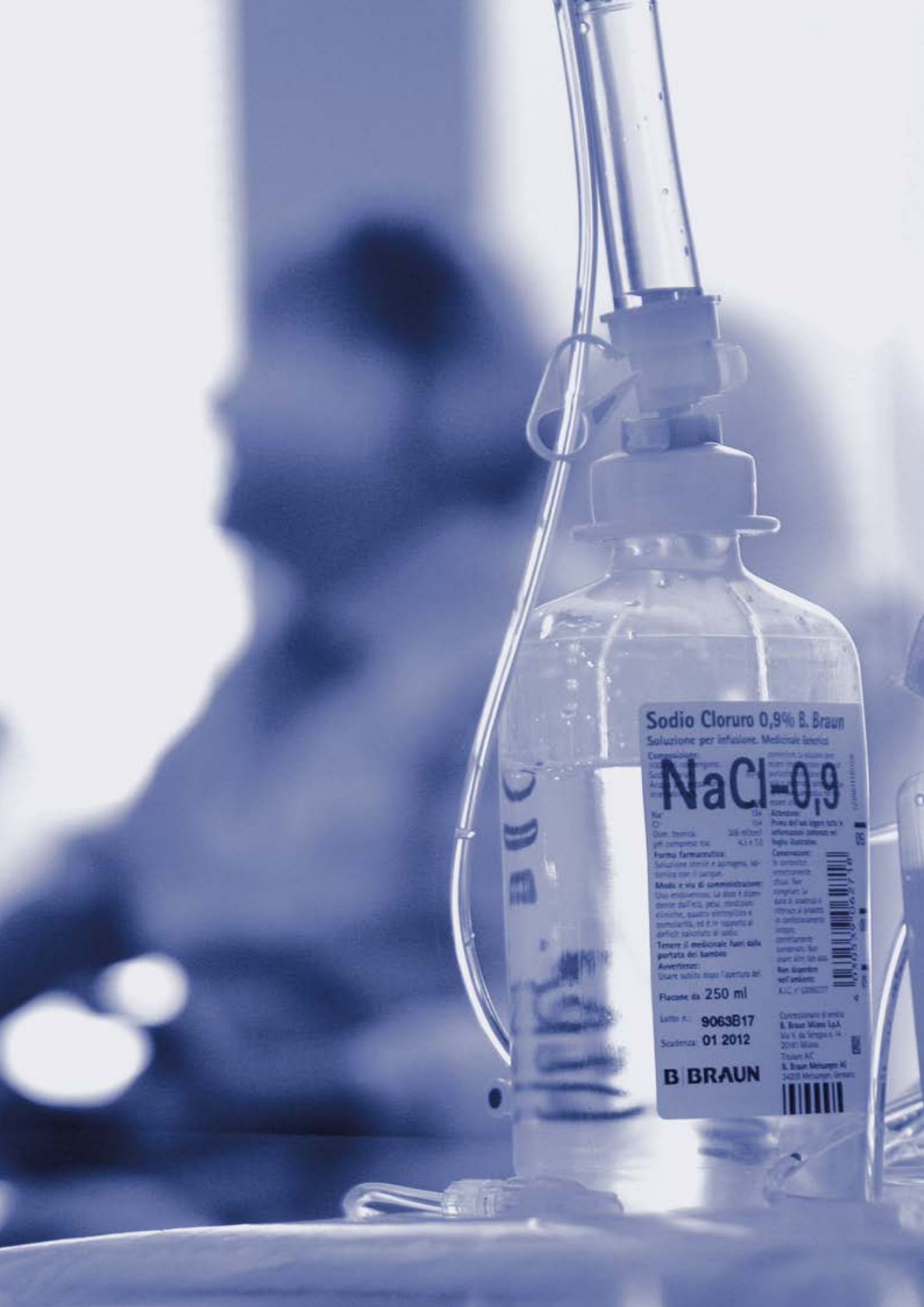
- NEWTON - Advanced nanosystems for a new molecular oncology
- ONCODIET
- PATRI (Piattaforma di Analisi TRaslazionale Integrata)

TRANSCAN: Italian Health Ministry & Europena Union

- BIO RARE - K-RAS mutations and DNA repair function in non-small cell lung cancer

Lombardy Region

- A study with diffusion tensor of radio-induced cerebral damage related to cognitive deficits in the pediatric population
- Utilizzo di donatori con lesioni encefaliche HBSAG positivi, anti-HBCORE positivi, o ANTI-HCV positivi secondo le linee guida nazionali:miglioramento del modello di allocazione del fegato attraverso la raccolta e la valutazione dei risultati di sopravvivenza di organo paziente a breve medio e lungo termine
- Lombardy Network in Oncology (ROL)
- ITACO - Secure management of the patient and risk control processes operating room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ETHICS COMMITTEE

The Institutional Ethics Committee reviews all new clinical studies submitted by investigators and previously approved by the Scientific Institutional Review Board. The Committee was established in 1973.

Updated national and regional rules on ethics committees issued during 2013 gave the Ethics Committee of this institute the additional role to connect the Ethics Committees of the twelve scientific institutions ("IRCCS") of the Lombardy Region. Therefore, during 2014, their representatives regularly met and discussed relevant items, such as issues pertaining to no-profit studies and conflicts of interest in clinical research. This speculative effort is in progress. On the other side, a core Regulation for all Ethics Committees of the IRCCSs was finalized in 2014 and approved by Lombardy Region, to harmonize their basic rules of functioning.

In 2014, 210 new studies were submitted to the Ethics Committee for approval: 101 were interventional trials, of which 54 were sponsored by pharmaceutical companies and 47 were investigator-driven; 109 were observational, of which 10 were sponsored by pharmaceutical companies and 99 were investigator-driven. Compared to 2012 and 2013, the number of clinical studies submitted was increased, respectively, by 28% and 10%. The increase is mainly due to the observational investigator-driven studies. However, there was also a slight increase of observational studies sponsored by pharmaceuticals industries aimed at collecting additional safety data to support the submission for AIC (EAP - Expanded Access Programs and PASS - Post Authorization Safety Studies).

The median time from submission to Ethics Committee discussion was in the range of one month (29 days), thus paralleling the satisfactory timelines of previous years.

During 2014, a total of 534 studies were active: 274 studies were enrolling, 166 studies were closed to accrual and 94 ended during the year. A total of 59,884 cases are involved, 16,551 of which were enrolled in 2014, most of them (13,599) involved in observational studies and the others (2,952) in interventional studies (706 patients in industry-sponsored trials and 2,246 in investigator-driven trials).

CHAIRMAN

Valter Torri

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ONGOING CLINICAL STUDIES

Breast Carcinoma

Study Code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
32/03	Prognostic significance of blood concentrations of testosterone and insulin in women with early breast cancer	F. Berrino	2003		Observational	2.467	Closed accrual
06/04	Immunization of patients with locally advanced/metastatic breast and ovarian cancer with autologous monocyte-derived dendritic cells loaded with apoptotic/necrotic autologous tumor cells exposed to heat shock	A. M. Gianni	2004		Pilot	4	Closed accrual
68/05	A phase II, single arm, multicentre study to evaluate the efficacy and safety of the combination of Omnitarg and Herceptin in patients with HER2 positive metastatic breast cancer	G. V. Bianchi	2006		II	7	Closed accrual
39/06	A randomized, open-label, 2-arm, multicentre, phase III study to evaluate the efficacy and safety of bevacizumab in combination with Trastuzumab/docetaxel compared with Trastuzumab/Docetaxel alone as first line treatment for patients with HER2 positive locally recurrent or metastatic breast cancer	A. Moliterni	2006	6/30/2014	III	14	Closed accrual
37/07	Randomized trial of diet, physical activity and breast cancer recurrences: the DIANA-5 study	F. Berrino	2007		-	1.667	Closed accrual
47/07	A randomized multicentric international phase II study of Herceptin® and docetaxel versus docetaxel in association with OmnitargTM and Herceptin® versus OmnitargTM and Herceptin® in the treatment of locally advanced HER-2 positive breast cancer, inflammatory or early breast cancer	G. Bianchi	2007	9/19/2014	II	28	Closed accrual
18/08	Phase II study. Safety of the scheme of adjuvant or primary sequential chemotherapy in operable breast cancer at high risk (AT x 3 - CMF x 3)	A. Moliterni	2008	3/1/2014	II	352	Closed accrual
76/08	Tevere project: primary prevention of breast cancer by diet, physical activity or Metformin assumption	F. Berrino	2009		III	453	92
16/09	A randomized, multicenter, phase III open-label study of the efficacy and safety of trastuzumab-MCC-DM1 vs capecitabine+lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy	G. Bianchi	2009		III	6	Closed accrual
33/09	A phase Ib, open label, dose escalation study of the safety and pharmacology of P13-kinase inhibitor GDC-0941 in combination with paclitaxel and bevacizumab in patients with locally recurrent or metastatic breast cancer	S. Cresta	2009		Ib	22	0
63/09	A randomized phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer	G. Bianchi	2010		III	8	Closed accrual
15/11	The SERISCAFFOLD Use in reconstruction post-market study for tissue support and repair in direct-to-implant breast reconstruction surgery	M. Nava	2011		-	4	Closed accrual
93/11	An open-label, multicenter extension study of trastuzumab- MCC-DM1 (T-DM1) administered as a single agent or in combination with other anti-cancer therapies in patients previously treated with the equivalent T-DM1 regimen in a Genentech and /or F. Hoffmann-La Roche Ltd. - sponsored - T-DM1 study	G. V. Bianchi	2011		II	1	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
101/11	Effect of oral red clover on the symptoms of menopausal syndrome induced by adjuvant hormonal treatment in women with a diagnosis of breast cancer	C. Ferraris	2012		IV	88	11
102/11	A randomized, two-arm, open label, multicenter phase II trial assessing the efficacy and safety of pertuzimab given in combination with trastuzumab plus in aromatase inhibitor in first line patients with HER 2-positive and hormone receptor-positive advanced (metastastic and locally advanced) breast cancer	G. V. Bianchi	2011		II	2	0
29/12	A phase III prospective, two-cohort non-randomized, multi-centre, miltinational, open label study to assess the safety of asisted-and self-admnistered subcutaneous trastuzumab as adjuvant therapy in patients with operable HER-2-positive early breast cancer	G. Mariani	2013		III	5	Closed accrual
51/12	Identification of genes associated with toxicity from radiation in breast cancer patients	L. Lozza	2012		Observational	126	39
64/12	An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane	G. Mariani	2012	7/29/2014	III	41	Closed accrual
78/12	A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer which progressed on or after aromatase inhibitor treatment	F. De Braud	2013		III	4	1
81/12	A randomized, blinded, single center study to assess the incidence of surgical site infections in breast cancer surgery after preoperative skin preparation with chlorhexidine 2% in alcohol 70% (CHLORAPREP ®) versus 10% povidone-iodine	M. Langer	2013		IV	1487	730
92/12	A randomized trial comparing sentinel lymph node biopsy vs no axillary surgical staging in patients with small breast cancer and a negative preoperative axillary assessment	R. Agresti	2013		-	86	51
109/12	SHARE - Cyberknife Partial Breast Irradiation for Early Stage Breast Cancer. A phase I prospective study	L. Lozza	2013		-	25	10
111/12	Metabolic disorders and breast cancer	R. Agresti	2012		Observational	2073	631
116/12	Assessment of the performance of tomosynthesis as diagnostic tool in adjunct to mammography in women with dense breasts evaluated also with breast ultrasound	C. Ferranti	2013	12/17/2014	Observational	298	93
125/12	A multicenter, single arm study of trastuzumab emtansine (T-DM1) in HER2 positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment	G. V. Bianchi	2013		III	5	Closed accrual
127/12	Impact of acellular dermal matrix in reduction of surgical complexity of breast reconstructions with implants	M. Nava	2013		-	35	20
146/12	Pre-operative evaluation of distress thermometer in breast cancer patients	R. Agresti	2013		Observational	1400	400
148/12	Screening of women at high family-genetic risk of breast cancer with only MRI: prospective randomized study with cost-effectiveness analysis (ISS-HIBCRIT3 – ISS High Breast Cancer Risk Italian Study n. 3)	P. Panizza	2013		-	56	20

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
01/13	A phase II, open label, single arm trial of neoadjuvant therapy in patients with triple negative breast cancer evaluating the efficacy of eribulin mesylate following anthracycline and taxane and correlative science studies attempting to identify predictors of response	S. Di Cosimo	2013		II	5	4
02/13	Circulating miRNAs as biomarkers predictive of breast cancer relapse	M. G. Daidone	2013	1/15/2014	Observational	44	3
24/13	A multicenter, open-label, dose escalation, Phase I study of LJM716 administered intravenously in combination with trastuzumab in patients with HER2 overexpressing metastatic breast cancer or gastric cancer	S. Cresta	2013		I	6	2
26/13	Neoadjuvant chemotherapy with nab-paclitaxel in women with HER2-negative high-risk breast cancer ETNA (Evaluating Treatment with naoadjuvant Abraxane)	A. Moliterni	2013		III	18	17
49/13	Postmastectomy radiotherapy in reconstructed breast: evaluation of dose distribution in partially and completed inflated tissue expanders	L. Lozza	2013		-	8	3
55/13	A randomized, multicenter, open-label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy	G. V. Bianchi	2013		III	4	3
67/13	Risk for local relapses after breast conserving surgery in patients with ductal carcinoma in situ of the breast	M. Gennaro	2013		Observational	250	Closed accrual
71/13	A multicenter randomised trial of contrast-enhanced MR imaging as a breast cancer screening tool alternative to mammography and ultrasonography in women at intermediate risk. Feasibility, and short term results. (MRIB Trial)	P. Panizza	2014		-	60	60
106/13	Randomized controlled trial of diet and physical activity in carriers of BRCA mutation	P. Pasanisi	2013		-	142	122
111/13	Assessment of breast cancer progression risk based on extracellular matrix characteristics	E. Tagliabue	2013		Observational	200	100
115/13	Pilot study for the identification of miRNA predictive of chemotherapy response with gemcitabine in metastatic breast cancer	S. Cresta	2013	2/12/2014	Observational	39	0
131/13	Role of extracellular matrix in breast cancer response to chemotherapy	E. Tagliabue	2013	12/15/2014	Observational	100	Closed accrual
136/13	FINESSE – An open, 3-cohort, phase II trial testing oral administration of lucitanib in patients with FGFR1-amplified or non-amplIfied oestrogeN rEceptor poSitive metaStatic breast cancEr	F. De Braud	2014		II	4	4
161/13	Modulation of the Immune System and Adjuvant Chemotherapy in Breast Cancer	S. Cresta	2014		-	2	2
165/13	Observational study to assess the impact of hormonal treatment with aromatase inhibitors on the psychological dimension of patients with breast cancer	C. Borreani	2013		Observational	36	35
174/13	Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of Fulvestrant (FASLODEX) with or without PD-0332991 (Palbociclib) Goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy	G. V. Bianchi	2014		III	5	5

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
177/13	Nipple-Areola Complex (NAC) Sparing Mastectomy after neoadjuvant chemotherapy: a retrospective cohort study	R. Agresti	2014	12/31/2014	Observational	572	572
179/13	Impact assessment of the type and time of surgery and of HER2 expression in the management and outcome of breast cancer: a retrospective cohort study	R. Agresti	2014	12/31/2014	Observational	900	900
180/13	Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in patients with T2 N0/1 breast cancer: analysis of a prospective non randomized study	G. Martelli	2014	12/31/2014	Observational	321	321
186/13	Circulating miRNAs to predict outcome and to guide treatment of breast cancer patients on preoperative systemic therapy	S. Di Cosimo	2014		Observational	35	35
29/14	PERtuzumab-trastuzumab plus lEtrozoLe In endocrine Sensitive breast cancer: a phase II neoAdjuvant study – PER ELISA	G. V. Bianchi	2014		II	2	2
30/14	Use of laser scanner volumeter in breast cancer upper arm lymphedema	A. Balzarini	2014		-	40	40
43/14	A randomized, multicenter, open-label, phase III trial comparing trastuzumab plus pertuzumab plus a taxane following anthracyclines versus trastuzumab emtansine plus pertuzumab following anthracyclines as adiuvant therapy in patients with operable HER2-positive primary breast cancer	G. V. Bianchi	2014		III	7	7
51/14	Selective axillary dissection vs complete axillary dissection. Randomized controlled clinical trial to evaluate the prevention of lymphedema in breast cancer treatment	M. Gennaro	2014		-	14	14
66/14	An international field study of the Reliability and Validity of an EORTC breast reconstruction questionnaire to assess quality of life in all types of breast reconstruction	M. Nava	2014		Observational	5	5
90/14	A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease	G. V. Bianchi	2014		III	1	1
100/14	Assessment of the performance of tomosynthesis in women eligible for or subjected to Breast Conserving Treatment for invasive breast cancer	C. Ferranti	2014		Observational	75	75
122/14	Retrospective observational study aimed at the analysis of mass spectrometric human breath profiles	R. Orlandi	2014	9/15/2014	Observational	26	26

Gastrointestinal Cancers

17/04	A phase II, open label study of PTK787/ZK222584 in the treatment of metastatic Gastrointestinal Stromal Tumors (GISTs) resistant to imatinib mesylate	P. Casali	2005		II	22	Closed accrual
11/05	Localized, completely resected, gastointestinal stromal tumors (GIST) expressing KIT receptor: a controlled randomized trial on adjuvant Imatini mesylate (Glivec) versus no further therapy after complete surgery	P. G. Casali	2005		III	36	Closed accrual
75/06	A prospective randomized, open-label trial comparing Sirolimus-containing versus mTOR -inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma	V. Mazzaferro	2006	7/28/2014	II	39	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
09/07	LIVER MATCH. An Italian multicentric study to evaluate the impact of donor-recipient matching in the outcome of liver transplantation at short, medium and long term	E. Regalia	2007		Observational	54	Closed accrual
52/07	A randomized trial investigating the role of FOLFOX-4 regimen duration (3 versus 6 months) and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer	M. Di Bartolomeo	2007		III	131	Closed accrual
27/08	Perioperative treatment with COI-E (capecetabine, oxaliplatin, irinotecan and cetuximab) of liver metastasis of colorectal carcinoma potentially resectable although at high risk of recurrences	R. Buzzoni	2008		II	34	0
38/08	A phase III randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment for hepatocellular carcinoma after surgical resection or local ablation (STORM)	V. Mazzaferro	2008	6/3/2014	III	46	Closed accrual
01/09	Open label extension study of lanreotide autogel 120 mg in patients with non functioning entero-pancreatic endocrine tumour	R. Buzzoni	2009		III	1	Closed accrual
21/09	A randomized, open-label, multicenter phase III study to evaluate the efficacy and safety of nilotinib versus imatinib in adult patients with unresectable or metastatic gastrointestinal stromal tumors	P. Casali	2009	10/23/2014	III	1	Closed accrual
79/09	Observational study of plasma levels of Imatinib in patients with gastrointestinal stromal tumor	P. Casali	2010		Observational	85	0
80/09	Controlled extension of conventional criteria for liver tranplantation in hepatocellular carcinoma (HCC): a prospective validation study	V. Mazzaferro	2009		II	37	5
21/10	A phase II, open label study to evaluate the activity and safety of Everolimus in association to Imatinib in PDGFRA-D842V unresectable or metastatic gastrointestinal stromal tumours (GISTs) as first line treatment	P. Casali	2010	11/25/2014	II	3	0
80/10	A randomized, double-blind, placebo-controlled phase III of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib	P. Casali	2011		III	10	Closed accrual
30/11	Phase 2 placebo-controlled double-blind trial of dasatinib added to gemcitabinae for subjects with locally-advanced pancreatic cancer	R. Buzzoni	2011	7/7/2014	II	5	Closed accrual
75/11	DOVIGIST: Phase II trial to evaluate the efficacy and safety of Dovitinib (TKI258) in patients with gastrointestinal stromal tumors refractory and/or intolerant to imatinib	P. Casali	2011	12/4/2014	II	3	Closed accrual
85/11	Phase I dose escalation study of S. 78454 (HDACi) in combination with FOLFOX in patients with locally advanced or metastatic digestive cancer	F. de Braud	2011	8/4/2014	I	12	4
94/11	Evaluation of diagnostic accuracy of diffusion-weighted magnetic resonance (DW-MRI) and perfusion magnetic resonance (DCE-MRI) in the dilation of mesorectal lymph nodes in colorectal cancer	D. Scaramuzza	2011	12/31/2014	Observational	34	2
100/11	A randomized, open-label, multicenter phase IIIb study comparing two trastuzumab dosing regimens, each in combination with cisplatin/capecitabine chemotherapy, as first-line therapy in patients with HER 2-positive metastatic gastric or gastro-esophageal junction adenocarcinoma who have not received prior treatment for metastatic disease	M. Di Bartolomeo	2011		III	7	0

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
06/12	Efficacy of tandem treatment with [90Y-DOTA, Tyr(3)] Octreotate and [177LuDOTA, Tyr(3)] Octreotate in patients with neuroendocrine tumour overexpressing somatostatin receptors and refractory to conventional therapy	E. Seregni	2012		II	77	25
15/12	Pseudomixoma peritonei: prognostic analysis of micro-RNA and other factors using tissue	M. Deraco	2012		Observational	46	22
16/12	Multicenter Italian study on the CEUS assessment of Response of colorectal cancer metastasis Treated with Avastin	R. Lanocita	2012		IV	2	0
22/12	A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin - RADIANT-4	R. Buzzoni	2012		III	23	Closed accrual
31/12	Peritoneal Mesothelioma: Optimize Outcomes by the Integration of new Prognostic Factors and Potential Therapeutic Targets in a Individualized Treatment based on Molecular Characterization and Chemosensitivity Profile on Primary Cultures	M. Deraco	2012		II	30	14
42/12	A multi-center, open-label study to assess pharmacokinetics of TKI258 in adult cancer patients with normal and impaired hepatic function	F. de Braud	2012	10/17/2014	I	9	1
60/12	A Randomized, Open-label, Two-Arm Phase II Trial Comparing the Efficacy of Sequential Ipilimumab versus Best Supportive Care Following First-line Chemotherapy in Subjects with Unresectable Locally Advanced/Metastatic Gastric or Gastro-Esophageal Junction Cancer	Maria Di Bartolomeo	2012	12/4/2014	II	16	0
73/12	Identification of circulating tumor cells in blood of patients with advanced colorectal cancer and assessment of their modifications during treatment with cetuximab or panitumumab, alone or associated with chemotherapy	F. de Braud	2012	7/26/2014	Observational	52	0
74/12	A Multicenter, Single arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen	Maria Di Bartolomeo	2012		III	15	Closed Accrual
77/12	A Non-Interventional Follow-Up to the VELOUR study (multicentre international study of aflibercept versus placebo in combination with FOLFIRI for metastatic colorectal cancer) – Translational Research	M. Di Bartolomeo	2013		Observational	10	0
97/12	A randomized, phase III, multicenter, double-blid, placebo-controlled study evaluating the efficacy and safety of onartuzumab (MetMab) in combination with metastatic HER2 negative, MET-Positive Gastriesophageal cancer	Maria Di Bartolomeo	2012		III	18	0
99/12	An open-label phase IIIb study of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy	M. Di Bartolomeo	2013	1/3/2014	III	15	Closed accrual
102/12	A multicenter, two stage, phase II study, evaluating the efficacy of oral BEZ235 plus best supportive care (BSC) versus placebo plus BSC in the treatment of patients with advanced pancreatic neuroendocrine tumors (pNET) after failure of mTOR inhibitor therapy	R. Buzzoni	2013		II	6	Closed accrual
107/12	Randomized, couble-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies	M. Di Bartolomeo	2013		III	9	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
117/12	Identification of circulating biomarkers of resistance to antiangiogenic treatment in patients with advanced colorectal cancer and assessment of their modification during therapy with antiangiogenic drugs (bevacizumab, aflibercept and regorafenib)	F. de Braud	2012		Observational	84	28
129/12	A randomized phase III study of low-docetaxel oxaliplatin, capecitabine (low-tox) vs epirubicin, oxaliplatin and capecitabine (EOX) in patients with locally advanced unresectable or metastatic gastric cancer	M. Di Bartolomeo	2014		III	5	5
139/12	A phase II, multicenter, open-label, randomized study evaluating the efficacy and safety of Folfiri + MEHD7945A versus Folfiri + Cetuximab in second line in patients with KRAS Wild type metastatic colorectal cancer	M. Di Bartolomeo	2013	9/29/2014	II	4	Closed accrual
03/13	Identification of Genetic Circulating Biomarkers for the Early Diagnosis of Colorectal Cancer	M. A. Pierotti	2013		Observational	238	123
07/13	A Phase III, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy	V. Mazzaferro	2013		III	13	4
20/13	Retrospective observational study on the use of off-label temozolomide in patients with metastatic colorectal cancer with methylation of the MGMT gene	M. Di Bartolomeo	2013		Observational	53	25
35/13	Prospective randomized phase II trial comparing mandatory second-look surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery, vs. standard postoperative follow-up in patients at high risk of developing colorectal cancer peritoneal metastases	D. Baratti	2013		-	5	2
36/13	Identification of Genetic Circulating Biomarkers for monitoring and early detection of recurrence in surgically treated colorectal Cancer patients	M. Gariboldi	2013		Observational	134	69
50/13	Perioperative treatment with COI-B (Capecitabine, Oxaliplatin, Irinotecan and Bevacizumab) of high risk or borderline resectable colorectal cancer liver metastases	F. De Braud	2013		II	20	13
79/13	A multicenter, stratified, open, randomized, comparator-controlled, parallelgroup phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours	E. Seregni	2013		III	7	6
87/13	Retrospective-prospective observational study on the natural history of brain metastases from colorectal cancer	F. De Braud	2013		Observational	39	0
105/13	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) versus systemic chemotherapy in the treatment of peritoneal carcinomatosis of colorectal origin. An open multicentric randomized clinical trial	D. Baratti	2014		II	2	2
110/13	IL-6-related inflammation signatures as a predictive marker of recurrence in liver cancer patients	V. Mazzaferro	2013		Observational	52	22
116/13	A prospective randomized clinical trial on 90Yttrium trans-arterial radio-Embolization (TheraSphere®) vs. Standard of care (sorafenib) for the treatment of advanced Hepatocellular Carcinoma (HCC) with Portal Vein Thrombosis (PVT)	V. Mazzaferro	2014		III	9	9
122/13	A Phase II study on Trabectedin in advanced retroperitoneal leiomyosarcoma and well differentiated/ dedifferentiated liposarcoma – TRAVELL Study	P. Casali	2014		II	4	4

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
126/13	Prospective observational study on the impact of genetic polymorphisms on the occurrence of chemotherapy-induced toxicity in gastrointestinal epithelial neoplasms	F. De Braud	2013		Observational	37	28
137/13	A Single-Arm, Open Label Study of Aflibercept as Maintenance Therapy Following Induction with Aflibercept in Combination with XELOX, as First-Line Treatment for Metastatic Colorectal Cancer Patient	M. Di Bartolomeo	2013		I-II	2	0
141/13	A prospective, single-arm, multicenter, uncontrolled, open-label Phase II trial of refametinib (BAY 86-9766) in patients with RAS mutant Hepatocellular Carcinoma (HCC)	V. Mazzaferro	2013	9/23/2014	II	25	17
155/13	A Randomized, Double-blind, Placebo-controlled Phase-III Study of Adjuvant Regorafenib Versus Placebo for Patients with Stage IV Colorectal Cancer After Curative Treatment of Liver Metastases	V. Mazzaferro	2014		III	6	6
159/13	DNA-seq analysis for prediction of outcome to first line irinotecan versus oxaliplatin-based regimens in advanced colorectal cancer patients enrolled in a randomized phase II, prospective study	M. Gariboldi	2013		Observational	43	0
184/13	Colorectal Cancer Control : Embracing the complexity, going back to basics	M. Gariboldi	2014		Observational	3	3
02/14	A multicenter, phase II, single arm, two cohort study evaluating the efficacy, safety, and pharmacokinetics of AMG 337 in subjects with MET amplified gastric/ gastroesophageal junction/esophageal adenocarcinoma or other MET amplified solid tumors	M. Di Bartolomeo	2014		II	37	37
14/14	Retrospective/Prospective observational study on the use of off-label FOLFOX-4 in patients with peritoneal pseudomyxoma relapsed and/or inoperable	F. De Braud	2014		Observational	20	20
37/14	Use of donors with encephalic lesions and positive for hepatitis B surface antigen or hepatitis B core antibodies or anti-HCV antibodies according to national guidelines: improvement of organ sharing policies through a collection and analysis of organs' and patients' survival results in the short, medium and long term period – transplant research program according to the provisions of the Regional Committee Resolution n IX/1301 dated 9.02.2011	V. Mazzaferro	2014		Observational	13	13
45/14	Activity and safety of Everolimus in combination with Octreotide LAR and Metformin in patients with advanced pancreatic well-differentiated Neuroendocrine Tumors (pWDNETs): a Phase II, open, monocentric, prospective study	F. De Braud	2014		II	7	7
50/14	The role of early systematic best palliative care versus on request palliative care consultation during standard oncologic treatment for patients with advanced gastric or pancreatic cancers: a randomized, controlled, multicenter trial	A. T. Caraceni	2014		-	3	3
82/14	"BIOGIST" Study: genomic analysis in gastrointestinal stromal tumors (GIST)	P. Casali	2014		Observational	10	10
101/14	The role of the natural fluorescence spectroscopy of human blood plasma for colorectal cancer management: study of the correlation between fluorescence intensity and disease clinical evolution and qualitative identification of fluorescence responsible agents	E. Leo	2014		Observational	20	20
102/14	Observational study on perioperative management with COI regimen (Capecitabine plus Oxaliplatin and Irinotecan) in patients with gastric or gastroesophageal locally advanced and technically resectable cancer	M. Di Bartolomeo	2014		Observational	7	7

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
112/14	An open-label, randomized, multicenter, phase II trial designed to compare the efficacy of CAPTEM combination versus FOLFIRI as second line treatment in patients who have progressed on or after first-line oxaliplatin-containing chemotherapy for advanced, MGMT methylated, RAS mutated colorectal cancer	F. De Braud	2014		II	1	1
118/14	Identification and Characterization of Molecular and Clinical Profiles, and Outcomes in Subjects With MET-Amplified Cancers	M. Di Bartolomeo	2014		Observational	1	1
123/14	Activation of the druggable pathways in gastric carcinomas and clinical outcomes of metastatic patients treated with trastuzumab	M. Di Bartolomeo	2014		Observational	1	1
134/14	A prospective, single-arm, multicenter, uncontrolled, open-label Phase II trial of refametinib (BAY 86-9766) in combination with sorafenib as first line treatment in patients with RAS mutant Hepatocellular Carcinoma (HCC)	V. Mazzaferro	2014		II	1	1
136/14	Retrospective and prospective observational study on the natural history of metastatic colorectal cancer, refractory to chemotherapy	F. De Braud	2014		Observational	100	100
177/14	Detection of circulating tumor cells and ct DNA blood levels in patients with advanced intra- and extra-hepatic cholangiocarcinoma and evaluation of their changes during treatment	L. Celio	2014		Observational	1	1

Genital Apparatus

46/07	Prostate cancer research international: active surveillance (PRIAS)	R. Valdagni	2007		Observational	412	85
54/07	Identification of Men with a genetic predisposition to Prostate Cancer: Target Screening in BRCA1/2 mutation carriers and controls - the IMPACTstudy	N. Nicolai	2008		Observational	21	5
10/09	Carboplatin and Paclitaxel administered every three weeks vs Carboplatin and Paclitaxel administered weekly to patients with ovary carcinoma: multicentric randomized study	F. Raspagliesi	2009		III	39	Closed accrual
65/09	LION - Lymphadenectomy in ovarian neoplasm. An open randomized prospective multicenter trial. A project of the AGO Study Group	F. Raspagliesi	2010		-	32	Closed accrual
68/09	A multi-centre, open-label, randomised, two arm phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer	F. Raspagliesi	2010	2/6/2014	III	3	Closed accrual
71/09	A phase III study to evaluate the efficacy and safety of pazopanib monotherapy versus placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer	F. Raspagliesi	2010		III	2	Closed accrual
22/10	An open label, phase II study of vaccination with surviving peptides emulsified in Montanide ISA 51VG after IMP 321TM injection in prostate carcinoma patients with biochemical failure	L. Rivoltini	2010	4/15/2014	II	26	Closed accrual
38/10	Tandem transplantation of autologous hematopoietic progenitors in relapsed/refractory patients with metastatic germinal tumors	R. Salvioni	2010		II	47	3

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
50/10	Multicentric observational study DUE-01: urinary and erectile dysfunction after radical external beam therapy in localized prostate cancer	S. Villa	2010		Observational	174	26
03/11	A phase III, randomized, double-blind trial of weekly paclitaxel plus AMG386 or placebo in women with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers	F. Raspagliesi	2011		III	12	Closed accrual
11/11	Breathing analysis by electronic nose for detection of ovarian cancer in general population and in population at risk	F. Raspagliesi	2011		Observational	211	52
61/11	Randomized multicentric study comparing the efficacy of additional cytoreductive surgery vs exclusive chemotherapy in patients with platinum-sensitive recurrent ovarian cancer	F. Raspagliesi	2011		IV	7	0
63/11	NGR018: randomized phase II study of NGR-hTNF plus pegylated liposomial doxorubicin (PLD) versus PLD in platinum-resistant ovarian cancer	F. Raspagliesi	2011		II	33	Closed accrual
87/11	A Randomized phase III study comparing stabdard first-line docetaxel prednisone to docetaxel prednisone in combination with custirsen (CGX-011) in men with metastatic castrate resistant prostate cancer	G. Procopio	2011	9/22/2014	III	5	Closed accrual
95/11	Active surveillance "SA INT" in prostate cancer patients with low progression risk	R. Valdagni	2011		Observational	56	16
105/11	A randomized controlled study on the effectiveness of first-line chemotherapy (carboplatin and paclitaxel) versus chemo-immunotherapy (carboplatin-paclitaxel-oregovomab) in patients with advanced epithelial ovarian, adnexal or peritoneal carcinoma	F. Raspagliesi	2011		II	11	0
106/11	A randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer	F. Raspagliesi	2011		II	13	Closed accrual
107/11	Phase III International Multicenter Randomized Study Testing the Effect on Survival of Prolonging Platinum-free Interval in Patients With Ovarian Cancer Recurring Between 6 and 12 Months After Previous Platinum Based Chemotherapy	F. Raspagliesi	2013		III	13	5
108/11	Randomized multicentric phase II study with weekly pazopanib plus taxolo versus weekly taxolo alone in platinum-resistant or refractory ovarian carcinoma	D. Lorusso	2011		II	16	Closed accrual
02/12	A phase III randomized, double-blind, placebo-controlled, multi-center study of AMG 386 with paclitaxel and carboplatin as first-line treatment of subjects with FIGO stage III-IV epithelial ovarian, primary peritoneal or fallopian tube cancers	F. Raspagliesi	2012		III	11	Closed accrual
18/12	A randomized phase II trial of carboplatin-paclitaxel compared to carbplatin-paclitaxel-bevacizumab in advanced (stage III-IV) or recurrent endometrial cancer	F. Raspagliesi	2012		II	26	5
19/12	A phase II randomized Open label study of MM-121 in combination with paclitaxel versus paclitaxel alone in patients with platinum resistant/refractory advanced ovarian cancer	F. Raspagliesi	2012	7/28/2014	II	11	Closed accrual
20/12	Phase II study of trabectedi (Yondelis) in BRCA1 e BRCA2 mutation carrier and BRCA ness phemotype advanced ovarian cancer patients	F. Raspagliesi	2012		II	18	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
32/12	A phase II, open-lebal, singlie-arm, non randomized, multicenter study to evaluate the efficacy of oral TK258 as second-line therapy in patients with either FGFR2 mutated or wild-type advanced and/or metastatic endometrial cancer	F. Raspagliesi	2012	7/28/2014	II	10	Closed accrual
33/12	Study of circulanting biological factors in gynecological cancer (ovary, uterine cervix, endometrium)	F. Raspagliesi	2012		Observational	29	Closed accrual
50/12	Does Palliative Chemotherapy Improve Symptoms in Women with Recurrent Ovarian Cancer? Measuring subjective improvement as well as objective response to estimate the benefit of palliative chemotherapy in women with platinum resistant or refractory ovarian cancer	F. Raspagliesi	2013		Observational	33	6
68/12	Rare tumors in gynecologic oncology: retrospective and prospective collection data on diagnosis and treatment of rare gynecologic neoplasia	D. Lorusso	2012		Observational	360	79
70/12	Evaluation of the geriatric care needs and pathways after initial treatment in elderly patients with urogenital cancer (prostate, kidney, bladder and penis)	R. Valdagni	2012		Observational	110	32
110/12	Phase II study of the Pan-HER inhibitor Dacomitinib (PF-00299804) for patients with locally advanced or metastatic squamous cell carcinoma of the penis	A. Necchi	2013		II	11	10
123/12	Phase II study of single-agent Pazopanib (Votrient®) for patients with relapsed or refractory germ-cell tumors (GCT)	A. Necchi	2013		II	27	14
124/12	Radium-223 Chloride (Alpharadin) in Castration-resistant (Hormone-Refractory) Prostate Cancer Patients with Bone Metastasis	G. Procopio	2013	6/23/2014	III	7	Closed accrual
126/12	A multicenter study in patients with stage III-IV epithelial ovarian cancer treated with carboplatin/paclitaxel with bevacizumab: clinical and biological prognostic factors	D. Lorusso	2013		IV	60	8
12/13	NGR018: Randomized phase II study of NGR-hTNF plus an anthracycline versus an anthracycline alone in platinum-resistant ovarian cancer	F. Raspagliesi	2013		II	12	Closed accrual
25/13	A Phase 3, Randomized, Double-Blind Trial of Pegylated Liposomal Doxorubicin (PLD) Plus AMG 386 or Placebo in Women With Recurrent Partially Platinum Sensitive or Resistant Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	F. Raspagliesi	2013		III	14	Closed accrual
30/13	Brentuximab vedotin (SGN-35) as salvage therapy for males with advanced and platinum-resistant germ-cell tumors. An open label, single group, phase 2 trial	A. Necchi	2013		II	6	4
33/13	External radiotherapy for intermediate or high risk prostate cancer: Irradiation of the pelvis and boost to the prostate in two 9 Gy fractions	S. Villa	2013		-	7	5
53/13	Non-invasive diagnosis of prostate cancer using urine samples – Feasibility study	C. Marenghi	2014		Observational	22	22
74/13	A multicenter phase II randomized study with second line chemotherapy plus or minus bevacizumab in patients with platinum sensitive epithelial ovarian cancer recurrence after a bevacizumab/chemotherapy first line	D. Lorusso	2014		III	7	7
82/13	A Double-blind, Placebo-controlled, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of Maintenance Therapy With PankoMab-GEX™ After Chemotherapy in Patients With Recurrent Epithelial Ovarian Carcinoma	F. Raspagliesi	2013		II	22	19

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
101/13	Pertuzumab in Platinum-resistant low HER3 mRNA epithelial ovarian cancer (Pertuzumab nel carcinoma ovarico epiteliale a bassa espressione di mRNA di HER3, resistente al platino)	D. Lorusso	2013		III	11	6
125/13	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy	F. Raspagliesi	2014		III	11	11
128/13	RUAB2012-11: A retrospective study for the identification of predictive and prognostic biological factors in penile squamous cell carcinoma	A. Necchi	2014		Observational	18	18
140/13	A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer	D. Lorusso	2014		III	5	5
157/13	A randomized Phase III, factorial design, of cabazitaxel and pelvic radiotherapy in patients with localized prostate cancer and high-risk features of relapse	R. Valdagni	2014		III	1	1
03/14	Open label, randomized, pilot study on the activity of olanzapine with or without delayed dexamenthasone versus dexamenthasone alone for the prevention of delayed nausea and vomiting in patients with gynecologic cancers receiving carboplatin and paclitaxel-based chemotherapy and guidline-directed prophylactic anti-emetics	L. Celio	2014		IV	76	76
05/14	A multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with nonmetastatic castration-resitant prostate cancer	G. Procopio	2014		III	5	5
12/14	A multicenter, randomized, doubli-blind, placebo-controlled phase 3 study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum sensitive, high-grade serous or endometrial ephitelial ovarian, primary peritoneal or fallopian tube cancer	D. Lorusso	2014		III	15	15
16/14	What do primary and recurrent ovarian caner (OC) patients expect from maintenance therapy? (EXPRESSION IV OVAR STUDY)	D. Lorusso	2014		Observational	36	36
18/14	Hematopoietic stem cell collection and engraftment results in patients with germ cell tumours (GCT) who are candidates to myeloablative chemotherapy: a retrospective analysis from the Solid Tumours Working Party of the European Blood and Marrow Transplantation	A. Necchi	2014		Observational	106	106
32/14	A Prospective, Longitudinal, Multinational, Observational Study to Describe Patterns of Care and Outcomes of Men who are at High Risk for Poor Clinical Outcomes after Experiencing Biochemical Failure Following Definitive Prostate Cancer Therapy, Men with Castration-Resistant Prostate Cancer and Men with Metastatic Prostate Cancer at Initial Diagnosis Sponsored	G. Procopio	2014		Observational	12	12
67/14	Multicenter prospective observational study of intestinal, haematological and urinary toxicity from irradiation of the pelvic lymph node (IHU WPRT TOX) in prostate cancer	R. Valdagni	2014		Observational	2	2
68/14	A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)	G. Procopio	2014		III	6	6

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
77/14	A multicentre study to examine the short and long term outcomes of the conservative management of benign-looking adnexal masses and the pre-operative characterisation of ovarian tumours	F. Raspagliesi	2014		Observational	92	92
86/14	Outcome evaluation of metastatic castration resistant prostate cancer (mCRPC) patients long responding to treatment with abiraterone acetate	E. Verzoni	2014	12/31/2014	Observational	178	178
138/14	International endometrial tumor analysis (IETA): an observational non-interventional academic multicentre study on the ultrasound features of the endometrium	F. Raspagliesi	2014		Observational	6	6
178/14	Evaluation of the role of parametrial state in adjuvant treatment of patients with locally advanced cervical cancer after neoadjuvante chemotherapy and surgery	F. Raspagliesi	2014		Observational	21	21

Head & Neck and Thyroid Tumors

04/09	Phase II, multicenter, open-labe, single arm trial to evaluate the safety and efficacy of oral E7080 in medullary and iodine-131 refractory, unresectable differentiated thyroid cancers, stratified by histology	L. Licitra	2009		II	11	Closed accrual
05/09	An internationall, randomized, double-blinded, phase 3 efficacy study of XL184 versus placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer	L. Licitra	2009		III	9	Closed accrual
29/10	Sorafenib in recurrent and/or metastatic salivary gland carcinomas	L. Locati	2010	12/15/2014	II	37	Closed accrual
40/10	Phase II study of preoperative TPF chemotherapy in locally advanced resectable oral cavity squamous cell cancer in order to improve the rate of pathological complete response	L. Licitra	2010		II	11	2
65/10	A double-blind, randomized phase III study evalutating the efficacy and safety of Sorafenib compared to placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer	L. Licitra	2011		III	5	Closed accrual
07/11	A randomized, international, open-Label, multi-centre, phase III study to assess the effect of a patient outreach program on the percentage of time patients with locally advanced or metastatic medullary thyroid cancer experience grade 2 or higher adverse events during the first 12 months of treatment with Vandetanib	L. Licitra	2011	8/4/2014	III	8	Closed accrual
35/11	Cetuximab and Cisplatin with or without Paclitaxel in recurrent/metastatic head and neck cancer	L. Licitra	2012		II	21	8
44/11	Randomized, double-blind, multicenter two-stage adaptive phase 3 study of intravenous adnìministration of REOLYSIN (Reovirus type 3 dearing) in combination with paclitaxel and carboplatin versus the chemotherapy alone in patients with metastatic or recurrent squamous cell carcinoma of the head and neck who have progressed on or after prior platinum-based chemotherapy	L. Licitra	2011	5/28/2014	III	9	Closed accrual
45/11	A single arm, open-label, phase II, multicentre study, to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma	L. Licitra	2011		II	34	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
57/11	A randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of afatinib (BIBW 2992) as adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced head and neck squamous cell carcinoma	L. Licitra	2011		III	3	0
68/11	A randomised, open-label, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy	L. Licitra	2011		III	24	Closed accrual
69/11	A phase 2, multi-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of ALD518 in the reduction of oral receiving concomitant chemotherapy and radiotherapy	L. Licitra	2011	4/9/2014	II	17	Closed accrual
70/11	An open -label, multi-center phase II study of the BRAF inhibitor RO5185426 in patients with metastatic or unresectable papillary thyroid cancer (PTC) positive for the BRAF V600 mutation and resistant to radioactive iodine	L. Licitra	2011		II	1	Closed accrual
71/11	A multicentre, randomized, double-blind, placebo-controlled, phase III trial of E7080 in ^{131}I-Refractory differentiated thyroid cancer	L. Licitra	2011		III	15	Closed accrual
91/11	Radioiodine therapy of differentiated thyroid carcinoma with maximized activity based on individualized dosimetry	E. Seregni	2011		II	9	1
35/12	An international, randomized, double-blind, two-arm study to evaluate the safety and efficacy of vandetanib 150 and 300 mg/day in patients with unresecable locally advanced or metastatic medullary thyroid carcinoma with progressive or symptomatic disease	L. Licitra	2012		IV	13	Closed accrual
36/12	Continuing access ti the tyrosine kinase inhibitor of vegfr-2, ag-013736 (A406) for patienys previously receiving ag-013736 in clinical trials	L. Licitra	2012		III	1	Closed accrual
44/12	TP53 as a biomarker to personalize chemotherapy for patients with head and neck cancer	P. Bossi	2012	11/15/2014	Observational	48	40
76/12	Neoadjuvant afatinib based treatment strategies followed by surgery in squamous cell carcinoma of the head and neck: an EORTC NOCI-HNCG window study	L. Licitra	2012		II	12	4
28/13	Multidisciplinary approach for poor prognosis sinonasal tumors: phase II study of chemotherapy, surgery, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in operable patients	L. Licitra	2014		II	2	2
29/13	Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II study of chemotherapy, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in inoperable patients.	L. Licitra	2013		II	7	3
69/13	INduction chemoThERapy followed by CEtuximab Plus definiTive radiOtheRapy versus radiation plus cisplatin	L. Licitra	2013		III	4	3
92/13	A Randomised, Double-Blind, Placebo-Controlled, Multi-Centre Phase III Study to Assess the Efficacy and Safety of Vandetanib (CAPRELSA™) 300 mg in Patients with Papillary or Poorly Differentiated Thyroid Cancer That Is Either Locally Advanced or Metastatic Who Are Refractory or Unsuitable for Radioiodine (RAI) Therapy	L. Licitra	2013		III	10	7

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
95/13	A phase II study exploring the safety and efficacy of nintedanib (BIBF1120) as second line therapy for patients with either differentiated or medullary thyroid cancer progressing after first line therapy	L. Licitra	2014		II	5	5
121/13	Phase II multicenter randomized, double blind, placebo controlled study assessing the efficacy of buparlisib (BKM120) plus paclitaxel vs. placebo plus paclitaxel in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma	L. Licitra	2013		II	7	6
178/13	Molecular Profile of metastatic sporadic medullary thyroid cancer (sMTC) patients and possible correlation with vendetanib therapy	L. Locati	2014		Observational	26	26
187/13	Identification of a molecular predictor of response to Cetuximab based on a phase II trial in recurrent/metastatic HNSCC	S. Canevari	2014		Observational	48	48
48/14	Health and economic outcomes of two different follow up strategies in effectively cured advanced head and neck cancer	L. Licitra	2014		-	7	7
61/14	An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)	L. Licitra	2014		III	8	8
92/14	Efficacy and safety of single agent pan-HER inhibitor Dacomitinib in the treatment of locally advanced unresectable or metastatic squamous cell cancer of the skin or with clinical contraindication to surgery	P. Bossi	2014		II	5	5
135/14	Phase II study on Inlyta® (axitinib) in recurrent and/or metastatic salivary gland cancers (SGCs) of the upper aerodigestive tract	L. Licitra	2014		II	3	3
137/14	A retrospective observational study on patients treated with concurrent cetuximab and radiotherapy for locally advanced Squamous Cell Carcinoma of the Head&Neck	L. Licitra	2014		Observational	15	15
160/14	Prospective Observational Trial to Assess the Impact of Mucositis in pazietnts treated with targeted therapy in Oncology	P. Bossi	2014		Observational	8	8

Hematologic Malignancies

32/04	Prospective observational study in the adult with Burkitt's lymphoma of a polychemotherapy scheme in use in pediatrics	A. M. Gianni, M. Di Nicola	2004		Observational	23	2
02/05	A multicenter, open label study of oral melphalan, and CC-5013 (Revlimid) (MPR) as induction therapy in elderly newly diagnosed multiple mieloma patients	P. Corradini	2005		I-II	4	Closed accrual
12/06	A phase II, multicenter study of bortezomib, pegylated liposomal doxorubicin, dexamethasone (PAD) as induction and melphalan 100 mg/m2 (MEL 100) as transplant, in elderly newly diagnosed multiple myeloma patients	P. Corradini	2006		II	12	Closed accrual
13/06	A phase III, multicenter, randomized open label study of velcade, melphalan, prednisone and thalidomide (V-MPT) versus velcade, melphalan, prednisone (V-MP) in elderly untreated multiple myeloma patients	P. Corradini	2006	9/29/2014	III	9	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
14/06	A phase 3, prospective, randomized clinical study with velcade-thalidomide-dexamethasone versus thalidomide-dexamethasone for previously untreated patients with symptomatic multiple myeloma who are candidates to receive double autologous transplantation	P. Corradini	2006		III	13	Closed accrual
28/06	Zevalin at myeloablative doses in aggressive lymphomas of elderly patients	P. Corradini	2006		III	4	Closed accrual
50/06	A phase II, multicenter study of melphalan 100 mg/m2 (MEL 100) as transplant, Revlimid and Prednisone (RP) as consolidation and Revlimid alone as maintenance in elderly newly diagnosed multiple myeloma patients	P. Corradini	2006		II	12	Closed accrual
67/06	A phase II, multi-center, randomized, open label study of Velcade, Doxorubicin and Dexamethasone (PAD) vs Thalidomide and Dexamethasone (TD) in advanced and refractory multiple myeloma patients	P. Corradini	2007	4/30/2014	II	1	Closed accrual
38/07	A multicentric randomized trial in adult patients with acute myelogenous leukemia (AML) to compare: 1) a standard-dose versus high-dose remission induction regimen, and 2) an autologous blood stem cell transplantation versus an autologous blood cell-supported multicycle high-dose chemotherapy program, within a risk-oriented postremission strategy reserving allogeneic stem cell transplantation for high-risk cases	P. Corradini	2007		III	11	Closed accrual
48/07	Reduced intensity conditioning with high-dose rituximab followed by allogeneic transplantation of hematopoietic cells for the treatment of relapsed/refractory B-cell non Hodgkin's lymphomas	P. Corradini	2007		II	25	4
55/07	Treatment with imatinib mesylate (Glivec) of severe chronic scleroderma-like GVHD, refractory to conventional immunosuppressive therapy	P. Corradini	2008		II	8	Closed accrual
63/07	Lombardy registry of HCV positive lymphomas	P. Corradini	2008	5/5/2014	Observational	7	Closed accrual
02/08	A phase 3, multicentre, randomized, controlled study to determine the efficacy and safety of lenalidomide, melphalan and prednisone (MPR) versus melphalan (200 mg/m2) followed by stem cell transplant in newly diagnosed multiple myeloma subjects	A.M. Gianni, P. Corradini	2008		III	16	Closed accrual
34/08	Randomized study comparing intravenous busulfan (i.v. BU;Bulsivex) plus fludarabine (BUFLU) versus intravenous busulfanplus Cyclophosphamide (BUCY2) as conditioning regimes prior to allogenic hematopoietic stem cell transplantation (ALLOHSCT) in patients (aged >=40 and <=55 years) with acute myeloid leukemia (AML) in complete remission (CR)	P. Corradini	2008	10/27/2014	III	4	Closed accrual
44/08	Comparison of Whole Body Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) with skeletal X-Ray and MRI of the spine for the assessment of bone disease in Multiple Myeloma (MM)	P. Corradini	2008		Observational	68	18
49/08	Multicentre clinical study with early treatment intensification in patients with high-risk Hodgkin lymphoma, identified as FDG-PET scan positive after two conventional BVD courses	A. M. Gianni, P. Corradini	2008		II	52	5
09/09	Phase III study comparing rituximab-supplemented ABVD (R-ABVD) with ABVD followed by involved-field radiotherapy (ABVD-RT) in limited-stage (stage I-IIA with no areas of bulk) Hodgkin's lymphoma	A. M. Gianni, P. Corradini	2009		III	16	1

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
13/09	Safety and efficacy of lenalidomide as main therapy in patients with newly diagnosed multiple myeloma following a tandem autologous-allogeneic transplant	P. Corradini	2009		II	1	0
39/09	A phase 3 intergroup multicentre, randomized, controlled 3 arm parallel group study to determine the efficacy and safety of lenalidomide in combination with dexamethasone (Rd9 versus melphalan, prednisone and lenalidomide (MPR) versus cyclophosphamide, prednisone and lenalidomide (CPR) in newly diagnosed multiple myeloma subjects	P. Corradini	2009		III	16	Closed accrual
46/09	A phase 3, multicentre, randomized, controlled study to determine the efficacy and safety of ciclophosphamide, lenalidomide and dexamethasone (CRD) versus melphalan (200 mg/m2) followed by stem cell transplant in newly diagnosed multiple myeloma subjects	P. Corradini	2009		III	11	Closed accrual
69/09	A multicenter, randomized, doble-blind, placebo controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma	P. Corradini	2010		III	12	Closed accrual
76/09	Brief induction chemoimmunotherapy with rituximab + bendamustine + mitoxantrone followed by rituximab in elderly patients with advanced stage previously unrtreated follicular lymphoma	P. Corradini	2010		II	4	Closed accrual
07/10	Monitoring of human polyomavirus reactivation in patients with lymphoproliferative disease treated with chemotherapy, chemotherapy and rituximab, and rituximab alone	P. Corradini	2010		Observational	8	0
12/10	A phase I/II, multicenter, open label study of pomalidomide cyclophosphamide and prednisone (PCP) in patients with multiple myeloma relapsed and/or refractory to lenalidomide	P. Corradini	2010		I-II	11	Closed accrual
13/10	Prospective audit on stem cell mobilization in malignant lymphoma	P. Corradini	2010		Observational	8	Closed accrual
27/10	Randomized phase II trial on primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation vs high-dose chemotherapy supported by autologous stem cells transplantation for immunocompetent patients with newly dignosed primary CNS lymphoma	M. Di Nicola	2010	12/31/2014	II	2	0
31/10	A randomized, double-blind, placebo-controlled phase 3 study of SGN-35 (brentuximab vedotin) and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT)	A. M. Gianni	2010		III	7	Closed accrual
48/10	Intensified program including bendamustine followed by PBSC mobilization and high dose therapy and autograft for patients with relapsed or resistant $CD20^+$ follicular Non Hodgkin Lymphoma: a multicenter, pivotal GITIL study	P. Corradini	2010		II	4	2
56/10	A randomized, open label study of Ofatumumab and Bendamustine combination therapy compared with Bendamustine monotherapy in indolent B-cell non-Hodgkin's lymphoma unresponsive to Rituximab or a Rituximab-containing regimen during or within six months of treatment	P. Corradini	2013		III	2	0

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
57/10	A phase III trial comparing bertozomib, cyclofosfamide and dexamethasone versus lenalidomide cyclofosfamide and dexamethasone in patients with multiple myeloma at first relapse	P. Corradini	2010		III	20	6
83/10	A phase III, double-blind, randomized, placebo-controlled, multicenter clinical trial to study the safety, tolerability, efficacy and immunogenicity of 212 in recipients of autologous hematopoietic cell transplants	P. Corradini	2010		III	3	Closed accrual
08/11	A multicenter phase II study of subcutaneous velcade plus oral melphalan and prednisone or plus oral cyclophosphamide and prednisone or plus prednisone in newly diagnosed elderly multiple myeloma patients	P. Corradini	2011		II	3	Closed accrual
33/11	A phase III, multicenter, open label randomized trial comparing the efficacy of GA 101 (RO50722759) in combination with CHOP (G-CHOP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL)	P. Corradini	2011		III	15	1
34/11	An open-label, single-arm, phase I study of AEB071 (a protein kinase C inhibitor) in patients with CD79-mutant diffuse large B-cell lymphoma	P. Corradini	2011	1/31/2014	I	12	0
37/11	A multicenter, open label phase II study of carfilzomib, cyclophosphamide and dexamethasone in newly diagnosed multiple myeloma patients	P. Corradini	2011		II	2	Closed accrual
58/11	A phase 3, randomized, open label trial of lenalidomide/ dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma	P. Corradini	2011		III	3	Closed accrual
72/11	An open label non randomized phase 2 study evaluating SAR3419, an anti-CD19 antibody-maytansine conjugate administred as single agent by intrevnous infusion to patients with relapsed or refractory $D19^{+}$ diffuse large B cell lymphoma	A. M. Gianni	2011		II	3	Closed accrual
80/11	Prospective, phase I/II, non -randomized, open label, multicenter study to determine safety and efficacy of Nilotinib in a population with steroid-refractory/or steroid-dependent cGVHD	P. Corradini	2011		I-II	2	1
89/11	A randomized phase III study to compare Bortezomib, melphalan, prednisone (VMP) with high dose melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma	P. Corradini	2011		III	25	4
110/11	Cardiac biomarkers and innovative echocardiographic parameters as predictors of cardiotoxicity in B-cell non-Hodgkin/Hodgkin's lymphoma patients treated with anthracyclines or high-dose chemotherapy	P. Corradini	2011		Observational	49	17
53/12	An open label, phase 2, non randomized, multicentre trial to assess the feasibility of induction treatment with 5-Azacitidine (5-AZA) followed by allogeneic stem cell transplantation (allo-SCT) or continued 5-AZA treatment in patients without a suitable -sibling or unrelated- stem cell donor with IPSS Int-2/High risk myelodysplastic syndromes (MDS)	P. Corradini	2012		II	4	1
66/12	A phase III multicenter, randomized study comparing consolidation with 90YTTRIUM-LABELED IBRITUMOMAB TIUXETAN (ZEVALIN®) radioimmunotherapy vs autologous stem cell transplantation (ASCT) in patients with relapsed follicular lymphoma (FL) aged 18-65 years	P. Corradini	2013		III	3	1

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
80/12	Bendamustine, lenalidomide and rituximab (R2-B) combination as a second-line therapy for first relapsed-refractory mantle cell lymphomas: a phase II study	P. Corradini	2013		II	1	Closed accrual
112/12	Observational retrospective/prospective study in Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma patients who received SGN35 according to compassionate use (named patient program)	P. Corradini	2013		Observational	4	Closed accrual
131/12	A randomized open-label multicenter phase II trial evaluating the safety and activity of DCDT2980S in combination with Rituximab or DCDS4501A in combination with Rituximab in patients with relapsed or refractory B-cell Non-Hodgkin's lymphoma	A. M. Gianni	2013		II	2	Closed accrual
133/12	Chronic Lymphocytic Leukemia (CLL) Registry: a prospective, observational study within the Rete Ematologica Lombarda	P. Corradini	2013		Observational	36	24
138/12	A multicenter, single-arm, open-label study with pomalidomide in combination with a low dose of dexamethasone in subjects with refractory or relapsed and refractory multiple myeloma	P. Corradini	2013		III	47	19
144/12	An open-label phase II study of BKM120 in patients with relapsed and refractory diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma	P. Corradini	2013		II	4	1
151/12	Genetics-driven targeted management of lymphoid malignancies. Improving molecular characterization and diagnosis of hairy cell leukemia and classical hodgkin lymphoma	A. M. Gianni	2013		Observational	2	Closed accrual
11/13	Myeloablative Conditioning, followed by Unmanipulated Haploidentical Bone Marrow Transplantation and post-transplant high dose Cyclophosphamide , for Patients with Hematologic Malignancies: a Phase II study	P. Corradini	2013		II	6	4
31/13	A multicenter, open label, study of weekly carfilzomib, cyclophosphamide and dexamethasone (wCCyd) in newly diagnosed multiple myeloma (MM) patients	P. Corradini	2013		I-II	10	6
47/13	Phase II randomized study with R-DHAP +/- Bortezomib as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients before High-Dose chemotherapy BEAM with autologous stem cell transplantation (ASCT): BR-DHAP + BEAM + ASCT versus R-DHAP + BEAM + ASCT	P. Corradini	2014		II	2	2
51/13	An observational prospective study on fertility and gonadal function in young adult female patients with lymphoma or sarcoma, who choose to undergo fertility preservation by mature ovocytes cryopreservation before starting chemotherapy	S. Viviani	2013		Observational	10	6
57/13	A phase I/II study of Danusertib in Combination with romidepsin in adult patients with mature peripheral T-Cell lymphoma (PTCL)	A. M. Gianni	2013		II	3	2
58/13	Chronic Myeloid Leukemia Register - Lombardy Hematologic Network	P. Corradini	2014		Observational	1	1
63/13	An open label, single arm, phase II study of nilotinib 300 mg BID in newly diagnosed CPCML patients, in order to verify disappearance of $CD34^+/lin^-Ph^+$ cells from bone marrow during treatment	P. Corradini	2013		II	2	1
83/13	A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma	S. Viviani	2014		III	4	4

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
86/13	Identification of possible genetic causes responsible of a familiar form of Multiple Myeloma	P. Corradini	2013		Observational	4	2
100/13	Multi-center, phase II study to assess the safety and efficacy of haploidentical bone marrow transplantation using reduced intensity conditioning (RIC) regimen and post-transplant cyclophosphamide, in patients with poor prognosis lymphomas	P. Corradini	2013		II	4	2
113/13	Role of T memory stem cell in the process of immune reconstitution following bone marrow transplantation	P. Corradini	2013		Observational	16	5
118/13	An open-label, single-arm, Phase Ib/II study of AEB071 (a protein kinase C inhibitor) and everolimus (mTOR inhibitor) in patients with CD79-mutant or ABC subtype diffuse large B-cell lymphoma	P. Corradini	2014		I-II	4	4
119/13	Prospective REsearch Assessment in Multiple Myeloma: an OBservationaL Evaluation (PREAMBLE)	P. Corradini	2014		Observational	23	23
134/13	A Phase 1B, Multi-center, Open-label Study of Novel Combinations of CC-122, CC-223, CC-292 and Rituximab in Diffuse Large B-cell Lymphoma	P. Corradini	2014		I	6	6
135/13	A single arm, multicentre, phase IIIb study to evaluate safety, efficacy and pharmacokinetic (PK) of subcutaneous (SC) rituximab administered during induction phase or maintenance in previously untreated patients with $CD20^+$ diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL)	P. Corradini	2014		III	7	7
142/13	Phase IIa study on the role of Gemcitabine plus Romidepsin (GEMRO regimen) in the treatment of relapsed/refractory peripheral T-cell lymphoma patients	P. Corradini	2014		II	6	6
149/13	Retrospective observational study on monitoring of serum levels of TARC and PET results of patients with Hodgkin's lymphoma undergoing allogenic hematopoietic stem cell	P. Corradini	2013	3/31/2014	Observational	24	2
154/13	A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma	P. Corradini	2014		III	9	9
156/13	A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma	A. M. Gianni	2014		III	1	1
21/14	Ofatumumab-Bendamustine for relapsed/refractory indolent lymphoma: a multicenter phase 2 trial	P. Corradini	2014		III	3	3
35/14	Retrospective study to validate GITMO criteria for the identification of Poor Mobilizers (PMs) in multiple myeloma and lymphoma patients	P. Corradini	2014	6/3/2014	Observational	180	180
36/14	A prospective, multicenter survey of Severe Infections by Gram Negative Bacteria in patients submitted to autologous and allogeneic stem cell transplant	P. Corradini	2014		Observational	56	56
41/14	Risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia	P. Corradini	2014		II	2	2
62/14	Single-Arm, Open-Label Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Follicular Lymphoma (FL)	P. Corradini	2014		II	2	2

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
63/14	Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT	P. Corradini	2014		II	2	2
72/14	A phase Ib/II, multi-center, study of oral LGH447 in combination with oral BYL719 in patients with relapsed and refractory multiple myeloma	P. Corradini	2014		I	6	6
83/14	Observational retrospective study in Cutaneous and Peripheral T-cell Lymphoma patients who received romidepsin as salvage treatment due to relapse or refractoriness under the Named Patient Programme	P. Corradini	2014	7/10/2014	Observational	2	2
85/14	Reduced intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after a prior autologous stem cell transplantation. A retrospective analysis from the LWP of the EBMT	P. Corradini	2014	9/29/2014	Observational	3	3
87/14	Romidepsin in combination with Choep as first line treatment before hematopoietic stem cell transplantation in young patients with nodal peripheral T-cell lymphomas: a phase I-II study	P. Corradini	2014		I-II	3	3
95/14	Identification of biological/clinical prognostic factors in patients with not-transformed Hodgkin Lymphoma	P. Corradini	2014		Observational	4	4
96/14	Retrospective case-control study evaluating the efficacy of autologous transplantation as first line therapy in Peripheral T-cell Lymphomas	P. Corradini	2014		Observational	3	3
97/14	Prospective data collection of elderly patients (>= 65 years) with Diffuse Large B-cell Lymphoma (DLBCL) receiving at the time of diagnosis Multidimensional Geriatric Assessment (VGM)	P. Corradini	2014		Observational	3	3
117/14	Observational study on the effectiveness of Brentuximab Vedotin (BV) in patients with relapsed or refractory Hodgkin Lymphoma (R/R HL) considered ineligible for a transplant procedure	S. Viviani	2014		Observational	26	26
119/14	Observational Retrospective Multicenter Study designed to evaluate the efficacy of treatment with Lenalidomide in diffuse large cell lymphoma DLBC relapsed or refractory to previous lines of chemotherapy treatments and not candidates for autologous and allogeneic stem cell transplantation prescribed by law 648	L. Devizzi	2014	12/31/2014	Observational	12	12
124/14	Prevalence study of eye disorders in patients with symptomatic multiple myeloma	V. Montefusco	2014		Observational	64	64

Lung Cancer

53/05	MILD project. Spiral CT, biomarkers and proteomic analysis, associated to a program of primary prevention for the early diagnosis of lung cancer: randomized study in subjects at high risk	U. Pastorino	2006		-	4.099	Closed accrual
18/07	START - stimulating Targeted Antigenic Responses To NSCLC	M. Platania	2007		III	5	Closed accrual
27/09	Randomized phase II study of NGR-hTNF in combination with standard chemotherapy versus standard chemotherapy alone in previously untreated patients with advanced non-small cell lung cancer (NSCLC)	N. Zilembo	2009		II	31	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
66/09	Multicenter phase III randomized study of cisplatin and etoposide with or without bevacizumab as first-line treatment in extensive stage (ED) small cell lung cancer (SCLC)	N. Zilembo	2013		III	4	3
75/09	A randomized, multicenter, open-label phase 3 study of pemetrexed-cisplatin chemotherapy plus IMC-11F8 versus pemetrexed-cisplatin chemotherapy alone in the first-line treatment of patients with non squamous stage IIIb or IV non-small cell lung cancer (NSCLC)	N. Zilembo	2010		III	9	Closed accrual
23/10	Phase III randomized trial of BIBW 2992 plus weekly paclitaxel versus investigator's choice of chemotherapy following BIBW 2992 monotherapy in non-small cell lung cancer patients failing previuos erlotinib or geftinib treatment	M. Platania	2010		III	5	Closed accrual
45/10	An exploratory phase II study of pemetrexed and ciplatin as preoperative chemotherapy in the treatmnet of stage IIIAN2 nonsquamous non small cell lung cancer	U. Pastorino	2011		II	13	Closed accrual
72/10	The airINTrial: a prospective randomized phase III trial of the use of different modalities of pleural aspiration for the management of breath loss after lung surgical resection	F. Leo	2011		-	580	0
21/11	BioMILD: a prospective study of efficacy of plasma microRNA as first line test for early dignosis of lung cancer	U. Pastorino	2013		Observational	2.063	1.059
52/11	An open label two-stage study of orally administered BKM120 in patients with metastatic non-small cell lung cancer with activated PI3K pathway	F. De Braud	2012	12/3/2014	II	4	0
92/11	Phase III randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harboring a traslocation or inversion event involving the anaplastic lymphoma kinase (alk) gene locus	F. de Braud	2011		III	2	Closed accrual
21/12	A randomized, open-label, multicenter, phase 3 study to compare the efficacy and safety of eribulin with treatment of physician's choice in subjects with advanced non-smal celle lung cancer	M. Platania	2012		III	8	Closed accrual
40/12	A randomized, phase II, multicenter, double-blind, placebo-controlled study evaluating the efficacy and safety of MetMab in combination with paclitaxel + cisplatin or carboplatin as first -line treatment for patients with stage IIIb (T4 disease) or IV squamous non-small cell lung cancer (NSCLC)	F. de Braud	2012	9/17/2014	II	1	Closed accrual
41/12	A randomized, phase II, multicenter, double-blind, placebo-controlled study evaluating the efficacy and safety of MetMab in combination with either bevacizumab +platinum + paclitaxel or pemetrexed + platinum as first -line treatment for patients with stage IIIb or IV non-squamous non-small cell lung cancer (NSCLC)	F. de Braud	2012	9/17/2014	II	11	Closed accrual
48/12	Be-positive: Beyond progression after tki in egfr positive NSCLC patients	M. Garassino	2012		Observational	5	0
49/12	Maintanance metronomic per os navelbine in advanced NSCLC patients after previous platinum based chemotherapy: a multicenter randomized best supportive care controlled phase II study MANILA	M. Platania	2013		II	23	18
63/12	Phase II study of oral PHA-848125AC in patients with thymic carcinoma previously treated with chemotherapy	M. Garassino	2012		II	19	7

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
98/12	PASS Pleural mesothelioma Strategies Study	U. Pastorino	2014		-	1	1
100/12	An Open-label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)	M. Garassino	2013		III	8	Closed accrual
136/12	A multicenter, open-label, randomized phase II study to evaluate the efficacy of AUY922 vs pemetrexed or docetaxel in NSCLC patients with EGFR mutations who have progressed on prior EGFR TKI treatment	N. Zilembo	2013		II	3	1
137/12	An Open-Label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Metastatic Non-squamous Non-small cell Lung Cancer (NSCLC)	M. Garassino	2013		III	11	Closed accrual
13/13	A Phase IB/II, open label, multicenter study of INC280 administered orally in combination with gefitinib in adult patients with EGFR mutated, c-MET-amplified non-small cell lung cancer who have progressed after EGFR inhibitor treatment	F. De Braud	2014		I	1	1
18/13	K-RAS mutations and DNA Repair Function in NSCLC	M. Garassino	2014		Observational	44	44
34/13	Phase II study of oral PHA-848125AC in patients with malignant thymoma previously treated with multiple lines of chemotherapy	M. Garassino	2013		II	6	4
45/13	A Phase II study of the selective BRAF kinase inhibitor GSK2118436 in subjects with advanced non-small cell lung cancer and BRAF mutations	N. Zilembo	2014		II	22	22
61/13	POST-ALK: observational study of treatment and outcome after crizotinib in advanced ALK-positive NSCLC patients	M. Garassino	2013		Observational	9	2
65/13	Post-operative pulmonary complications in major abdominal surgery. A prospective multicenter observational study	F. Piccioni	2013	11/10/2014	Observational	122	Closed accrual
78/13	An open label trial of afatinib in treatment-naive (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)	N. Zilembo	2014		III	4	4
91/13	LUME Study - Long survivors in pleural mesothelioma	G. Gatta	2014		Observational	2.400	2.400
99/13	Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma	M. Garassino	2013		I	16	4
108/13	E-Cigarette and Normal Cigarette Sidestream Analysis and Comparison Project	R. Boffi	2013	10/31/2014	-	3	Closed accrual
138/13	A Phase 2, Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma	M. Garassino	2014		II	8	8
164/13	E-Lung. Lung cancer: from the needs of the patient, the answers of oncology	M. Garassino	2014	12/31/2014	Observational	80	80
169/13	Rationale for the use of anti-PD-L1 in patients with malignant pleural mesothelioma	M. Garassino	2014		Observational	100	100
172/13	A single arm, open-label, phase II study to assess the efficacy of the dual VEGFR-FGFR tyrosine kinase inhibitor, lucitanib, given orally as a single agent to patients with FGFR1-driven lung cancer	M. Garassino	2014		II	6	6

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
19/14	C4d as a novel risk biomarker in the context of CT-screening for lung cancer	G. Sozzi	2014		Observational	150	150
40/14	Role of germline and somatic DNA changes in modulating the survival of patients with lung adenocarcinoma	T. A. Dragani	2014		Observational	32	32
42/14	A phase II, multicenter, single-arm study of MPDL3280A in patients with PD-L1 positive locally advanced or metastatic non small cell lung cancer	M. Garassino	2014		II	66	66
64/14	Intratumor heterogeneity of lung adenocarcinoma by using next generation sequencing analysis: a feasibility study	G. Pelosi	2014		Observational	20	20
79/14	Retrospective observational study in patients with dual neoplasia: breast cancer and lung cancer	M. Garassino	2014		Observational	61	61
89/14	Protective versus conventional ventilation during thoracic surgery	F. Piccioni	2014		-	16	16
111/14	A Phase II, Non-comparative, Open label, Multi-centre, International Study of MEDI4736, in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) who have received at least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen (ATLANTIC)	M. Garassino	2014		II	41	41
132/14	A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene (AURA3)	M. Garassino	2014		III	4	4
145/14	Analysis of next generation sequencing of large cell carcinoma of the lung: a retrospective observational study	G. Pelosi	2014		Observational	30	30
162/14	Molecular characterization of sarcomatoid carcinoma, a life-threatening subtype of lung cancer	G. Pelosi	2014		Observational	80	80
166/14	A Randomized Open-Label Phase III Trial of pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer	M. Garassino	2014		III	1	1

Melanoma

52/08	A double-blind, randomized, placebo-controlled phase III study to assess the efficacy of recMAGE-A3 + AS15 ASCI as adjuvant therapy in patients with MAGE-A3 positive resected stage III melanoma	M. Santinami	2009		III	37	Closed accrual
42/09	An open label, multicenter, phase III trial of ABI-007 vs dacarbazine in previously untreated patients with metastatic malignant melanoma	M. Del Vecchio	2010	4/7/2014	III	19	Closed accrual
06/10	BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previuosly untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine	M. Del Vecchio	2010		III	10	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
24/10	The TEAM trial (Tasigna efficacy in advanced melanoma): A randomized, phase III, open label, multi-center, two-arm study to compare the efficacy of Tasigna® versus dacarbazine (DTIC) in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation	M. Del Vecchio	2011	9/19/2014	III	11	Closed accrual
25/10	An open, dose-escalation phase I/II study to assess the safety, immunogenicity and clinical activity of rec-PRAME + AS15 Antigen-specific Cancer Immunotherapeutic as first-line treatment of patients with PRAME-positive metastatic melanoma	M. Santinami	2010	11/25/2014	I-II	12	Closed accrual
33/10	An open-label, multicenter, randomized, phase Ib/II study of E7080 in combination with dacarbazine versus dacarbazine alone as first line therapy in patients with stage IV melanoma	M. Del Vecchio	2010	6/23/2014	Ib-II	9	Closed accrual
34/10	A phase II single arm study of the combination of Ipilimumab and fotemustine in patients with non-resectable stage III or stage IV melanoma	M. Santinami	2010		II	9	Closed accrual
62/10	An open phase I study of immunization with the rec-NY-ESO-1 + AS15 antigen-specific cancer immunotherapeutic in patients with NY-ESO-1 positive unresectable and progressive metastatic cutaneous melanoma	M. Santinami	2010		I	26	0
01/11	A phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAFV600E/K mutation-positive melanoma	M. Del Vecchio	2011		III	5	Closed accrual
16/11	An open-label, multicenter expanded access study of RO5185426 in patients with metastatic melanoma	M. Del Vecchio	2011		III	78	Closed accrual
39/11	Identification of circulating microRNAs as potential indicators of progression in metastatic melanoma	L. Rivoltini	2011		Observational	268	20
40/11	A study of immunomodulatory effect of BRAF and MEK inhibitors in melanoma patients	L. Rivoltini	2011		Observational	88	23
76/11	An open-label, multicenter, single arm, phase I dose. escaltion with efficacy tail extension study of Vemurafenib (RO5185426) in pediatric patients with surgically incurable and unresctable stage IIIC or stage IV melanoma harboring BRAFV600 mutations	A.Ferrari	2013		I	2	1
23/12	A Randomized Double-Blind phase III study of Ipilimumab Administered at 3 mg/kg vs at 10 mg/kg in subjects with previously treated or untreated unresectable or metastatic melanoma	M. Del Vecchio	2012		III	40	Closed accrual
28/12	Tracing the melanoma lineage: cancer stem cells and genetic noise	M. Santinami	2012		Observational	26	Closed accrual
37/12	Malignant skin lesions in patients with cancer: an observational prospective study	A. T. Caraceni	2012		Observational	101	2
38/12	A phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (STAGE IV) BRAF V600E/K mutation-positive cutaneous melanoma	F. de Braud	2012		III	20	Closed accrual
52/12	A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma	M. Del Vecchio	2013		III	13	Closed accrual

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
58/12	Potentiating clinical and immunological effects of chemotherapy by neutralizing acidic pH at tumor site: a phase II randomized study in melanoma patients	M. Santinami	2012	4/3/2014	II	4	0
71/12	A phase II study of intratumoral application of L19IL2/ L19TNF in melanoma patients in clinical stage III or stage IV M1a with presence of injectable cutaneous and/or subcutaneous lesions	M. Santinami	2012		II	19	4
103/12	A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated locally advanced or metastatic malignant cutaneous melanoma	Filippo De Braud	2012		II	8	0
106/12	An open-label, single-arm, phase II, multicenter study to evaluate the efficacy of vemurafenib in metastatic melanoma patients with brain metastases	M. Del Vecchio	2013		II	1	Closed accrual
140/12	A Randomized, Open-Label Phase 3 Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy	M. Del Vecchio	2013		III	2	Closed accrual
143/12	COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection	M. Santinami	2013		III	39	26
42/13	A Phase 3, Randomized, Double-Blind Study of BMS-936558 vs Dacarbazine in Subjects with Previously Untreated Unresectable or Metastatic Melanoma	F. De Braud	2013		III	11	2
43/13	A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma	F. De Braud	2013		III	11	Closed accrual
44/13	A randomized, Phase III study of Fotemustine versus the Combination of Fotemustine and Ipilimumab in Patients with Metastatic Melanoma with brain metastasis	M. Del Vecchio	2013		III	5	2
64/13	Constitution of a Clinical National Melanoma Registry (CNMR)	M. Del Vecchio	2014		Observational	3	3
94/13	A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma	M. Del Vecchio	2013		III	14	1
117/13	ZeSS: A Prospective Observational Safety Study of Patients with BRAFV600 Mutation-positive Unresectable or Metastatic Melanoma Treated with Vemurafenib (Zelboraf®)	M. Del Vecchio	2014		Observational	1	1
124/13	Identification of molecular markers of multiple cutaneous melanoma - MULTIMELMARKERS	L. Rivoltini	2014		-	47	47
152/13	Activity of Fotemustine on angiogenesis and lymphangiogenesis factors and on peripheral blood monocytes in advanced melanoma patients	A. Anichini	2014		Observational	3	3
27/14	Immunomodulatory effect of esomeprazole antitumoral and high-dose in patients with melanoma in stage III. Multi-stage pilot study (AdESOM2)	L. Rivoltini	2014		II	33	33

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
34/14	Dabrafenib Metastatic Melanoma Named Patient Programme Retrospective Chart Review	M. Del Vecchio	2014	11/17/2014	Observational	13	13
44/14	A Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation-Positive Melanoma that has Metastasized to the Brain	M. Del Vecchio	2014		II	1	1
60/14	The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma	M. Del Vecchio	2014		III	7	7
69/14	A phase III randomized, 3-arm, open label, multicenter study of LGX818 plus MEK162 and LGX818 monotherapy compared with Vemurafenib in patients with unresectable or metastatic BRAF V600 mutant melanoma	M. Del Vecchio	2014		III	3	3

Palliative Care

36/10	An open-label randomized controlled clinical trial to compare the analgesic efficacy of therapeutic strategies with Oxycodone, Fentanyl and Buprenorphine versus Morphine in patients with cancer-related pain of moderate-severe intensity, since the start of third-step treatment of the WHO analgesic scale	A. Caraceni	2011	9/30/2014	IV	25	2
123/13	Sublingual Fentanyl versus subcutaneous morphine for the management of severe cancer pain episodes in patients on opioid treatment: a double-blind randomized non-inferiority trial	A. Caraceni	2013		IV	80	75
98/14	A multi-centre, non-interventional investigation of the relationship between pain intensity numeric rating scale scores and health status, as assessed with the EQ-5D, in patients with cancer-related chronic pain	A. T. Caraceni	2014		Observational	20	20
99/14	Time and Motion (T&M) Study of Denosumab (XGEVA) Subcutaneous (SC) Injection and Zoledronic Acid (ZOL) Intravenous (IV) Infusion in Patients with Metastatic Bone Disease in Europe	A. T. Caraceni	2014		Observational	30	30
120/14	Action - Observation Therapy in young patients with upper limb neuromotor outcomes from brain tumor	F. Gariboldi	2014		Observational	3	3

Pediatric Tumors

26/95	Immunotherapy (IL-2 and activated circulating mononucleate cells) and pre/post-surgical antineoplastic chemotherapy in the primary treatment of osteosarcoma	C. Meazza	1995		II	86	0
40/01	Protocol NB-AR-01: First European Cooperative Study for high-risk neuroblastoma	R. Luksch	2002		III	62	4
12/03	Second protocol for diagnosis and treatment of ependymoma in a pediatric age	M. Massimino	2003		Observational	52	3
13/03	Non-controlled clinical study for the treatment of Ewing's sarcoma in relapse	R. Luksch	2003		II	24	1
14/03	Wilms' tumor: diagnostic-therapeutic protocol AIEOP 2003	F. Spreafico	2003		Observational	120	4
16/03	Germ cell tumors: diagnostic-therapeutic protocol AIEOP 2003	M. Terenziani	2003		III	116	13

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
17/05	Phase II protocol with combined chemotherapy and 131I-MIBG in the treatment of patients with neuroblastoma resistant or in relapse (I-METCH)	R. Luksch	2005		II	1	Closed accrual
08/07	LCH-III. Treatment protocol of the third international study for Langerhan's cell histiocytosis	S. Catania	2007	3/31/2014	III	62	6
13/08	Open-label, multi -center, randomized, two stage adaptive design study of the combination of bevacizumab with standard chemotherapy in minor patients with metastatic rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma or Ewing sarcoma/soft tissue primitive neuroectdermal tumour	M. Casanova	2008		II	10	Closed accrual
17/08	HL PED 2008 Hodgkin's lymphoma. A therapeutic protocol for sequels reduction	M. Terenziani	2008		II	29	4
22/09	A phase II study on the efficacy of dose intensification in patients with non-metastatic Ewing's sarcoma	P. Casali, R. Luksch	2009		III	31	5
25/09	Therapeutic protocol with high-dose chemotherapy, radiotherapy, maintenance therapy with low-dose Cyclophosphamide and anti-COX2 in metastatic Ewing's sarcoma: ISG/AIEOP study	P. Casali, R. Luksch	2009		II	28	3
53/10	Phase 1/2 combined dose ranging and randomised, open-label, comparative study of efficacy and safety of plerixafor in addition to standard regimens for mobilisation of haematopoietic stem cells into peripheral blood, and subsequent collection by apheresis, vesus standard mobilisation regimens alone in pediatric patients, aged 2 to<18 years, with solid tumours eligible for autologous transplants	R. Luksch	2012		I-II	2	Closed accrual
84/10	Evaluation and treatment of bone mass and body composition alterations in pediatric patients with oncological disease of central nervous system	E. Seregni	2010		Observational	46	3
02/11	A phase I study of LDE225 in pediatric patients with recurrent or refractory medulloblastoma or other tumors potentially dependent on the Hedgehog-signaling pathway	M. Casanova	2011	10/3/2014	I	8	Closed accrual
20/11	Neurocognitive outcome correlated to radiation dose and diffusion-tensor MRI information (DTI) in children focally irradiated for primitive pediatric malignant brain tumours	M. Massimino	2011	5/6/2014	Observational	26	5
46/11	A phase II open-label. Randomized, multi-centre comparative study of bevacizumab-based therapy in paediatric patients with newly dignosed supratentorial high-grade glioma	M. Massimino	2011		II	14	6
49/11	International randomized phase ii trial of the combination of vincristine and irinotecan with or without temozolomide (VI or VIT) in children and adults with refractory or relapsed rhabdomyosarcoma	M. Casanova	2011		II	2	0
07/12	Nimotuzumab and vinorelbina concomitantly to radiation and as maintenance for newly diagnosed diffuse pontine glioma in childhood	M. Massimino	2012		Observational	22	6
43/12	European Low an Intermediate Risk Neuroblastoma	R. Luksch	2013		III	6	2
93/12	PanCareSurFup: PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies	M. Terenziani	2013		Observational	164	Closed accrual
145/12	A phase III multi-center, open-label, randomized, controlled study of the efficacy and safety of oral LDE225 versus temozolomide in patients with Hh-pathway activated relapsed medulloblastoma	M. Casanova	2013		III	5	3

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
147/12	Assessment of symptoms in children and adolescents with malignant disease during treatment	S. Macchi	2013		Observational	62	29
05/13	Re-induction protocol for patients with high-risk neuroblastoma at first relapse	R. Luksch	2013		II	2	1
14/13	Intergroup trial for children or adolescents with b-cell NHL or B-AL: evaluation of rituximab efficacy and safety in high risk patients	F. Spreafico	2013		II	6	4
16/13	A phase I/II dose schedule finding study of CH14.18/ CHO continuous infusione combined with subcutaneous aldesleukin (IL-2) in patients with primary refractory or relapsed neuroblastoma. A SIOPEN Study	R. Luksch	2013		I-II	1	0
68/13	The school activity during cancer treatment in developmental age: a survey about limits and resources through the administration of a questionnaire to parents	G. Casiraghi	2013	3/31/2014	Observational	33	0
80/13	A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)	M. Casanova	2013		I	8	3
103/13	A Phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability, and preliminary efficacy of weekly nab®-paclitaxel in pediatric patients with recurrent or refractory solid tumors	M. Casanova	2014		I	2	2
147/13	The point of view of adolescents with cancer	A. Ferrari	2013	6/1/2014	Observational	24	0
176/13	Retrospective and prospective study of late radiation damages after focal radiotherapy for childhood brain tumors	L. Gandola	2014		Observational	37	37
103/14	Observational retrospective and prospective study on patients enrolled in AIEOP and IPINET Centers	M. Massimino	2014		Observational	32	32
126/14	REACT: REsources in Adolescent Cancer Treatment	C. A. Clerici	2014		Observational	4	4
127/14	Quality of life in long-term survivors pediatric patients treated for metastatic medulloblastoma	M. Massimino	2014		Observational	10	10
139/14	Italian peripheral neuroblastic tumors Registry (RINB) - AIEOP (Italian Association of Pediatric Hematology Oncology) Registry	R. Luksch	2014		Observational	3	3

Sarcomas

31/03	EUROpean Bone Over 40 Sarcoma Study. A European treatment protocol for bone-sarcoma in patients older than 40 years	P. Casali	2003		II-III	14	1
46/03	Ifosfamide at high doses in prolonged continuous infusion by a portable infusion system in soft-tissue sarcomas typical of the adult in an advanced phase in second/ further line chemotherapy	R. Bertulli	2004	5/21/2014	II	21	Closed accrual
01/04	Gemcitabine in leiomyosarcoma in an advanced phase in second or further line of chemotherapy	R. Bertulli	2004	5/21/2014	II	15	Closed accrual
31/05	EpSSG RMS 2005 - A protocol for non metastatic Rhabdomyosarcoma	A. Ferrari	2005		III	112	10
32/05	EpSSG NRSTS 2005. A protocol for localized non-rhabdomyosarcoma soft tissue sarcomas	A. Ferrari	2005		III	171	16

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
53/06	Trabectedin (ET743) in metastatic or locally advanced cell liposarcoma pretreated with chemotherapy	P. Casali	2007	10/22/2014	II	27	Closed accrual
45/08	A randomized, multicenter, phase III trial of Trabectedin (yondelis) versus doxorubicin-based chemotherapy as first-line therapy in patients with traslocation related sarcomas (TRS)	P. Casali	2008	10/22/2014	III	3	Closed accrual
62/08	Open label, multi-center, phase 2 study denosumab in subject with giant cell tumor of bone	P. Casali	2008		II	26	0
78/09	A phase II randomized - non comparative - study onthe activity of trabectedin or gemcitabine + docetaxel in metastatic or locally relapsed uterine leiomyosarcoma pretreated with conventional chemotherapy	P. Casali	2010		II	7	3
30/10	Randomized phase II study evaluating two doses of NGR-hTNF administered either as single agent or in combination with doxorubicin in patients with advanced soft tissue sarcoma (STS)	P. Casali	2010		II	11	Closed accrual
44/10	Phase II study on imatinib in combination with RAD001 in advanced chordoma	S. Stacchiotti	2011		II	44	13
66/10	Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadjuvant chemotherapy	A. Gronchi	2010		II	53	17
85/10	Evaluation of the role of immunosuppressive mechanisms in the prognosis and response to treatment with targeted therapy drugs in sarcoma patients	L. Rivoltini	2010		Observational	162	19
05/11	Translational study on modulation of gene transcription induced by Trabectedin in patients with myxoid/round cell liposarcoma	P. Casali	2011		Observational	2	0
19/11	A randomized, open label, multicenter, phase 3 study to compare the efficacy and safety of eribulin with dacarbazine in subjects with soft tissue sarcoma	P. Casali	2011		III	4	Closed accrual
28/11	Rabdomiosarcoma of adults. An observational prospective study	R. Bertulli	2011		Observational	10	3
59/11	STARSS: a phase III randomized STudy of preoperative RAdiotherapy plus Surgery versus surgery alone for patients with Retroperitoneal Sarcoma (RPS)	A. Gronchi	2011		-	23	11
73/11	ABCB1/P- glycoprotein expression as factor for the biologic stratification of the metastatic osteosarcoma of the extremities: a prospective study	R. Bertulli	2011		II	23	10
13/12	Tailore Beta-catenin mutational approach in extra-abdominal sporadic desmoid tumor patients	A. Gronchi	2013		Observational	22	11
119/12	Y-IMAGE: a non-interventional multicenter, prospective study to evaluate treatment outcome assessment methods used in routine clinical practice on patients with advaced soft tissue sarcoma treated with trabectedin according to the Summary of Product Characteristics (SmPC)	P. Casali	2013		Observational	7	0
142/12	Multicentric, prospectic, randomized study for the treatment of patients with relapsed osteosarcoma	C. Meazza	2014		II	1	1
54/13	Observational study of whole-trascriptome and whole-exome sequencing analysis in tumor samples of extraskeletal myxoid chondrosarcoma, malignant myoepithelioma, and dermatofibrosarcoma protuberans with or without fibrosarcomatous component	S. Stacchiotti	2013		Observational	20	12

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
114/13	Patients with atipical osteosarcoma and/or are not elegible in other ISG clinical trials	R. Bertulli	2013		Observational	2	1
188/13	Overcoming anti-angiogenetic therapy resistance in selected sarcomas	S. Pilotti	2014		Observational	8	8
13/14	Long term morbidity and quality of life after multivisceral resection for primary retroperitoneal soft tissue sarcomas: a prospective observational study	M. Fiore	2014		Observational	17	17
17/14	Assessment of BoNT/A effects on muscle cells and fibroblasts	C. Colombo	2014		Observational	5	5
33/14	Votrient® Sarcoma Named Patient Programme Chart (SPIRE)	P. Casali	2014	11/11/2014	Observational	20	20
93/14	A Phase II Open-Label Trial of Pazopanib Administered as a Single Agent in Patients with Unresectable or Metastatic Solitary Fibrous Tumor (SFT) and Extraskeletal Myxoid Chondrosarcoma (EMC)	S. Stacchiotti	2014		II	2	2
182/14	Trabectedin in advanced synovial sarcomas: a multicenter retrospective study from four European institutions and the Italian Rare Cancer Network	P. Casali	2014	11/28/2014	Observational	25	25
183/14	High-dose continous-infusion ifosfamide in advanced well-differentiated/dedifferentiated liposarcoma	P. Casali	2014	11/28/2014	Observational	28	28

Urinary Apparatus

53/07	Sunitinib treatment of renal adjuvant cancer (S-TRAC): a randomized double-blind phase 3 study of adjuvant sunitinib vs placebo in subjetcs with high risk RCC	G. Procopio	2007		III	6	Closed accrual
51/08	Axitinib (AG 013736) as second line therapy for metastatic renal cell cancer: AXIS trial	G. Procopio	2008		III	5	Closed accrual
11/10	Phase II study of sunitinib in metastatic renal cancer with non-clear cell histology	G. Procopio	2010		II	11	Closed accrual
52/10	A phase II study of neoadjuvant Cisplatin and Gemcitabine plus Sorafenib for patients with transitional cell carcinoma of the bladder	R. Salvioni	2010		II	36	10
09/11	A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of pazopanib as adjuvant therapy for subjects with localized or locally advanced RCC following nephrectomy	G. Procopio	2011		III	18	Closed accrual
10/11	Biotech of prostate cancer	N. Zaffaroni	2011		Observational	132	19
32/11	An open-label, randomized, multicenter, phase III study to compare safety and efficacy of TK1258 versus soafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and m-TOR inhibitor) therapies	G. Procopio	2011	6/30/2014	III	4	Closed accrual
09/12	An open label pharmacokinetic and tolerability study of cabazitaxel in patients with solid tumors with moderately and severely impaired and with normal renal function	F. De Braud	2012	3/18/2014	I	5	Closed accrual
46/12	Evaluation of microRNA expression in prostate cancer for the identification of novel diagnostic and prognostic markers	D. Zaffaroni	2012		Observational	17	4

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
47/12	The decision making of patients with prostate cancer in multidisciplinary visit	R. Valdagni	2013	3/7/2014	Observational	122	29
62/12	A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of Sorafenib in patients with advanced Renal Cell Carcinoma (RCC) after a radical resection of the metastases	G. Procopio	2012		II	21	10
65/12	PRINCIPAL: A Prospective Observational Study of Real World Treatment Patterns and Treatment Outcomes in Patients with Advanced or Metastatic Renal Cell Carcinoma Receiving Pazopanib	G. Procopio	2012		Observational	40	18
94/12	A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs. Prednisone in Metastatic Castration-resistant Prostate Cancer Patients who have Received Prior Docetaxel and Prior Abiraterone or MDV3100	G. Procopio	2013	11/28/2014	III	7	Closed accrual
108/12	A Randomized, Open-Label, Phase 3 Study of BMS-936558 vs. Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy	G. Procopio	2013		III	14	Closed accrual
48/13	Personalizing antiangiogenic treatment in advanced urothelial cancer	A. Necchi	2014		Observational	5	5
98/13	A phase Ib/II study of GDC-0068 or GDC-0980 with abiraterone acetate versus abiraterone acetate in patients with castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy	G. Procopio	2013		I-II	8	7
162/13	Retrospective analysis of eventual relationship between previous AWS (Antiandrogen withdrawal sindrome) and response to Enzalutamide in Docetaxel refractory metastatic castrate-resistant prostate cancer (mCRPC) patients	G. Procopio	2013	10/13/2014	Observational	25	16
171/13	A re-treatment safety study of radium-223 dichloride in subjects with castration-resistant prostate cancer with bone metastases who received an initial course of six doses of radium-223 dichloride 50 kBq/kg every four weeks	G. Procopio	2014		II	2	2
04/14	A Phase III trial to evaluate the efficacy of orasol plus mouthwash associated with oral hygiene standard (vs oral hygiene standard) in the prevention of stomatitis of everolimus in patients with advanced renal cell carcinoma (everolimus-induced STOmatitis Prevention trial)	G. Procopio	2014		-	6	6
25/14	A Phase 2 study of Paclitaxel and Ifosfamide plus either Cisplatin or Carboplatin for patients with metastatic non-transitional cell carcinoma of the bladder and the urinary tract	A. Necchi	2014		II	1	1
31/14	Gene expression profiling in advanced Bellini duct carcinoma	G. Procopio	2014	7/28/2014	Observational	16	16
46/14	Activity and safety of second line SOrafenib After Pazopanib in patients with metastatic renal cell carcinoma (SOAP Study)	G. Procopio	2014		II	4	4
49/14	Advanced urothelial cancer of the bladder, urethra, or the upper urinary tract who are resistant to platinum-based therapy	A. Necchi	2014		II	10	10
59/14	A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer	A. Necchi	2014		II	25	25

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
94/14	Activity and safety of third line tyrosin kinase inhibitor (TKI) after 2 tyrosin kinase inhibitors (TKIs) in patients with metastatic renal cell carcinoma (mRCC) (Tokio Study)	G. Procopio	2014		II	1	1
115/14	Feasibility of a home-based Pre-habilitation Program for Patients with Muscle Invasive Bladder Cancer, submitted to Neo-Adjuvant Chemotherapy and candidates to Radical Cystectomy with Urinary Reconstruction	M. Maffezzini	2014		-	7	7
121/14	Outcome evaluation of patients with pancreatic metastases from renal cell carcinoma (PmRCC) treated with targeted therapies	G. Procopio	2014	12/31/2014	Observational	276	276
125/14	Impact of previous perioperative cisplatin-based chemotherapy on outcomes of various first-line chemotherapies for advanced urothelial carcinoma (UC)	A. Necchi	2014	10/15/2014	Observational	13	13
133/14	A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer	A. Necchi	2014		III	4	4

Others

66/05	Registry of congenital malformations in Lombardy	G. Tagliabue	2006		Observational	20332	1364
40/07	Dose-finding study of Caelix and RAD001 in patients with advanced solid tumors	S. Cresta	2007	3/4/2014	I	23	Closed accrual
12/08	An open-label, safety, pharmacokinetics and pharmacodynamic dose escalation phase Ib study of pazopanib in combination with epirubicin or doxorubicin in subjects with advanced solid tumors	G. Capri	2008	8/4/2014	Ib	57	Closed accrual
32/09	Epidemiologic studies on environmental risk factors and their interactions with genetic factors of bladder cancer and sarcomas	A. Decarli	2009		Observational	813	133
35/09	Efficay of thermal treatment for respiratory airways in heavy smokers	U. Pastorino	2009		Observational	468	Closed accrual
47/09	A phase I, open label, multicenter, study to assess the safety, tolerability and pharmacology of AZ D2281 in combination with liposomal doxorubicin (Caelyx) in patients with advanced solid tumors	S. Cresta	2009		I	8	Closed accrual
54/09	Phase Ib study of CC-5013 and paclitaxel in patients with advanced solid tumors	G. Capri	2009		I	11	Closed accrual
16/10	The role of spiritual and religious behaviours and beliefs as search of meaning, in the coping with cancer. Pivotal study on factibility and on the impact of a religious intervention	C. Ripamonti	2010	12/31/2014	Observational	25	0
32/10	Dose-escalation, PK and safety study with single agent CetuGEX in patients with locally advanced and/or metastatic cancer	S. Cresta	2010	6/4/2014	I	6	Closed accrual
54/10	Phase II study of nilotinib efficacy in pigmented villo-nodular synovitis/tenosynovial giant cell tumour (PVNS/TGCT)	P. G. Casali	2011		II	5	Closed accrual
55/10	Evaluation of the response according to dimensional and tissue criteria using contrast-enhanced amplifier ultrasonography in patients with soft tissue sarcomas or gastrointestinal stromal tumors (GIST) after molecular target therapies - CONTICANET	C. Morosi	2010	12/31/2014	Observational	34	4

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
27/11	Role of chemotherapy in trastuzumab cytotoxic activity	E. Tagliabue	2011		Observational	15	4
41/11	Prospective, phase II randomized to compare busulfan-fludarabine reduced-intensity conditioning (RIC) with thiotepa-fludarabine RIC regimen prior to allogeneic transplantation of hematopoietic cells for the treatment of myelofibrosis	P. Corradini	2011		II	1	0
42/11	SUTNET Trial: biological and clinical phase II study of sunitinib in patients with unresectable and/or metastatic pheochromocytomas/paragangliomas	R. Buzzoni	2011		II	26	10
56/11	A phase I dose-escalation study of PHA-739358 administered in combination with docetaxel or gemcitabine or bevacizumab or carboplatin in adult patients with advanced solid tumors, including Hodgkin's and non-Hodgkin's lymphoma	A. Guidetti	2011		I	11	0
104/11	An open label, multicenter, expanded access study of INC424 for patients with primary myelofibrosis (PMF) or post polycythemia myelofibrosis (PPV MF) or post-essential thrombocythemia myelofibrosis (PET-MF)	P. Corradini	2011		III	7	3
112/11	Toremifene in desmoid tumor: prospective clinical trial and identification of potential molecular targets	C. Colombo	2011		II	12	0
08/12	Hypercoagulation screening as an innovative tool for risk assessment, early diagnosis and prognosis in cancer	F. de Braud	2012		Observational	345	116
25/12	Identification and validation of microRNAs as novel biomarkers and therapeutic targets in diffuse malignant peritoneal mesothelioma	N. Zaffaroni	2012		Observational	70	8
39/12	A phase I dose escalation study of NMS-1191372 in adult patients with advanced/metastatic solid tumors	F. de Braud	2012		I	29	12
59/12	Identification of Polymorphisms Predicting Bevacizumab-Related Side Effects: SToPtrial	M. Di Bartolomeo	2012		Observational	72	9
61/12	A Phase 1b, multi-center, open label, dose escalation study of oral LDE225 in combination with BKM120 in patients with advanced solid tumors	F. de Braud	2012		I	9	6
75/12	A Phase 1a/1b, Multi-Center, Open-Label, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of the Pleiotropic Pathway Modifier CC-122 Administered Orally to Subjects with Advanced Solid Tumors, Non-Hodgkin's Lymphoma or Multiple Myeloma	F. De Braud	2013		I	7	1
104/12	Incidence of thromboembolic events during chemotherapy in metastatic/advanced cancer patients	R. Buzzoni	2012		Observational	9	Closed accrual
105/12	The Lombardy Rare Donor Programme	F. Arienti	2012		Observational	63	29
122/12	Phase 1b study of the tumor-targeting human L19TNFalfa monoclonal antibody-cytokine fusion protein in combination with doxorubicin in patients with advanced solid tumours	F. De Braud	2013		I	9	1
134/12	Informative Note Project on Informed Consent: understandability and usefulness of informed consent in clinical interventional trials	C. Borreani	2013		Observational	50	30
135/12	Expectations, experiences and preferences of patients and physicians involved in the informed consent process for Phase 2 and Phase 3 clinical trials: construction of a model	C. Borreani	2013		Observational	18	8

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
06/13	Cross-tumoral phase 2 clinical trial exploring crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET ("CREATE")	P. G. Casali	2013		II	18	10
10/13	A Phase I open-label dose escalation study with expansion to assess the safety and tolerability of INC280 in patients with c-MET dependent advanced solid tumors	F. De Braud	2013		I	3	0
21/13	Variation of respiratory function and chest wall mechanics after resection and rib-like costal reconstruction	F. Piccioni	2013		-	15	6
23/13	The costs of social care of cancer patients	M. Gariboldi	2013	6/1/2014	Observational	296	29
32/13	Multicenter, randomized, double-blind, placebo controlled, study to evaluate the activity of a ginger (Zingiber officinale) food supplement in the management of nausea in patients receiving highly emetogenic treatments and standard anti-emetogenic therapy	P. Bossi	2013		-	71	38
46/13	An open-label, multi-center everolimus roll-over protocol for patients who have completed a previous Novartis sponsored everolimus study and are judged by the investigator to benefit from continued everolimus treatment	R. Buzzoni	2013		IV	2	Closed accrual
56/13	Italian Oncologic Pain multiSetting - Multicentric Survey (IOPS-MS)	A. T. Caraceni	2013		Observational	190	160
76/13	An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours	F. De Braud	2013		I	16	13
77/13	Dose escalation, safety, pharmacokinetic and pharmacodynamic, first in man study, of SAR125844 single agent administered as slow intravenous infusion in adult patients with advanced malignant solid tumors	F. De Braud	2013		I	36	18
85/13	Randomized controlled trial of metformin and dietary restriction to prevent age-related morbid events in people with metabolic syndrome	F. Berrino	2014		III	50	50
107/13	PreveDi (Prevention Disease) - Prevention of chronic degenerative diseases	A. Villarini	2013		-	422	272
129/13	Evaluation of outpatients's needs with solid or haematological tumors at the S.S.D. "Supportive Care Unit"	C. Ripamonti	2013	4/9/2014	Observational	302	102
130/13	Tumor molecular markers able to predict benefit from trastuzumab treatment	E. Tagliabue	2013	12/15/2014	Observational	70	0
132/13	Analysis of the expression levels of biomarkers in the blood of healthy donors	M.G. Daidone	2013	1/15/2014	Observational	90	18
143/13	Innovative approaches in the treatment of giant congenital nevi melanocytes	A. Colombetti	2013		-	25	15
146/13	Prospective observational study on the management of oral mucositis in cancer patients treated with chemotherapy and/or radiotherapy of "Fondazione IRCCS Istituto Nazionale dei Tumori" of Milan	G. Antonacci	2014		Observational	20	20
148/13	Procedures, complications and follow-up of tracheostomy techniques in intensive care	L. Persiani	2014		Observational	19	19
160/13	Evaluation of the effect and tolerability of pneumatic pressure therapy in the treatment of lymphedema of the upper and lower limbs, secondary to cancer surgery	A. T. Caraceni	2013	2/14/2014	Observational	112	0

Study code	Title	Coordinator	Activated	Closed	Phase	Total patients	Patients enrolled in 2014
166/13	Novel molecular mechanisms of genetic predisposition to early-onset breast cancer	P. Radice	2014		Observational	1150	1150
170/13	A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors	F. De Braud	2014		I-II	21	21
183/13	Experimental evidence of tollerance to high intra abdominal pressure (IAP) during HIPEC	S. Kusamura	2014		II	1	1
08/14	Comparison pilot study between complex decongestive therapies for the treatment of secondary lower limbs lymphedema in cancer patients	A.T. Caraceni	2014		-	14	14
20/14	Phase IB study of MK-3475 in Subject with select advanced solid tumors	F. De Braud	2014		I	44	44
23/14	A RandomisEd, double-bLind, placebo-controlled study to evaluate the Efficacy of two different dose levels of orVEpitant (1 0 and 30 mg) compared with placebo on EGFRi-induced intense pruritus in oncology subjects	P. Bossi	2014		II	2	2
24/14	REQUITE Study Protocol Validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality-of-life in cancer survivors	R. Valdagni	2014		Observational	112	112
76/14	Observations on the use of the homoeopathic preparation Homeogénè 46 in patients who show symptoms of anxiety or claustrophobia when undergoing magnetic resonance imaging examination	A. Laffranchi	2014	7/31/2014	Observational	187	187
114/14	A phase Ib open-label, multi-center, dose escalation and expansion study of orally administered MEK162 plus BYL719 in adult patients with selected advanced solid tumors	F. Raspagliesi	2014		I	2	2
174/14	Prospective observational study on the characteristics and treatments of Fatigue in oncological patients in Italy - "Fatigue" Study	C. Ripamonti	2014	12/18/2014	Observational	126	126

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