

SCIENTIFIC REPORT

2020
EXECUTIVE SUMMARY



INT

THE NATIONAL CANCER INSTITUTE (FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI, REFERRED TO AS INT IN THIS REPORT), FOUNDED IN 1928, IS THE FIRST AMONG THE ITALIAN ONCOLOGICAL IRCCS₅ ACCORDING TO THE EVALUATION CRITERIA OF THE ITALIAN MINISTRY OF HEALTH. IT IS A NATIONAL AND INTERNATIONAL REFERENCE CENTER FOR THE MOST FREQUENT AND MOST COMMON CANCERS, BUT ALSO FOR RARE AND PEDIATRIC CANCERS. WITH **650 PEOPLE** DEDICATED TO RESEARCH (**463 RESEARCHERS**), **27 LABORATORIES** AND A SECTIONAL RESEARCH BUDGET OF APPROXIMATELY 45 MILLION EUROS, IT IS A CENTER OF EXCELLENCE FOR PRECLINICAL, TRANSLATIONAL AND CLINICAL, EPIDEMIOLOGICAL AND HEALTH RESEARCH. INT MANAGES MORE THAN **17.000 ADMISSIONS** PER YEAR, ABOUT **1.100.000 CONSULTATIONS**, **482 BEDS** AND **20 INSTANCES** OF MAC (COMPLEX OUTPATIENT MACRO-ACTIVITY).

ISTITUTO NAZIONALE DEI TUMORI



AMADEO LAB



CAMPUS CASCINA ROSA



AROUND
2000
PERSONNEL
WORKING AT INT
OF WHICH
650
DEVOTED
TO RESEARCH



27
RESEARCH LABS
3600_{SQM}
SURFACE

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INTRODUCTION

This report provides an overview of the available research output for 2020. It is worth mentioning that the emergency of the COVID-19 pandemic, ongoing for almost all of 2020, has had a substantial impact on Lombardy's Regional Health System and has affected INT's healthcare capacity and research priorities during 2020 and part of 2021. In tackling the emergency, INT has been designated by the Lombardy Region as one of its two reference hubs for cancer patients and, in collaboration with other members of Cancer Core Europe, INT was involved in the preparation of a European consensus document describing the key actions for the care and management of cancer patients in the new COVID era - not only in terms of containment and prevention of viruses but also new organizations of cancer hospitals and health management. Finally, INT has been designated as a vaccination center for workers, patients and the frail population.

The Scientific Directorate has promoted and supported several activities to get more insights on the impact of COVID-19 on cancer. Among them, the activation of spontaneous observational prospective or retrospective clinical studies (some of which funded by the Scientific Directorate) and the promotion of the internal "Cancer and Covid" call for clinical research or outcome research projects. To facilitate these objectives, accreditation for access to the Lombardy Region's database of COVID-19 patients was obtained, of high importance for health outcome studies. 105 COVID-related publications appeared in national and international journals.

Nevertheless, INT's four research priorities - Primary Prevention, Secondary Prevention and Early Diagnosis; Precision Medicine and Technological Innovation; Complexity and Rare Tumors; Effectiveness Studies and Outcome Research - still provided strong guidance in the planning of current and future initiatives. These priorities emphasize the focus on translational research, where research activities and healthcare are linked through multidisciplinary programs designed and coordinated by scientific teams with different clinical and scientific backgrounds. In this context, the Scientific Directorate's three-years initiative, started in 2019, aimed at funding projects strictly related to topics of the four institutional research lines has become operational: in 2020, 10 additional projects were financed following an evaluation by the Scientific Director and the research line coordinators.

The scientific output in 2020 has seen an upward trend. 960 papers have been published with a total impact factor of 7.338,49, compared to 794 in 2019. The active 450 clinical trials, besides offering the best possible treatment, also give access to innovative drugs and other health technologies to patients. Although research activity's indicators have apparently not been affected by the COVID lockdowns so far, we cannot exclude a possible delayed effect on scientific productivity in the near future. On healthcare indicators, on the contrary, a strong impact has been observed, in particular a strong reduction of inpatients and consultations especially when considering patients outside the Region.

INT has conducted actions aimed at the analysis and the construction of a new model for the career paths of researchers, which is considered a strategic priority. A first step in this direction was the initial application of the Law 205/2017 and of the regulation updating the National Collective Labour Agreement (CCNL) for health personnel (the so-called "Pyramid"). This new infrastructure led to the recruitment of 161 researchers and research support personnel on fixed-term employment contracts for a five-year duration, who were then included in their corresponding positions on the pre-existent salary scales for their profiles. The second step will be represented by the definition of individual performance-related financial rewards and the novel round of recruitment of research figures in the 2021 iteration of this legislative framework.

INTRODUCTION

In these last years, INT increased its standing and authority at an international level by investing in a network of close relationships with the main European cancer centers through the participation to consortia such as Cancer Core Europe (CCE) and the Organization of the European Cancer Institutes (OECI). At a national level it has intensified its engagement within the Italian networks of excellence such as Alliance Against Cancer (ACC), the Rare Cancer Network and the Lombardy Hematology Network.

Future strategic actions will be increasingly directed towards “*taking the lead*” in these networks in the national and European setting. A particular effort will be directed toward an ever-greater coherence between the institute’s strategic choices, activities, operational proposals, funding and the scenario outlined at a national level by the Pact for Health 2019 and by the National Program for Health Research 2020-2022 (PNRS), the National Oncological Plan (PON), as well as the objectives set in the European context of the Cancer mission and the new Horizon Europe framework program.



MARCO VOTTA
President



GIOVANNI APOLONE
Scientific Director

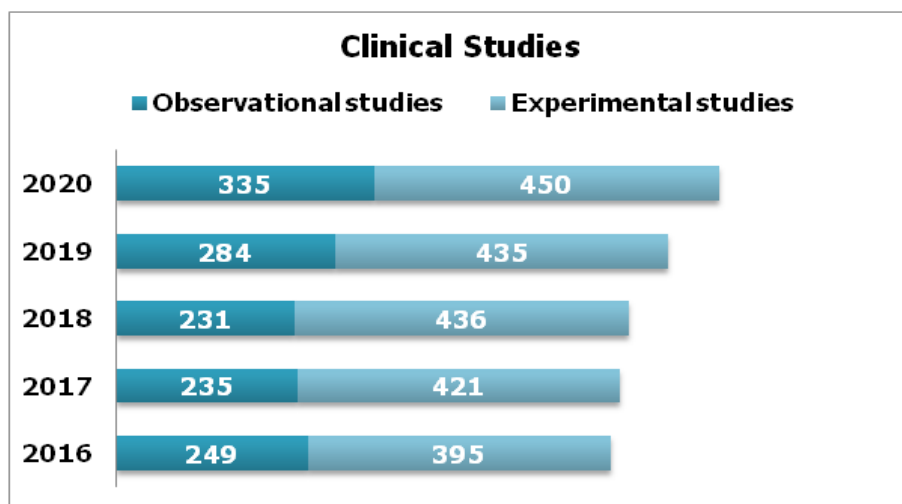


STEFANO MANFREDI
General Director

THE ESSENTIAL ABOUT INT 2020

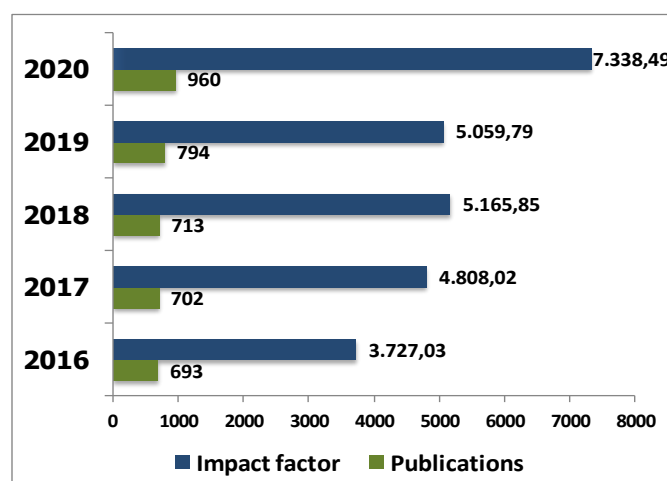
CLINICAL RESEARCH DATA

335	Observational studies
450	Experimental studies
785	Clinical studies (Total)
36.955	Patients enrolled in observational studies
1.905	Patients enrolled in experimental studies
37.205	Patients enrolled in registries
76.065	Patients included in clinical studies (Total)



SCIENTIFIC ACTIVITY

Publications	960
Impact factor	7.338,49
Publications as first/last author	394 (41%)



RESEARCH FUNDING

7.935.945 € Ministry of Health (Ricerca Corrente)

10.326.126 € Funding agencies

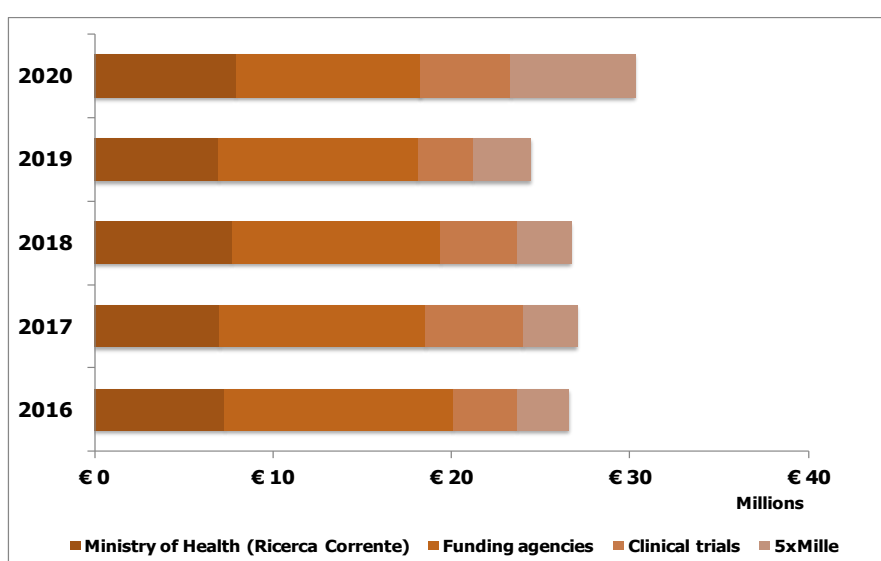
5.079.002 € Clinical trials

6.983.236 € 5xMille*

30.324.310 € Total

* Funds
obtained
by Italian

Ministry of Health and Italian Ministry of University and Research (MUR) through the allocation of 0.5 percent contribution of taxpayers' income tax devolved to research institution of choice



PATENT PORTFOLIO

12 Total Patents

4 INT Owner

8 INT Co-owner

EDUCATION

97 Events/training courses

6.273 Participants

35.349 Formative hours

HEALTHCARE DATA

482 Beds

14.712 Total inpatients

2.557 Of which
Day Hospital

1.136.637 Consultation

FOCUS ON MAJOR EVENTS



MINISTRY OF HEALTH SITE VISIT FOR IRCCS ACCREDITATION RENEWAL

On January 23rd, INT received the Ministry of Health's site visit for the periodical evaluation aimed at its accreditation as an IRCCS and the allocation of funding for the coming years. Formal accreditation of INT as one of the Italian scientific excellences in the oncology field has been obtained on July 15th.



INSTITUTIONAL RETREAT

On February 14th and 15th the Scientific Directorate organized the annual edition of the Institutional Retreat, held in Cascina Erbatici, Mezzana Bigli (PV). The event, named “Research and Healthcare: toward a Strategic Organizational Plan”, was aimed at outlining the intervention strategies detailed in the Strategic Research Plan, integrating them with

the institutional research lines and priorities. Several invited speakers described the national and European contexts, as well as the available and upcoming platforms and networks in order to better exploit cooperation opportunities.



An update on the results of projects funded by “5xmille funds” related to institutional research lines was also presented.

MOLECULAR TUMOR BOARD

In May, the first institutional MTB was established at INT. Its aim is harmonizing the methods of access to molecular analyses and helping oncologists in the choice of appropriate therapies which take into account the clinical context and tumor biology. The MTB deals with the identification of patients eligible for molecular testing and of the most suitable and cost-effective method and panel of genes, the interpretation of data from molecular analysis in order to define the biological meaning and therapeutic actionability of the genetic abnormalities for the identification of potentially active drugs, and the integration of clinical-genomic data to define the optimal treatment for the patient

MISSION CANCER

In collaboration with APRE, INT hosted the first edition of the event “Mission Cancer”. The event’s core topic was the role and the opportunities for Italy in European actions to conquer cancer, focusing on awareness and system building. The event, planned in February, has been postponed and held on September 10th in an online format.



YOUNG RESEARCHER AWARD

The Scientific Directorate launched the annual ‘Young Researcher Award’ initiative in order to support the commitment in clinical-epidemiological, basic and translational research of INT’s young researchers for their research activities in 2019- 2020. Federica Morano, Rihan El Bezawy and Giovanni Fucà have been awarded for the excellence of their research activities in the clinical, preclinical and translational fields respectively.

CANCER CORE EUROPE



On November 3rd, INT hosted Cancer Core Europe’s Annual Meeting. The event was held in a virtual modality due to pandemic restrictions. It was moderated by the Scientific Director and attended by 130 participants representing the 7 partner centers.

INSTITUTIONAL RESEARCH PRIORITIES



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 targets 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.

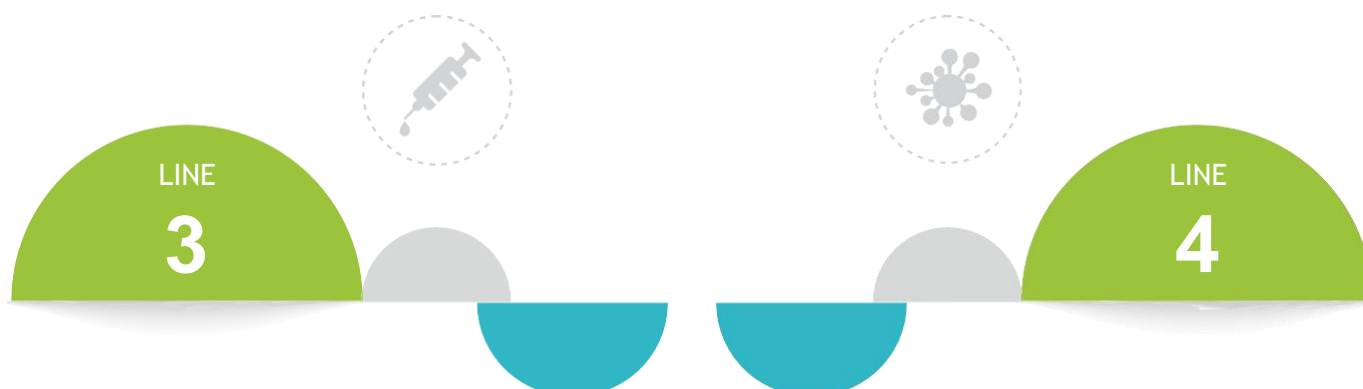
Thanks to new technologies that generate and interpret “omics” data, it is possible to identify molecular alterations common to various tumor types - this allows optimized prevention interventions and a more rational use of therapies, in particular to prevent toxicity.

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 the optimization of the therapeutic 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 its associated complexities. 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 is carried out by intense **networking activity**, necessary for conducting both research and treatment of rare diseases. The institute benefits from its central role as a reference center worldwide for some rare diseases.

The Institute is indeed coordinator of the Rare Tumors Network, of important epidemiological projects and of the recently closed European 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 the **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 institute's organization, and 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 is directed at 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).

FOCUS ON COVID-RELATED ACTIVITIES



INSTITUTIONAL CALL FOR CLINICAL AND OUTCOME RESEARCH PROJECTS ON CANCER & COVID-19

In May 2020, the Scientific Directorate promoted a specific call within the research line 4, the “Cancer & COVID-19” call aimed at funding projects on clinical health research based on real-world data. The focus of the call was to study the reciprocal effects between cancer and COVID-19, whether and how the two conditions mutually modify their clinical pictures, drug responses, prognosis, immune response and outcome. Findings will be integrated with the administrative flows of the Lombardy Region. Following a peer review process, five projects were selected and funded for a total of 320.000€.

RESEARCH ACTIVITY IN THE COVID PERIOD: PUBLICATIONS

105 scientific papers were submitted to national and international journals providing measures and real-time strategies adopted by hospitals, in particular cancer centers, to provide guidance to other institutions and contribute to the development of a pandemic-proof organization.

RESEARCH ACTIVITY IN THE COVID PERIOD: GRANTS, CLINICAL STUDIES

From the beginning of the COVID-19 pandemic, INT has implemented a series of strategic interventions in a health emergency regime to support and guarantee healthcare management, as well as to protect patients and monitor the possible spread of SARS-CoV-2 among healthcare personnel.

The Scientific Directorate actively contributed to such actions by funding research projects aimed at studying and monitoring the impact of COVID-19 on healthcare personnel and patients. INT participated to several working groups and task forces, at both an institutional and a regional level, aimed at optimizing the interventions and the allocation of resources of the healthcare system. During the COVID-19 emergency, a total of 35 clinical studies (prospective observational or retrospective non-drug studies) were launched. Among them, the Scientific Directorate promoted, in April 2020, a prospective longitudinal study (INT 65/20) aimed at screening healthcare personnel without overt symptoms via nasopharyngeal swabs. IgM/IgG levels were monitored every 40-45 days by SARS-CoV-2-specific serology to assess the persistence of humoral immunity and record the occurrence of COVID-19 symptoms by questionnaire. Following the vaccination, the Scientific Directorate emended the study to verify the effectiveness of the immunization and to monitor its persistence over time.



RESEARCH ACTIVITY IN THE COVID PERIOD: GRANTS, CLINICAL STUDIES AND PUBLICATIONS

Since July 2021, a total of 9 clinical studies (prospective observational or retrospective non-drug studies) were launched and 62 scientific papers were submitted to national and international journals. In March 2021, the Scientific Directorate promoted - within the INT 65/20 study - a new prospective longitudinal study, offered to all INT staff (enrolling ~1600 people), aimed at quantifying the specific antibody titer induced by vaccination one month after the second vaccine administration, followed by a second quantification 6 months later. In parallel, several studies were implemented to evaluate the effectiveness of the immunization in patients with oncological malignancies.

VAX4FRAIL is a national multicentric observational prospective study, involving several IRCCSs, aimed at assessing the immune response of COVID-19 vaccination in terms of induction of humoral and cell-mediated immune responses in selected fragile (i.e. altered immunocompetence) patients with solid and hematological neoplasms, neurodegenerative and rheumatic-autoimmune diseases who have been vaccinated since March 2021.

The **COVAXIMM** INT-promoted study aims at building up a registry of patients diagnosed with solid cancers eligible to receive anti SARS-CoV-2/COVID-19 vaccine at INT. It also plans to evaluate the efficacy in terms of immune response of COVID-19 vaccination in patients with solid malignancies. This observational study is conducted on two patient cohorts, both eligible to receive anti SARS-CoV-2/COVID-19 vaccine according to national guidelines and international recommendations; healthcare workers at INT will serve as control group to compare the immunogenicity/reactogenicity and safety of vaccination in a cancer-free population.

RESEARCH CORE FACILITIES

<https://www.istitutotumori.mi.it/web/guest/research-core-facilities>



PLATFORM OF INTEGRATED BIOLOGY (PIB)

It is a multi-disciplinary group that includes biologists, bioinformaticians and laboratory technicians that supports researchers through all the experimental and analytical steps of genomics, transcriptomics, epigenomics and metagenomics studies, including study design, sample processing, quality controls, data generation, analysis and integration. PIB activities are conducted using the following state-of-the-art equipment: 4200 Tapestation (Agilent), Nanodrop and Qubit (Thermo Fisher) for quantity and quality control of nucleic acids; JANUS (Perkin Elmer) and STARlet (Hamilton) automated workstations for liquid handling; iScan (Illumina), SureScan Microarray Scanner (Agilent) and Gene Chip System 3000 (Affymetrix, Thermo Fisher) platforms for microarray analysis including mRNA, miRNA and lncRNA expression, DNA methylation, CGH and CNV, SNP genotyping; QuantStudio 12K Flex Real- Time PCR System with OpenArray (Thermo Fisher); Ion Chef Instrument, Ion PGM and Ion S5XL (Thermo Fisher).

IMMUNOHISTOCHEMISTRY: performs histological and cytological processing through a wide range of histological techniques, immunohistochemistry, in situ hybridization, and autoradiography.

CELL IMAGING FACILITY: provides access to the BioRad Radiance 2000 and Leica SP8 AFC AOBS WLL HyD laser confocal microscopes allowing for a wide range of fluorescent dye use, sequential and simultaneous up to 8 channel bright field image collection, and live cell imaging.

FLOW CYTOMETRY AND CELL SORTING: provides support and advanced instrumentation to the researcher to analyze and sort the different types of cells constituting the tumor and the tumor-associated microenvironment according to their specific molecular phenotype. The facility is currently equipped with BD FACSAria™ Ilu cell sorter and two BD FACSCelesta™ flow cytometers.



LABORATORY ANIMAL FACILITY

It is authorized by the Italian Ministry of Health for housing transgenic and immunodeficient mice under specific pathogen-free conditions (SPF) and it is composed by 9 independent rooms that host the mice (360 Individually Ventilated Cages (IVC) per room) and 4 fully equipped laboratories. Animal health care is provided by the Animal Welfare Manager and by a Veterinarian specialized in laboratory animals.



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 validated SOPs. All clinical samples are collected following the informed consent of the patients and are linked to dedicated databases of pathological and clinical information. Aliquots are attributed to individual studies after approval by the Internal Review Board and the Ethical Committee.



CLINICAL TRIALS CENTER

The CTC supports Clinical Researchers in many aspects of investigational clinical studies, such as feasibility analysis of the study, submission to Ethics Committees/ regulatory authorities, budget definition, coordination of the clinical trial in all its phases (from activation to conclusion).

The organization of the CTC and the presence of dedicated and trained staff (clinical study coordinators and research nurses) allows to guarantee the conduct of the clinical trials in compliance with the good clinical practice (GCP).



INTERNAL REVIEW BOARD

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



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.



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; assists researchers in the submission process, and supports final financial reports and audit processes.



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.



TECHNOLOGY TRANSFER OFFICE

INT's 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.

SELECTED 2020 PAPERS

SCIENTIFIC REPORT 2020

1

Pazopanib for treatment of typical solitary fibrous tumours: a multicentre, single-arm, phase 2 trial

Martin-Broto J, et al LANCET ONCOLOGY

Solitary fibrous tumor is an ultra-rare sarcoma, which comprises different clinicopathological subgroups. In this single-arm, phase 2 trial, we investigated the efficacy and safety of pazopanib in adult patients with metastatic or unresectable progressive typical solitary fibrous tumour of any location. The manageable toxicity and activity shown by pazopanib in this cohort suggest that this drug could be considered as first-line treatment.

2

Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

Mazzaferro V, et al LANCET ONCOLOGY

In this open-label, multicentre, randomized, controlled trial we showed that liver transplantation after hepatocellular carcinoma downstaged with locoregional, surgical, or systemic therapies improved tumor event-free survival and overall survival compared with non-transplantation therapies.

3

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study

Gounder M, et al LANCET ONCOLOGY

Epithelioid sarcoma is a rare and aggressive soft-tissue sarcoma subtype. Over 90% of tumors have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2. In this open-label phase 2 trial, patients with epithelioid sarcoma characterized by loss of INI1/SMARCB1 were treated with Tazemetostat, an oral selective EZH2 inhibitor, which demonstrated clinical activity and favorable tolerability.

4

Factors Affecting Sentinel Node Metastasis in Thin (T1) Cutaneous Melanomas: Development and External Validation of a Predictive Nomogram

Maurichi A, et al JOURNAL OF CLINICAL ONCOLOGY

We investigated the determinants of sentinel node (SN) status for incorporation into an externally validated nomogram to better select patients with T1 disease for SNB. The six identified variables predictors of SN status (age, Breslow thickness, mitotic rate, ulceration, lymphovascular invasion and regression) were used to construct the nomogram. Our decision curve analyses showed that the nomogram was able to reduce the number of unnecessary SNBs.

5

Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups

Gronchi A, et al JOURNAL OF CLINICAL ONCOLOGY

In this randomized, open-label, phase III trial we showed that histology-tailored neoadjuvant chemotherapy was not associated with a better disease-free survival and overall survival compared to anthracycline plus ifosfamide chemotherapy in patients with high-risk soft tissue sarcoma of extremity or trunk wall.

6

Differential Benefit of Adjuvant Docetaxel-Based Chemotherapy in Patients With Early Breast Cancer According to Baseline Body Mass Index

Desmedt C, et al JOURNAL OF CLINICAL ONCOLOGY

We investigate whether the efficacy of docetaxel-based chemotherapy differs from non-docetaxel-based chemotherapy in patients with breast cancer according to their baseline body mass index (BMI). Our results highlight a differential response to docetaxel according to BMI, which calls for a body composition-based re-evaluation of the risk-benefit ratio of the use of taxanes in breast cancer.

7

Transcriptional profiles and stromal changes reveal bone marrow adaptation to early breast cancer in association with deregulated circulating microRNAs

Chiodoni C, et al *CANCER RESEARCH*

We provided evidence of significant changes occurring in the bone marrow of a spontaneous model of mammary carcinogenesis as early as preinvasive disease stages. Bone marrow alterations include a transcriptional rewiring toward innate/inflammatory response programs of the hematopoietic compartment, associated with changes in specific immune cell subsets and modifications in the stromal architecture. These early events are concomitant with deregulation of circulating miRNAs that could serve as early diagnostic markers.

8

Infiltrating Mast Cell-Mediated Stimulation of Estrogen Receptor Activity in Breast Cancer Cells Promotes the Luminal Phenotype

Majorini MT, et al *CANCER RESEARCH*

We demonstrated that mast cells (MCs) directly affect the phenotype of breast cancer cells through stimulation of the estrogen receptor pathway and ultimately modifying the outcome of the disease. MCs promote tumor growth and metastasis in MMTV-PyMT mice and when co-cultured with breast cancer cells prevent the activation of HER2 and of basal drivers such as EGFR and cMET, and simultaneously promote expression and activity of the estrogen receptor. A direct correlation between MC density and expression of the estrogen receptor is also found in patients with breast cancer.

9

COPZ1 depletion in thyroid tumor cells triggers type I IFN response and immunogenic cell death

Di Marco T, et al *CANCER LETTERS*

We demonstrated that depletion of COPZ1, a non-oncogene addiction for thyroid cancer, prompts an anti-tumor immune response. Its silencing in thyroid tumor cell lines activates type I IFN pathway and viral mimicry responses, induces immunogenic cell death that in turn stimulates dendritic cell maturation and T cell activation. COPZ1 may represent a promising therapeutic approach for advanced thyroid cancer.

10

The molecular and gene/miRNA expression profiles of radioiodine resistant papillary thyroid cancer

Colombo C, et al *JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH*

We described different molecular profiles in radioiodine-avid and radioiodine-refractory metastatic papillary thyroid cancers. BRAFV600E tumors displayed intrinsic radioiodine refractoriness, while tumors with fusion oncogenes were more frequently able to uptake radioiodine, but without therapeutic efficacy. Gene/miRNA expression profile did not stratify refractory tumors according to tissue type or radioiodine uptake but only to the driver genetic alteration and BRAF-/RAS-like subtype suggesting different oncogene-driven mechanisms leading to radioiodine refractoriness.

11

The curious phenomenon of dual-positive circulating cells: Longtime overlooked tumor cells

Reduzzi C, et al *SEMINARS IN CANCER BIOLOGY*

We identified dual positive (DP) cells, expressing both epithelial and leukocyte markers, in the blood of patients with several solid tumor types and we defined their malignant genotype by single cell copy number analysis. Thus, we classified them as DP-circulating tumor cells (CTC), a new subpopulation of CTCs that offers, for the first time, evidence connecting the hybrid theory and the process of metastatization.

12

A Mediterranean Dietary Intervention in Female Carriers of BRCA Mutations: Results from an Italian Prospective Randomized Controlled Trial

Bruno E, et al *CANCERS*

In this multicenter prospective two-armed randomized controlled trial we showed that six-month Mediterranean dietary intervention with moderate protein restriction in women with deleterious mutations in the BRCA1/2 genes significantly lowered serum levels of IGF-I, and other metabolic modulators of BRCA penetrance (weight, waist circumference, hip circumference, total cholesterol and triglycerides) with respect to the control group.

INT AND TECHNOLOGY

INT HAS IMPLEMENTED ITS EQUIPMENT WITH CUTTING-EDGE TECHNOLOGIES TO FACE NEW RESEARCH CHALLENGES AND CLINICAL NEEDS



MACS QUANT TYTO CELL SORTER (MILTENYI BIOTEC)

It is the latest generation of benchtop cell sorter with the unique feature to perform high-speed, multiparameter flow sorting in a safe, fully enclosed cartridge that prevents aerosol and droplet formation, providing a safe environment for operator and eliminating risk of sample contamination. The Tyto cell sorter can be exploited to integrate preclinical, clinical and translational research and opens new possibilities in basic research and medical applications.



GeoMX DIGITAL SPATIAL PROFILER (DSP) (NANOSTRING TECHNOLOGIES)

It combines spatial and molecular profiling technologies by generating whole transcriptomes and profiling data of several hundred proteins in a single analysis, directly on FFPE or fresh frozen tissue slide. Based on detection and quantification by nCounter Analysis System of antibodies against proteins and RNA probes associated with oligonucleotide tags, the readout expression levels can be associated to specific tissue compartments or cell types providing an accurate comparison of protein/RNA expression between different areas for in-depth characterization of tumor heterogeneity and its microenvironment.



MALDI TOF/TOF ULTRAFLEX TREME MASS SPECTROMETER

Complete with a workstation, flexControl software for managing the spectrometer and flexAnalysis for processing the acquired spectral data (Bruker). It enables 'omic' profiling and marker identification directly from FFPE or fresh frozen sections. This platform, shared between INT, Policlinico and Besta, provides unprecedented analytical and matrix flexibility in workflows from protein tissue imaging, intact proteins analysis, glycoproteomics, biologics or oligo QC, polymer analysis. It allows for mass resolution over a very wide range, providing a great mass resolving power and accuracy for proteins identification. The dynamic range and extreme flexibility of this tool allow for a wide variety of complementary research, biopharmaceutical, proteomics and applied applications.



DEPArray NxT (MENARINI-SILICON BIOSYSTEM)

The latest evolution of DEPArray technology, to isolate live or fixed circulating tumor cells (CTC) from blood of oncologic patients or very rare cells from heterogeneous samples. This benchtop automated platform is designed to select cells, based on 5-different fluorescence channels and morphology and to rapidly recover them by moving single cells through a dielectrophoretic field. The recovered cells can be exploited for a wide range of downstream applications, including mutational profiling and single-cell transcriptome analysis to dissect tumor cell complexity at the single cell level.

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.

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. Pandemic regulations prevented the attribution of travel and conference grants in 2020. 18 students were enrolled in the PhD Programme, 8 successfully applied while 5 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 Hemato-oncology, including the Chairman, Medical Statistics and Biometry, Anesthesiology, and Pathology, with medical students and students from the medical biotechnology and nursing degree; postgraduate training for the residencies of oncology, hematology, general surgery, radiotherapy, anesthesiology and intensive care are also provided.

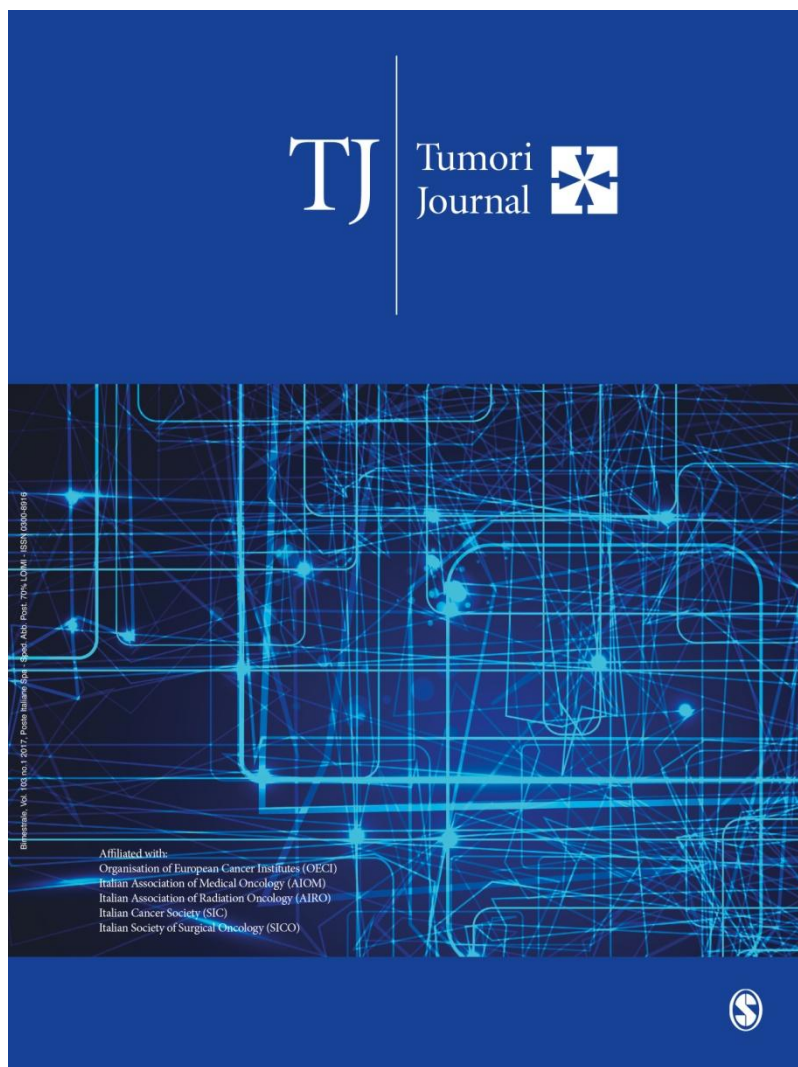
Young people have a natural curiosity towards the scientific rules governing the world.

To favor this attitude and increase their scientific knowledge, INT offers the possibility of brief stages to high school students to visit laboratories, meet INT researchers, and learn of the importance of new technologies for advancement in oncology research.

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

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

INT OFFERS
THE POSSIBILITY OF BRIEF
STAGES TO HIGH SCHOOL
STUDENTS



TUMORI JOURNAL IS THE INSTITUTIONAL EDITORIAL AND COVERS ALL ASPECTS OF CANCER SCIENCE AND CLINICAL PRACTICE WITH A STRONG FOCUS ON PREVENTION AND TRANSLATIONAL MEDICINE

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

Affiliations

Organisation of European Cancer Institutes (OECI); Italian Association of Medical Oncology (AIOM); Italian Association of Radiation Oncology (AIRO); Italian Cancer Society (SIC); Italian Society of Surgical Oncology (SICO); Italian Paediatric Hematology Oncology Association (AIEOP).



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