SCIENTIFIC REPORT 2018

EXECUTIVE SUMMARY

Fondazione IRCCS
Istituto Nazionale dei Tumori

Sistema Socio Sanitario
Regione Lombardia

INT

THE FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI (**INT**) HAS BEEN ESTABLISHED IN 1928. INT IS A COMPREHENSIVE CANCER CENTER WHOSE ACTIVITIES RANGE FROM EPIDEMIOLOGY TO CANCER DIAGNOSIS, TREATMENT, REHABILITATION AND PALLIATIVE CARE THROUGH INNOVATIVE THERAPIES AND PREVENTION STRATEGIES, WITH EXPERIMENTAL AND CLINICAL UNITS LOCATED IN THE SAME OR NEARBY BUILDINGS FAVOURING THE CONTINUOUS INTERACTIONS, WITH CENTRALIZED SERVICES.

ISTITUTO NAZIONALE DEI TUMORI

AMADEO LAB

CAMPUS CASCINA ROSA

AROUND
2000
PERSONNEL
WORKING AT INT
OF WHICH
540
DEVOTED
TO RESEARCH

27
RESEARCH LAB

3600 SQM
SURFACE

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FROM THE PRESIDENT

MARCO VOTTA

Italian oncology was born at the National Cancer Institute (INT) on 12 April 1928. Thanks to the high quality of research and care pathways present, the Institute immediately established itself as the first Italian cancer center. The evaluation of the Ministry of Health, drawn up on the basis of scientific and assistance criteria, also this year places INT in first place among all the Italian oncological IRCCS.

The Institute is classified as a Comprehensive Cancer Center, awarded by OECI, the Organization of European Cancer Institutes, coordinator of the European Joint Action on rare cancers of the JARC, International Agency for Research on Cancer, member of the Cancer Core Europe consortium formed by the seven principal European Cancer Center. INT is the regional reference center for liver transplants in cancer patients, as well as being the implementing body of the ROL, Lombardy Oncological Network. The INT is recognized as the managing body for taking care of chronic cancer patients, as per Regional Law n. 23/2015.

In the future the realization of the City of Health and Research in Sesto San Giovanni is planned, a public integrated system of complex functions and clinical and scientific excellence in oncology and neurology. The new complex will host a high-level medical-scientific center, in partnership with the University of Milan and the University of Milan-Bicocca. It will be a cutting-edge center that will offer innovative research and treatment paths.

FROM THE GENERAL DIRECTOR

STEFANO MANFREDI

I am very proud to have taken the position of General Director of the National Cancer Institute of Milan in 2018. The standing of this institution with its great burden of knowledge and scientific culture, which has made this place the site of numerous milestones in cancer research and treatment, makes me very aware of the important commitment and challenge I have assumed.

The Institute, first among the 12 Italian oncology IRCCS (Italian Research and Treatment Center recognized by the Italian Ministry for Health), stands out for its multidisciplinary approach, for increasingly personalized medicine and cutting-edge care pathways. My wish is to collaborate to further strengthen INT position and facilitate the process to become more and more a "reference center" for ensuring greater appropriateness in the field of oncology treatment at regional and national level.

The path, already started by my predecessors I intend to further support, tries to guarantee to patients more and more access to the best care and research in the oncology field, also through the concentration and coordination of the most complex assistance in centres of excellence (hub) and the organization of a functionally integrated peripheral system (spoke) that could guarantee real and continuous continuity of the care path in the future.

The National Cancer Institute of Milan manages 18,049 admissions per year, 1,238,267 consultations, 482 beds, 18 MAC (Complex Outpatient Macro-activity) and 27 research laboratories, thanks to the work and high standing of over 2000 professionals: doctors, surgeons, researchers, nursing staff, administrative staff, collaborators and scholarships.

These figures are also joined by volunteers who daily work with passion and committement for a public good: those of the patient and his medical support at in a time of great difficulty.

FROM THE SCIENTIFIC DIRECTOR

GIOVANNI APOLONE

The Scientific Report 2018 - Executive summary, as part of the new and renewed publishing project for the Scientific Report, takes into consideration the assessment carried out by the Scientific Directorate at the end of the 2017-2018 period.

This new publication provides available research outputs for the year 2018 including the new strategic directions towards 4 novel research priorities - Primary prevention, secondary prevention and early diagnosis, Precision medicine and technological innovation (pharmacological and non), Complexity and rare tumors, Effectiveness Studies and "Outcome Research".

The new four research priorities offer a strong guidance and planning of current and future initiatives, stressing the focus on translational research, where research activities and healthcare are connected through multidisciplinary programs designed and coordinated by science teams with diverse clinical and scientific backgrounds.

The scientific output in 2018 has enjoyed an upward trend according to all indicators conventionally used to classify and evaluate research activity: the clinical trials conducted in 2018 were 667, with an increase of the number of patients entering in clinical studies and research protocols that, besides offering them the best possible treatment, also gave them access to innovative drugs and other health technologies. In 2018 we published 722 scientific papers (5220.2 IF).

Through the INT Strategic Research Plan 2016-19, a four-year agenda aiming at a better planning of the research strategy, a more consistent decision-making process for research processes and experimentations and a more intensive effort to rationalize research-supporting resources and structures has been pursued.

In this framework, new mechanisms for sustaining innovative multidisciplinary projects and initiatives have been introduced dedicated to in-house research and investigator-initiated projects. In 2017 and 2018 the Scientific Directorate devoted most part of its Research Fund resources to the launching of competitive yearly peer reviewed calls to support preclinical and clinical multidisciplinary projects as well as researchers in early stages of their career: 14 projects in 2017 and 16 in 2018 have been financed.

In 2018 INT was also concentrated in developing more stable and systematic relationship between in-house and external research Institutions through the creation of permanent networks for studying specific diseases or methodologies, aimed at conducting multicentric clinical trials. A steady flow of communication with important research institutes and funding agencies was established to discuss common strategies and medium/long-term joint ventures.

In this year INT increased the weight and authority both at international level, by investing on creating a network of relations with the main European cancer centers, such as Cancer Core Europe (CCE) and the Organizatin of the European Cancer Institues (OECI) and, at national level, by intensifying its engagement with the networks of excellence that the Institute is already participating in or working with as leading partner (such as the Alliance Against Cancer, Rare Cancer Network and the Lombardy Hematology Network). All these activities provided important results, witnessed by the increasing number of publications, granted projects at national and international level and the number of clinical trials.

These outstanding results have been possible thanks to the synergic committeemen of the Presidency , the General Directorate and the strong effort of all researchers, clinicians and the administrative staff.

FOCUS ON MAJOR EVENTS

CANCER CORE EUROPE

On February 2018, the Scientific Directorate sponsored the participation of a large group of INT experts and researchers at the Annual Cancer Core Europe (CCE) Conference held in Paris and organized by the Gustave Roussy Institute.
As member of CCE, in 2018 INT started collaborating in ongoing projects carried out by the consortium: the Basket of Baskets trial, the Melanoma project and the BRCA use case.

90TH INT ANNIVERSARY

The 90th INT anniversary (April 12th 1928-2018) represented an opportunity to focus on advances in oncology, value of scientific research, and new opportunities for treatment, taking into account investments for public health and for social and economic progress. Ninety years of study, passion and commitment to patients have made INT an Italian scientific excellences in the oncology field.

2018 JANUARY FEBRUARY MARCH APRIL MAY JUNE JULY

INSTITUTIONAL RETREAT

On March 2018 the Scientific Directorate organized the second edition of the 2-day meeting entitled "Intelligent Research - organization, resources and quality in INT's strategy" (Oreno di Vimercate, March 2nd-3rd). The seminar was aimed at discussing the new strategic directions and the priorities of the INT scientific research, in particular towards innovative organizational models in health care, and the future of the four institutional research priorities for 2018-2020.

CALL FOR RESEARCH VALUE

On April 2018 INT promoted the Third Call for Research Value aimet at offering opportunities to INT researchers through the funding of Start-up support, proof-of-concept projects dedicated to creation and validation of preliminary data. Following a peer review process, the Scientific Directorate financed 16 projects for a total of 600.000 euro.

GIORNATA DELLA RICERCA INT

On May 23rd INT celebrated the "Giornata della Ricerca". The event represented the opportunity to look back to the scientific accomplishments achieved during the year, presented by the Scientific Director. Moreover, INT researchers presented some of the ongoing projects funded by Call for research value 2016, financed by 5xmille funds, in order to give a feedback on destination of such resources.

AUGUST SEPTEMBER OCTOBER NOVEMBER DECEMBER 2019

PRESIDENT SERGIO MATTARELLA VISITED INT

For the 90th anniversary, INT had the honor of hosting the President of the Italian Republic, Hon. Sergio Mattarella. On September 20th the President visited INT and met authorities, patients and operators.

SUMMER SCHOOL IN TRANSLATIONAL CANCER RESEARCH

Four researchers of INT participated to the Summer School in Translational Oncology and one oncologist has been chosen to deliver a presentation about cancer and metabolism. This School is a yearly event promoted by CCE and organized by the DKFZ-NCT Heidelberg and the DKTK (Albufeira, Portugal, October 8-12, 2018).
This event represents an excellent opportunity for the next generation of oncologists to interact with prominent specialists in the field, create networks, and initiate collaborations in Europe and worldwide.

THE ESSENTIAL ABOUT INT

SCIENTIFIC ACTIVITY

722	Publications
5220.2	Impact factor
47.8 %	Publications as first/last author

RESEARCH

667	Clinical studies (Total)
231	Observational studies
436	Experimental studies
182,180	Patients included in clinical studies (Total)
396	Patients enrolled in biological observational studies
3925	Patients enrolled in prospective observational studies
120,293	Patients enrolled in retrospective observational studies
54,825	Patients enrolled in registries
2741	Patients enrolled in experimental studies

RESEARCH FUNDING

27,580,942 €	Total
7,373,142 €	Ministry of health
12,918,905 €	Funding agencies
4,259,345 €	Clinical trials
3,029,550 €	5xMille*

*Funds obtained by Italian Ministry of Health and Italian Ministry of Education (MIUR) through the allocation of 0.5 percent contribution of taxpayers income tax devolved to research institution of choice

CLINICAL DATA

482 Beds

18,049 Total inpatients

4,250 Of which day hospital

1,238,267 Consultations

PATENT PORTFOLIO

10 Total Patents

4 INT Owner

6 INT Co-owner

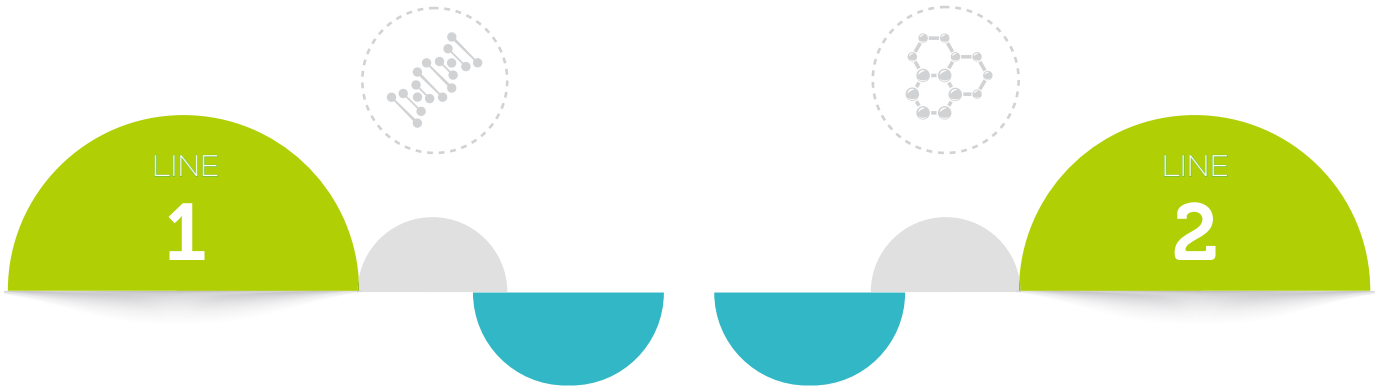
EDUCATION

198 Events/training courses

4,539 Participants

36,777 Formative hours

INSTITUTIONAL RESEARCH PRIORITIES 2018-2020



PREVENTION AND EARLY DIAGNOSIS

This line of research is focused on precision in cancer prevention, a revolutionary approach which takes into account individual differences in lifestyle, environment and biology. Research activities refer to primary, secondary and tertiary prevention considering high risk individuals as target of intervention, and are declined according to the "Hallmarks of Cancer" with a multidisciplinary approach.

The research projects of this line are aimed at improving the health prospects of the population with respect to cancer, its prevention through better information and the adoption of correct lifestyles, and the reduction of risk in groups exposed to predisposing causes or for familiarity. Early diagnosis remains the best prerequisite for effective treatment, therefore the search for prognostic and prediction response biomarkers, measurable in biological fluids, is the rationale for developing reliable and less invasive screening and diagnostic programs.

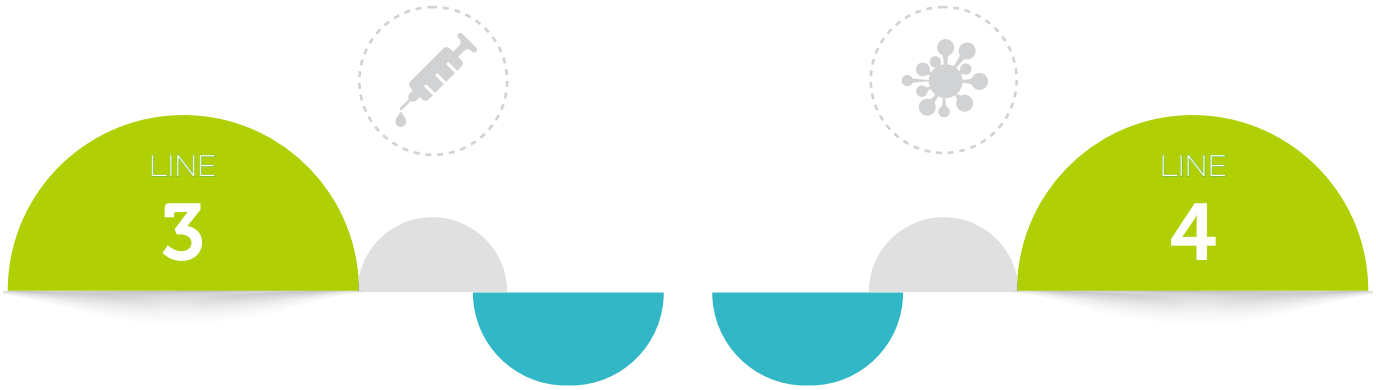
Thanks to new technologies that generate and interpret "omics" data, it is possible to identify molecular alterations common to various tumor types – this allows optimized prevention interventions and a more rational use of therapies, in particular to prevent toxicity.

PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

This line aims to study the new frontiers of precision medicine and innovative diagnostic-therapeutic technologies, at a multidisciplinary level, using a reverse translational approach. Starting from relevant clinical questions, translational research brings the results of the laboratory to the patient's bedside and, in reverse, reports the results of the interventions and the questions on which to develop their studies to preclinical research.

This research field is dedicated to the identification of alterations and omics profiles, clinically actionable and exploitable as biomarkers, and to the development of molecular-targeting drugs, integrating the molecular and clinical features of the patients to allow diagnostic and therapeutic stratification and optimize therapeutical approach.

In this process of pharmacological and non-pharmacological technological innovation, the use of non-invasive liquid biopsies for diagnosis and monitoring, and the study of tumor / host / environment interactions to modulate the immune response and epigenetics play an increasingly important role.



COMPLEXITY AND RARE TUMORS

Cancer is a multifactorial pathology that requires a direct approach not only to the disease but also to the complexities associated. Therefore, attention to rare oncological diseases, pediatric tumors (including adolescents and young adults), fragile populations (elderly patients with multiple pathologies, chronic patients and long-term survivors) represent focal points for complexity management.

This line of research analyzes complexity using a multi- and interdisciplinary approach from the genetic, molecular, clinical and social care point of view, taking into account the problems of access to treatment and inequalities, and of the particular attentions required by chronic, elderly, pediatric and long-term patients.

Improving the quality of care for patients with rare solid adult tumors, limiting health migration will be carried out by intense networking activity, necessary for conducting research and treatment dedicated to rare diseases, thanks to the central role of INT as world reference center for some rare diseases.

The Institute is indeed coordinator of the Rare Tumors Network, of important epidemiological projects and recently of the Joint Action on Rare Cancers.

EFFECTIVENESS STUDIES AND OUTCOME RESEARCH

This line of research is based on observational, intervention and organizational activities to obtain evidence of effectiveness of health interventions. This is done by collecting evidence and organizing clinical, biological and outcome data (using big data approaches) in databases that can be consulted and harmonized with other sources, such as the electronic clinical report.

Focus on outcome data analyses, systematic review of the literature and implementation of innovative management models are instrumental to evaluate the real impact of the intervention on the health of the population, on the company organization, on health expenditure. Therefore research projects in this field are aimed at collecting, organizing and analyzing the available clinical, dosimetric, toxicity and "omics" data deriving from preclinical, experimental, prevention, pharmacological and non-interventional studies, to verify their effectiveness.

Moreover, research will be directed to organizing PDTAs, evaluating the results and impact on organization in the real world (RWE, RWD), HTA of interventions and innovative technologies, experimentation with sustainability models, patients reported outcome (PRO).

RESEARCH AREAS

RESEARCH AT INT IS AIMED AT IMPROVING PREVENTION, EARLY DIAGNOSIS AND TREATMENT OF CANCER DISEASES, AND THE QUALITY OF LIFE OF CANCER PATIENTS. THE MULTIDISCIPLINARY RESEARCH ACTIVITY HINGES ON THE INTEGRATION AND SYNERGY BETWEEN

PRECLINICAL AND BASIC RESEARCH

Basic research in oncology investigates cellular and molecular mechanisms underlying the complex nature of tumors, from the transformation of a normal cell into a tumor to the different processes leading to metastatization, their evasion from immune system control and the development of drug resistance.

CLINICAL RESEARCH

The identification of several hallmarks of cancer by basic and translational research has already led to innovative therapies, whose efficacy has to be demonstrated through clinical trials. Patients participate in this process by being available to clinical and radiological controls over time, and is actively involved through assessments and reports on the quality of life during the therapy. In this way it is possible to identify those therapies that will become new standards able to improve patient life expectancy and maintain a persistent control of neoplastic diseases.

TRANSLATIONAL RESEARCH

Translational research in oncology is the research branch aimed at translating the laboratory's scientific discoveries into clinical applications to improve prevention, diagnosis and treatment of tumors and back again, reporting the outcomes of interventions and clinical questions to foster new ideas in preclinical research. This approach involves a close collaboration between clinicians and researchers facilitating the exchange of ideas, for the identification of new approaches for patients' benefit.

EPIDEMIOLOGICAL RESEARCH

Epidemiology investigates all the factors that determine the presence or absence of diseases and disorders, thus providing tools to understand how many people are affected by a disease or disorder, if those numbers are changing, and how the disorder affects our society and our economy. For this, national cancer registries are developed, as well as international cohort studies on the role of diet and prevention interventions. INT carries out research projects related to primary prevention, communicating that lifestyle, diet, and smoking cessation impact cancer risk.

QUALITY OF LIFE RESEARCH

Research in this field is aimed at improving rehabilitative and palliative care, defining personalized plans of psychological assistance to patients and families, and developing more effective approaches to clinical nutrition.

INT AND TECHNOLOGY

INT STANDS OUT FOR LATEST GENERATION EQUIPMENT, BOTH FOR DAILY CLINICAL USE AND RESEARCH PURPOSES. FAVOURED BY AN ADEQUATE HARDWARE AND SOFTWARE INFRASTRUCTURE, DIAGNOSTIC AND THERAPY WORK IN COMPLETE SYNERGY, BOTH IN THE CLINICAL AND RESEARCH FIELDS.

MOLECULAR ANALYSIS PLATFORMS

Experiments for large-scale studies on genomic, transcriptomic and epigenomic alterations of tumors take advantage from NGS platforms (Next Seq, Ion Torrent, IonXL5S), CGH, SNP and CNV analysis (GeneChip) and microarrays platforms for gene, miRNA, lcnRNA expression. NGS technologies are also dedicated to support therapeutic decisions and diagnosis, if deemed appropriate by the clinician, with dedicated CE-IVD certified Ion 5SXL and PGM. The nCounter Nanostring employs a novel digital barcode technology for direct multiplexed measurement of analytes. Research in the liquid biopsies field is favored by the DEP Array platform dedicated to recovery and analysis of rare cell types.

ENDOSCOPY AND SURGERY

The operating rooms at INT are provided with a state-of-the-art integration system to allow data consolidation, access to video, diagnostic images and centralized control for all the devices.
INT is also provided with a new telemetry system that provides real-time patient's information and allows data to be collected remotely. Of note, a videolaparoscopy system for fluorescence imaging and a broad band wide-angle endoscopy system for highly accurate gastroscopy and colonscopy are available.

DIAGNOSTIC IMAGING AND TREATMENT

Radiology at INT is characterized by the high quality of the obtained diagnostic images, balanced by the continuous search for an optimization (reduction) of the dose radiation delivered to the patient. Images are managed by a centralized system, locally accessible by the various professional figures on the basis of their clinical and research needs.

Personalized treatment concept applies to Radiation Oncology thanks to availability of highest technological equipment such as VMAT, integrated CBCT imaging devices, 6D couch, and flattening filter free high dose rate beams and high speed workstation for dose calculation. A modern brachytherapy facility is also available, including a suite fully dedicated to prostate treatments.

Nuclear Medicine meets the highest standards of functional imaging and metabolic therapy. In particular, with regard to therapy, INT is one of the very few centers in Italy treating liver tumours with ^{90}Y microspheres and a dedicated treatment planning system for 3D dose distribution calculation.

PHARMACY

INT is provided with a state-of-the-art facility for centralized and automated chemotherapy preparations, equipped with 2 robots for compounding sterile preparations and with 5 workflow engine system for the assisted preparation and computerized management of patients tailored treatments.

HIGHLIGHTS

- A new CT scanner was installed, that allows a reduction of the delivered dose of radation to the patient for specific clinical protocols. The system is currently used for several scientific studies, as for instance the MILD project for the early diagnosis of lung cancer on a cohort of selected patients.
- In 2018, in order to improve basic and translational research technology, INT planned the acquisition of Biacore T200, MALDI imaging system, IVIS Spectrum Imaging and Rad Source Technology RS2000.

RESEARCH CORE FACILITIES

GRANT OFFICE

The INT Grant Office provides timely advice and information to researchers on funding opportunities; coordinates the participation of the research projects to funding programs; provides information on the internal procedures for submissions of project proposals; supports researchers to the submission and the final financial report and audit processes.

TECHNOLOGY TRANFER OFFICE

The INT Technology Transfer Office (TTO) was created in 2009 to give value to research results in a scientific and economic key and to optimize technology transfer and intellectual property right management. The TTO offers support services for patent activities (from the beginning of a new invention to the filing and maintenance of the correspondent patent), spin off evaluation and dissemination of Intellectual Property culture within researchers.

FUNCTIONAL GENOMICS AND BIOINFORMATICS

The Functional Genomics And Bioinformatics (FGBCF) provides technological support to translational oncology through the development and implementation of advanced experimental methods with dedicated equipment and platforms. Genomics focuses on the genetic information stored in DNA and aim at identifying the different activity of genes in distinct cell populations or in response to different treatments. Bioinformatics develops and applies computational methods for analyzing genetic sequences or gene expression data.

CLINICAL TRIALS CENTER

The Clinical Trials Center supports Clinical Researchers in many aspects of investigational clinical studies, such as study design, statistical analysis/validation, data management, submission to Ethics Committees/regulatory authorities, budget and contract related issues, pharmacovigilance by dedicated personnel including study coordinators, data managers, statisticians, research nurses.

TISSUE AND CELL REPOSITORY

Departments of Pathology and DRAST have implemented and maintain a large bank of frozen and FFPE normal, tumor tissues and blood/plasma/serum samples, collected and stored within a short time from removal following SOPs. Thousands of well-annotated clinical specimens of different tumor histotypes, linked to dedicated databases of patho-biological and clinical information, are currently available. Patients sign an informed consent which allows INT investigators to use the left over material of biological samples collected during standard surgical and medical procedures for research purposes. Aliquots are attributed to individual studies after approval of Internal Review Board and Ethical Committee. All the material is stored in the Institutional BioBank for at least 20 years from the collection, including residual material of specific project studies.

LABORATORY ANIMAL FACILITY

Animal facilities is authorized by the Italian Ministry of Health for housing transgenic and immmunodeficient mice under standard pathogen-free conditions and, when needed, in isolators vented with sterile HEPA-filtered air.

ETHICS COMMITTEE

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

BIOMEDICAL LIBRARY

The INT Library is affiliated to the European Association for Health Information and Libraries. It offers a large collection of basic science journals and reference books, and electronic access to the full text of scientific and clinical journals, databases and books.

INTERNAL REVIEW BOARD

The Internal Review Board (IRB) is a Scientific Directorate committee, established in 2018, supporting the Scientific Director to assess scientific value, design, impact on disease and on Institution as well as adherence to good clinical practice of the new proposals of clinical intervention studies before submission to the Ethic Committee.

SELECTED PAPERS 2018

1

Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): An open-label, single-arm, phase II study

Necchi A, et al. - JOURNAL OF CLINICAL ONCOLOGY

The activity of pembrolizumab as neoadjuvant immunotherapy before radical cystectomy (RC) for muscle-invasive bladder carcinoma (MIBC) for which standard cisplatin-based chemotherapy is poorly used has been determined. Neoadjuvant pembrolizumab resulted in 42% of patients with pT0 and was safely administered in patients with MIBC. This study indicates that pembrolizumab could be a worthwhile neoadjuvant therapy for the treatment of MIBC when limited to patients with PD-L1-positive or high-TMB tumor.

2

Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer

Gandhi L, et al - NEW ENGLAND JOURNAL OF MEDICINE

The KEYNOTE-189 double blind phase 3 trial showed that in patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.

3

Metformin Enhances Cisplatin-Induced Apoptosis and Prevents Resistance to Cisplatin in Co-mutated KRAS/LKB1 NSCLC

Moro M, et ala.JOURNAL OF THORACIC ONCOLOGY

We retrospectively determined the frequency and prognostic value of KRAS/LKB1 co-mutations in tissue specimens from NSCLC patients enrolled in the TAILOR trial. LKB1 mutations, especially when combined with KRAS mutations, may define a specific and more aggressive NSCLC subtype. In preclinical model, metformin synergizes with cisplatin against KRAS/LKB1 co-mutated tumors, and may prevent or delay the onset of resistance to cisplatin by targeting CD133^{+} cancer stem cells. This study lays the foundations for combining metformin with standard platinum-based chemotherapy in the treatment of KRAS/LKB1 co-mutated NSCLC.

4

Modulation of Pulmonary Microbiota by Antibiotic or Probiotic Aerosol Therapy: A Strategy to Promote Immunosurveillance against Lung Metastas

Le Noci V, CELL REPORTS

We identified a role for lung microbiota in metastasis and showed that its targeting via aerosolization is a therapy that can prevent metastases and enhance responses to chemotherapy. In lungs of vancomycin/neomycin-aerosolized mice, a decrease in bacterial load was associated with reduced regulatory T cells and enhanced T cell and NK cell activation that paralleled a significant reduction of melanoma B16 lung metastases. Furthermore, probiotics or antibiotics improved chemotherapy activity against advanced B16 metastases.

5

Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma a multi-institutional case series

Frezza AM, et al - JAMA ONCOLOGY

Epithelioid sarcoma (ES) is an exceedingly rare malignant neoplasm with distinctive pathologic, molecular, and clinical features as well as the potential to respond to new targeted drugs. In the largest retrospective series of systemic therapy in ES, we confirm a moderate activity of anthracycline-based and gemcitabine-based regimens in ES, with a similar response rate and PFS in both groups. The value of pazopanib was low. These data may serve as a benchmark for trials of novel agents in ES.

6

Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma

Mazzaferro V, et al GASTROENTEROLOGY

Outcomes of liver transplantation for hepatocellular carcinoma (HCC) are determined by cancer-related and non-related events. We performed a competing-risk analysis to evaluate factors associated with survival of patients with HCC and developed a prognostic model based on level of AFP, tumor size, and tumor number, to determine risk of death from HCC-related factors after liver transplantation. This model might be used to select end points and refine selection criteria for liver transplantation for patients with HCC. To predict 5-year survival and risk of HCC-related death using an online calculator, please see www.hcc-olt-metroticket.org/.

7

Temozolomide and irinotecan (TEMIRI regimen) as salvage treatment of irinotecan-sensitive advanced colorectal cancer patients bearing MGMT methylation

Morano F, et al - ANNALS OF ONCOLOGY

We combined temozolomide and irinotecan (TEMIRI) in metastatic colorectal cancer patients selected for methylguanine-DNA methyltransferase (MGMT) methylation /microsatellite stability and benefit from previous irinotecan-based therapy. Response rate of 24% provides an option for patients failing standard regimens. Negative MGMT expression by immunohistochemistry refines patients' selection. TEMIRI regimen is a safe and active option in pre-treated, irinotecan-sensitive mCRC patients with MGMT methylation.

8

Tumor-derived microRNAs induce myeloid suppressor cells and predict immunotherapy resistance in melanoma

Huber V, et al JOURNAL OF CLINICAL INVESTIGATION

The accrual of myeloid-derived suppressor cells (MDSCs) represents a major obstacle to effective immunotherapy in cancer patients. A set of 8 microRNAs has been identified associated with MDSCs and resistance to treatment with immune checkpoint inhibitors in melanoma patients has been identified. The miRs were identified by transcriptional analyses as being responsible for the conversion of monocytes into MDSCs (CD14+HLA-DRneg cells) mediated by melanoma extracellular vesicles (EVs) MDSC-related miRs represent an indicator of MDSC activity in cancer patients and a potential blood marker of a poor immunotherapy outcome.

9

Cross-Talk between myeloid-derived suppressor cells and mast cells mediates tumor-specific immunosuppression in prostate cancer

Jachetti E,et al CANCER IMMUNOLOGY RESEARCH

In TRAMP mouse models we have determined that mast cells have an immunoregulatory effect on PMN-MDSCs activity through CD40L-CD40 interaction, favoring immunosuppression and tumor onset. In prostate cancer patients, *in silico* analyses correlated poor clinical outcomes with high expression of genes related to mast cells and PMN-MDSCs.

10

Analysis of the genomic landscape of multiple myeloma highlights novel prognostic markers and disease subgroups

Bolli N, LEUKEMIA

We used NGS to characterize the genomic landscape of 418 multiple myeloma cases at diagnosis and correlate this with prognosis and classification. Next-generation sequencing allows analysis of the integrated spectrum of gene mutations, aneuploidies and IGH translocations in multiple myeloma. Karyotypic events have a stronger impact on prognosis than mutations, and extended genotyping shows novel prognostic categories.

11

cIAP1 regulates the EGFR/Snai2 axis in triple-negative breast cancer cells

Majorini MT, et al CELL DEATH AND DIFFERENTIATION

We investigated the effect of IAP inhibition *in vivo* to identify novel downstream genes expressed in an IAP-dependent manner that could contribute to cancer aggressiveness. In preclinical model of immunocompromised mice engrafted subcutaneously with the triple-negative breast cancer MDA-MB231 cell line treated with SM83, a Smac mimetic that acts as a pan-IAP inhibitor, we have demonstrated that IAP-targeted therapy could contribute to EGFR inhibition and to the reduction of its downstream mediators. This approach could be particularly effective in tumors characterized by high levels of EGFR and Snai2, such as triple-negative breast cancer.

12

Activity and safety of afatinib in a window preoperative EORTC study in patients with squamous cell carcinoma of the head and neck (SCCHN)

Machiels JP, et al ANNALS OF ONCOLOGY

The activity and safety of afatinib in the preoperative treatment of squamous cell carcinoma of the head and neck (SCCHN) has been investigated in open-label, randomized, multicenter, phase II window of opportunity trial. Afatinib given for 2 weeks to newly diagnosed SCCHN patients induces a high rate of FDG-PET partial metabolic response and partial response according to RECISTv1.1. Afatinib can be safely administered before surgery. Although exploratory, the hypoxic gene signature needs further investigations as a predictive biomarker of afatinib activity.

EDUCATION

As a comprehensive cancer centre for excellence, INT is deeply committed to quality education and training. Postdoctoral research fellowships, graduate student training, medical residency training, psychology and social work training, as well as many opportunities for continuing medical education are part of the wide ranging academic options available at INT.

AS A COMPREHENSIVE CANCER CENTRE FOR EXCELLENCE, INT IS DEEPLY COMMITTED TO QUALITY EDUCATION AND TRAINING

To give new impulse to translational research, it is crucial attracting medical doctors working in our Institute, and giving them the opportunity to receive training in cutting-edge research technologies. Our aim is to implement a system that will allow young physicians to gain direct experience in research and help the translation of laboratory discoveries into effective treatments for patients.

Since 1997 and in partnership with The Open University (Milton Keynes, UK), INT has been offering a PhD Programme for young graduates in scientific disciplines. Academic quality of the educational Programme is annually certified. During the course of their studies, PhD students conduct their experimental work under the supervision of experienced researchers, have access to modern laboratories and advanced technologies, and benefit from a dedicated program of seminars. Continuous exchange of data and ideas is promoted through data session and journal clubs involving all PhD students from different laboratories. Moreover, the PhD Committee supports students who want to attend prestigious international conferences with travel grants supplied through a competitive selection. During 2018, 15 students attended INT PhD Programme and 4 received their PhD upon defense of their work in front of an examination panel which includes an international examiner with specific competence in the field.

INT is a formal partner of the Università degli Studi di Milano and hosts several professors of the Departments of Oncology and Hematoncology, including the Chairman, Medical Statistics and Biometry, Anesthesiology, and Pathology, with medical students and students from the medical biotechnology and nursingdegree; postgraduate training for the residencies of oncology, hematology, general surgery, radiotherapy, anesthesiology and intensive care are also provided.

INT IS A FORMAL PARTNER OF THE UNIVERSITÀ DEGLI STUDI DI MILANO

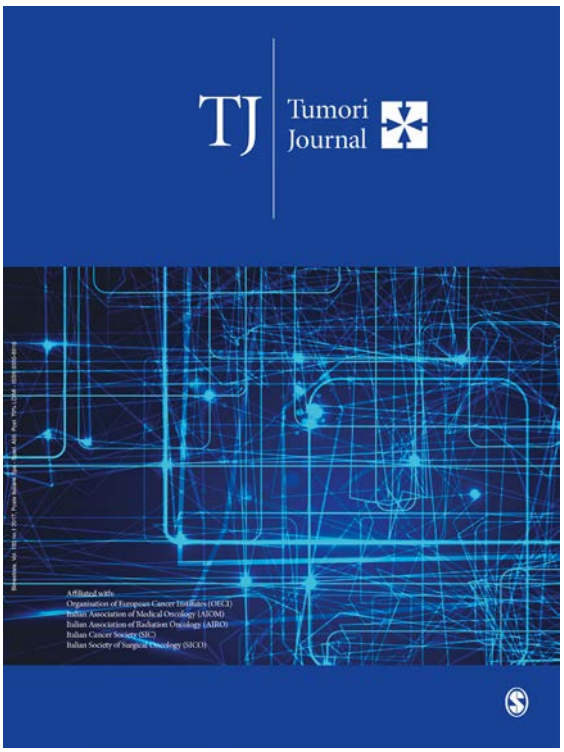
Young people have a natural curiosity towards the scientific rules governing the world.

To favour this attitude and increase their scientific knowledge, INT offers the possibility of brief stages to high school students for visiting laboratories, meeting INT researchers, learning importance of new technologies for advance in oncology research.

INT OFFERS THE POSSIBILITY OF BRIEF STAGES TO HIGH SCHOOL STUDENTS

THE INT JOURNAL

TUMORI JOURNAL,THE INSTITUTIONAL JOURNAL OF FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI, COVERS ALL ASPECTS OF CANCER SCIENCE AND CLINICAL PRACTICE WITH A STRONG FOCUS ON PREVENTION AND TRANSLATIONAL MEDICINE



Tumorijournal.com

Editor in Chief: Ugo Pastorino
ISSN: 0300-8916 - e-ISSN: 2038-2529
Frequency: 6 issues per year
Impact Factor: 1.304

The journal was completely renewed, establishing a new editorial board, creating a new graphic design, restoring the publisher, and replacing the old title in Tumori Journal (TJ).

- International reviewers panel: 63% from Europe, 27% from USA/Canada, 10% from ROW
- 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

Affililiations

Organisation of European Cancer Institutes (O E C I); Italian Association of Medical Oncology (AIOM); Italian Association of Radiation Oncology (AIRO); Italian Cancer Society (SIC); Italian Society of Surgical Oncology (SICO)

SCIENTIFIC REPORT 2018

EXECUTIVE SUMMARY

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Via G. Venezian, 1 - 20133 Milan - Italy
Scientific Directorate
Tel. +39 02 2390 2300
Fax +39 02 2390 3141
direzionescientifica@istitutotumori.mi.it

For more details see web site
www.istitutotumori.mi.it