FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

2022

SCIENTIFIC REPORT

Sistema Socio Sanitario

Fondazione IRCCS
Istituto Nazionale dei Tumori

Regione Lombardia

CONTENTS

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI, REFERRED TO AS INT IN THIS REPORT, FOUNDED IN 1928, IS THE FIRST-RANKED CANCER-FOCUSED IRCCS IN ITALY, CERTIFIED AS SUCH BY ANNUAL EVALUATION CRITERIA OF THE ITALIAN MINISTRY OF HEALTH. INT OBTAINED THE EUROPEAN CERTIFICATE AND ACCREDITATION AS "COMPREHENSIVE CANCER CENTER" IN ACCORDANCE WITH OECI QUALITY STANDARDS IN 2015, DESIGNATION AND CERTIFICATION RENEWED IN 2021.

INT IS BOTH A NATIONAL AND INTERNATIONAL REFERRAL CENTER IN THE FIELD OF COMMON AND RARE MALIGNANCIES IN ADULTS AND CHILDREN, AND REPRESENTS AN EXCELLENCE IN EPIDEMIOLOGICAL, PRECLINICAL, CLINICAL AND TRANSLATIONAL RESEARCH, RELYING ON A LARGE NUMBER OF RESEARCHERS, LABORATORIES AND FACILITIES.

*RESEARCH STAFF INCLUDES **700** PROFESSIONAL FIGURES OUT OF THE TOTAL OF AROUND **2000** EMPLOYEES, AND BENEFITS FROM **3.600** SQ. METERS DEDICATED TO RESEARCH, HOSTING **27** LABORATORIES. INT CAN COUNT ON THE AVAILABILITY OF A RESEARCH BUDGET OF **60 MILLION** EUROS.*

*FRAMEWORK AGREEMENTS WITH ACADEMIC INSTITUTES, THE UNIVERSITY OF MILAN IN PARTICULAR, PROVIDES SUPPORT FOR **10** PROFESSORS AND **5** RESEARCHERS AS INT STAFF MEMBERS.*

*ON THE CLINICAL SIDE, INT MANAGES ABOUT **17.000** INPATIENTS PER YEAR, PROVIDES OVER **12.000** DIAGNOSTIC SECOND OPINIONS, AND IS EQUIPPED WITH **482** HOSPITAL BEDS AND **20** INSTANCES OF COMPLEX OUTPATIENT MACRO-ACTIVITIES (MAC).*

27

research labs

~700

personnel devoted to research

AMADEOLAB
Via G.A. Amadeo 42

3600

SQM surface

CAMPUS CASCINA ROSA
Via A. Vanzetti 5

ISTITUTO NAZIONALE DEI TUMORI
Via G. Venezian 1

~2000

personnel working at INT

INTRODUCTION

This report provides a comprehensive overview of the Institute's research output for 2022.
The latter has confirmed the positive trend started in recent years: 853 papers have been published with a total impact factor of 8.775,322, 469 experimental studies were active and ongoing, (425 of which are pharmacological clinical trials), offering the best possible treatment while also giving access to innovative drugs and other health technologies to patients.

The year has been characterized by the entry into effect of the Institute's Strategic Research Plan for the 2022-2024 period, which identifies the research priorities and the lines of action foreseen for their realization in a 3-year development perspective, including financial aspects such as the Institutional Research Fund. The plan is in line and goes hand in hand with the new 3-year programming of the IRCCSs, approved by the Ministry of Health, in which research activities are described in 4 research lines, representing the planning tool governing the development of both old and new projects.
These priorities focus on translational research, linking research activities and healthcare through multidisciplinary programs designed and coordinated by scientific teams that see the collaboration between researchers from varios clinical and scientific backgrounds. In this context, an initiative from the Scientific Directorate started in 2019, aimed at funding projects strictly related to topics of the 4 institutional research lines is fully operational: at the end 2022 a total of 41 projects were financed following evaluation by the Scientific Director and the research line coordinators.

As a key step in 2022, Resolution 2022/028F of the Board of Directors adopted and implemented the Institutional Strategic and Operational Program (POAS), which represents the programming tool defining INT's mission and vision, as well as its organizational structure, designed in accordance to Lombardy Region regulations. Of note, the changes envisaged in the Strategic Research Plan 2022-2024 are fully consistent with the organizational and managerial changes in the research area, in order to optimize human resources and scientific skills, in a management structure that supports homogeneous research areas.

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) and DIGICORE.

In accordance to the vision of strengthening and consolidating the institutional presence on the European scene, the participation of researchers in numerous calls published under the new Horizon Europe framework programs EU4Health and Cancer Mission was promoted and encouraged throughout 2022. This strategy successfully resulted in 5 funded projects as coordinator and in the participation as a partner in 23 projects., for a total of 28 as of 2022.

The Scientific Director was elected President of OECI and has been appointed by the Italian Ministry of University and Research as the national representative within the "Cancer" subgroup in the Mission Board and in the EU Commission's Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (SGPP), specifically its subgroup on cancer.
Interestingly, starting from 2023, the Scientific Director will be supported by the External Scientific Advisory Board (SAB), envisaged in the new Statute and established in accordance with the criteria promoted by the OECI as part of its framework for the accreditation of European Comprehensive Cancer Centers.

PRESIDENT

Marco Votta

GENERAL DIRECTOR

Carlo Nicora

SCIENTIFIC DIRECTOR

Giovanni Apolone

INT IN THE IRCCS FRAMEWORK

A significant part of the Italian research and care system is structured around the network of 54 IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico). These IRCCS, both public and private institutions, are specialized centres that have a dual focus and commitment to treatment and clinical care on one hand and research on the other, structurally integrating basic and clinical research in a translational approach. Of these, 13 are dedicated to oncological care and research.

The excellence of each centre, and its capability to adhere to its objectives, is assessed through an annual evaluation of the IRCCS's activity, both in terms of clinical care and research output. The process of accreditation as an IRCCS and the confirmation of this status of a comprehensive healthcare centre is the purvey of the Ministry of Health.
The result of this assessment directly impacts the direct funding received from the Ministry on a yearly basis, and the criteria are measured from both a quantitative and qualitative standpoint.

These criteria are:
1) scientific productivity - evaluated on the basis of the publications presented during the year by the institute's affiliated staff in peer-reviewed journals and on the basis of a normalized Impact Factor and with particular attention to publications presenting raw data;
(2) clinical care activity – outpatient visits, new diagnoses, patients treated during the year;
(3) presence and active participation in national and international networks of excellence;
(4) capacity to attract resources, in other words the funding received from competitive grants and other sources that are not directly linked to the Ministry and
5) capacity to generate patented results and the impact and value of its intellectual property portfolio.

In the last years, INT has consistently ranked first among the oncology-specific IRCCS in the Ministry's evaluation and is second only to large general hospitals in the overall ranking of the Italian IRCCS, testimony of the excellence of its clinical care infrastructure, as well as the cutting-edge and highly impactful basic, clinical and translational research carried out by its staff.

CITTÀ DELLA SALUTE E DELLA RICERCA

The new project of "Città della Salute e della Ricerca" in Sesto San Giovanni was born from the ambitious idea of bringing together in a single large complex infrastructure the healthcare, treatment, training and research functions and activities provided by the great public IRCCS of Milan, Istituto Nazionale dei Tumori and Istituto Neurologico Carlo Besta.

Patient's clinical needs, psychological and physical well-being represent fundamental elements shared by the organizational models of the two Institutes. The possibility of integrating the multidisciplinary knowledge and organizational functions represents a great opportunity for the medical and scientific community. This will result in a new healthcare complex of research, clinical, and teaching, capable of responding readily to present and future needs.

The construction works started in 2021, and the end is scheduled for 2026.

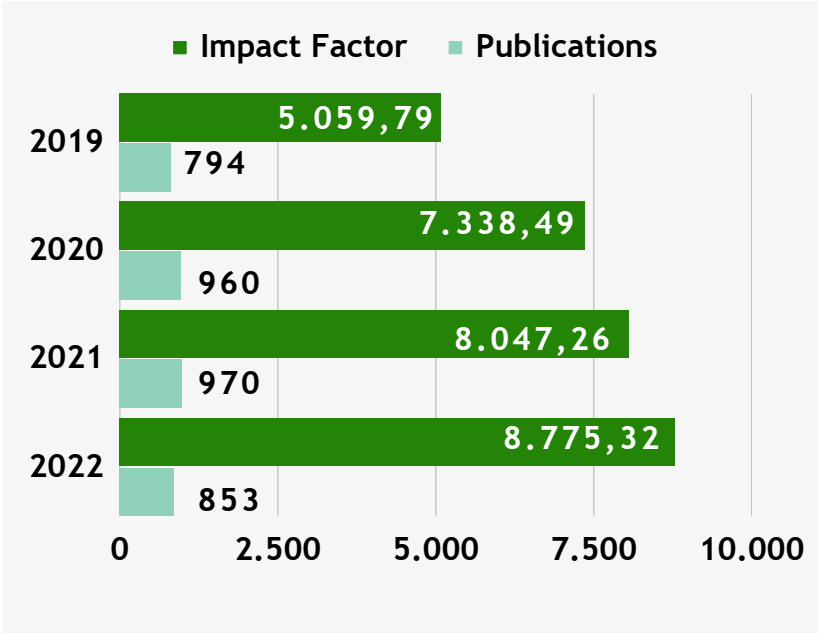
THE ESSENTIAL ABOUT INT 2022

SCIENTIFIC ACTIVITY: PUBLICATIONS

PUBLICATIONS 853

FIRST/LAST/ CORRESPONDING AUTHOR 43%

IMPACT FACTOR 8.775,322

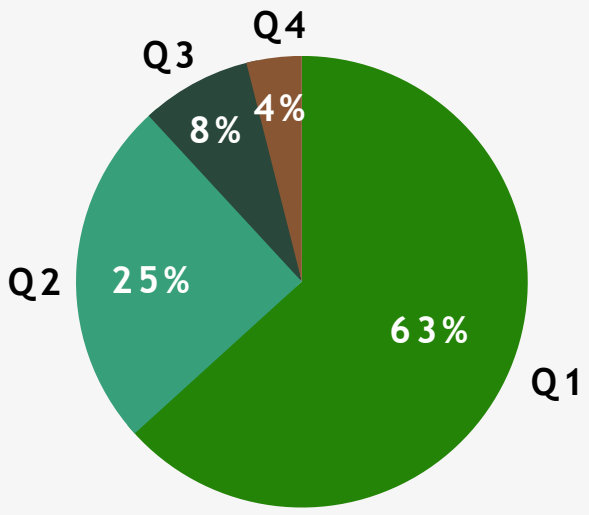


357 INSTITUTIONAL H-INDEX

H-INDEX INT RESEARCHERS

RANGE	1-97
MEDIAN	15
H-INDEX < 10	198
H-INDEX > 50	42

QUARTILE PLACEMENT*



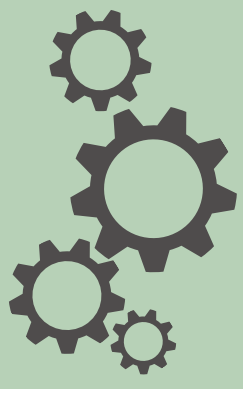
*69 publications without impact factor are excluded from the chart

SCIENTIFIC ACTIVITY: PROJECTS

ONGOING PROJECTS IN 2022	
National	108
Intenational	28
TOTAL	136

PROJECTS FUNDED IN 2022: NATIONAL GRANTS**	
MoH* - National Recovery and Resilience Plan (PNNR)	5
MoH* - National Plan for investments complementary (PNC)	2
MoH* - Ricerca Finalizzata	2
Fondazione Italiana per la Ricerca sul Cancro - AIRC	5
Other Grants	4
Fellowships	11
TOTAL	29

PROJECTS FUNDED IN 2022: INTERNATIONAL GRANTS**	
Projects led as coordinator	4
Involvement as a project partner	14
TOTAL	18



*Italian Ministry of Health

**For more details, see from page 64

CLINICAL RESEARCH DATA

ONGOING CLINICAL STUDIES

	STUDIES			PATIENTS	
	PROFIT	NO PROFIT	TOTAL	ENROLLED IN 2022	TOTAL
*Experimental**	268	201	469	1.308	13.612
Observational	11	322	333	16.538	418.884
Registries	-	16	16	1.188	58.626
TOTAL	**279**	**539**	**818**	**19.034**	**491.122**

CLINICAL STUDIES LAUNCHED IN 2022

	PROFIT	NO PROFIT	TOTAL
*Experimental**	48	27	75
Observational	2	75	77
Registries	0	1	1
TOTAL	**50**	**103**	**153**

PROGRESS OF CLINICAL STUDIES

	PROFIT	NO PROFIT	TOTAL
Concluded	58	114	172
In enrollement	99	294	393
Follow-up	121	131	252
Interrupted	1	0	1
TOTAL	**279**	**539**	**818**

*** For example are included drugs, devices, diets**

CLINICAL RESEARCH DATA

CLINICAL STUDIES PROMOTED BY INT

	TOTAL	LAUNCHED IN 2022
*Experimental**	72	8
Observational	94	48
Registries	7	-
TOTAL	**173**	**56**

PHARMACOLOGIAL CLINICAL TRIALS

PHASE	STUDIES	PATIENTS ENROLLED IN 2022	TOTAL PATIENTS ENROLLED
I	26	42	277
I/II	45	80	386
I/III	3	26	53
II	163	344	4.047
II/III	9	16	102
III	173	408	5.417
IV	6	0	24
TOTAL	**425**	**916**	**10.256**

	PROFIT	NO PROFIT	TOTAL
Monocentric	10	30	40
Multicentric	258	127	385
TOTAL	**268**	**157**	**425**

*** For example are included drugs, devices, diets**

OTHER DATA

HEALTHCARE DATA

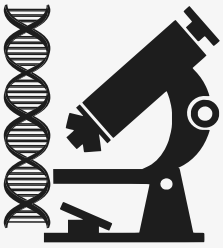
482 BEDS

12.510 ORDINARY ADMISSIONS

4.190 DAY HOSPITAL ADMISSIONS

1.222.495 CONSULTATIONS

MOLECULAR TUMOR BOARD

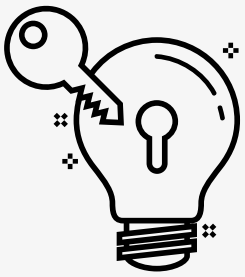


1.400 PATIENTS ANALYSED IN 2022

162 REPORTS SIGNED IN 2022

2.050 MOLECULAR TESTS IN 2022

PATENTS PORTFOLIO



14 PATENTS FAMILIES

7 OF WHICH INT OWNER

7 OF WHICH INT CO-OWNER

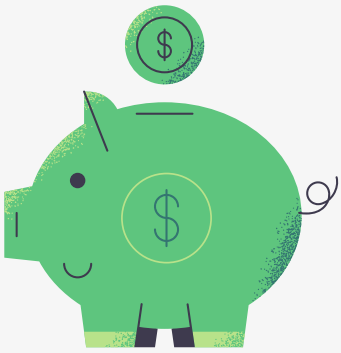
EDUCATION

230 EVENTS/TRAINING COURSES

7.575 PARTICIPANTS

48.420 OVERALL FORMATIVE HOURS

RESEARCH FUNDING



RESEARCH BUDGET

61.820.492,00 €

MAIN RESEARCH FUNDINGS

102.795,00 €	MoH Network (Alliance Against Cancer)
2.683.754,00 €	Donations and Bequests
3.488.158,73 €	5xMille*
4.550.000,00 €	Income from Clinical Trials
5.609.401,97 €	MoH Funding for Researchers' Careers
10.888.692,67 €	Structural Research Funds (Ricerca Corrente)
12.687.699,29 €	Competitive Grants
37.686.908,93 €	TOTAL

*0.5 percent share of income tax (contribution to research)

FOCUS ON MAJOR EVENTS

STRATEGIC RESEARCH PLAN 2022-2024

On February 25th INT approved the new Strategic Research Plan proposed by the Scientific Directorate. The Plan defines and put forward INT's research priorities, in line with the Institute's mission and the panorama of oncology research, and provides the actions to be taken to pursue these objectives, structured in a 3-years perspective (from 2022 to 2024). The plan has been implemented from a scientific standpoint through INT's 4 research lines and has been associated with a new Strategic and Operational Program (POAS) agreed with Regione Lombardia to formalize its organizational framework.

DEFINITION OF THE NEW INSTITUTIONAL RESEARCH LINES

Within the new 3-year programming of the IRCCSs, the INT's 4 institutional research lines represent the ideal continuity and evolution of the previous 4 years. The Scientific Directorate and the coordinators of each line have reorganized and grouped all institutional research activities in 30 projects, which have been presented to the Ministry of Health as the proposed scientific orientation for the Institute for the 2022-2024 period.

STRATEGIC AND OPERATIONAL PROGRAM

On May 25th the Board of Directors has approved the new Strategic and Operational Program (POAS). It represents both the programming tool through which INT defines its mission and vision and the organizational plan describing the different departments and units, along with the roles and functions of the institutional figures tasked with pursuing the strategy and objectives of care and research in the context of the national and regional healthcare service.

RENEWAL OF THE ADVISORY BOARD OF THE SCIENTIFIC DIRECTORATE

At the end of 2022 the Scientific Directorate renewed its Advisory Board, composed by 42 early and mid-career preclinical and clinical researchers. The Board is organized in 4 working groups, and provides support to the Scientific Directorate for its activities of internal and external scientific communication and dissemination, review of grant applications and reports, and organization of scientific events such as the Research Day. A group of 15 researchers collaborated to write this Scientific Report's edition.

FOCUS ON MAJOR EVENTS

EXTERNAL SCIENTIFIC ADVISORY BOARD

In accordance with OECI (Organization of European Cancer Institutes) standards, INT established a Scientific Advisory Board (SAB); the 5 members were identified among high-profile European and national scientists. The SAB is a consultative body tasked with assessing and giving feedback and recommendations on the clinical and translational research activities of the Institute. Members are involved in giving advice on the direction taken by INT research activity, pondering its strengths and weaknesses.

YOUNG RESEARCHER AWARD

The Scientific Directorate launched the annual 'Young Researcher Award' initiative in order to support young researchers' commitment in clinical, epidemiological, basic and translational research in 2022. Respectively Arsela Prelaj, Cristina Borzi, Giovanni Randon and Giovanni Centonze have been awarded for the excellence of their research activities.

THE RESEARCH DAY

On June 28th, the Scientific Directorate organized the annual Research Day, during which speakers illustrated institutional performance figures and the main scientific results, in particular projects granted by the Scientific Directorate with 5XMille funds by Internal calls for exploitation of institutional research (BRI), and took place the award ceremony for young researchers.

FOCUS ON MAJOR EVENTS

GENDER EQUALITY PLAN

The adoption and implementation of a Gender Equality Plan (GEP) has become a key obligation for Research Institutes under the provisions of Horizon Europe, to strengthen gender equity in European organizations. In 2022, INT came up with a GEP that includes a yearly overview of the situation regarding gender balance in the Institute, along with actions to identify and correct gender distortions and inequalities, defining goals and monitoring their achievement through appropriate indicators. Morevoer, a dedicated body monitors and promotes gender equality, the Equal Opportunities Committee.

CALL FOR EXPLOITATION OF INSTITUTIONAL RESEARCH

In 2022 5 projects have been granted to INT investigators through “call for exploitation of institutional research” (BRI), promoted by the Scientific Directorate and funded with 5XMille funds. These calls aim to support preclinical, clinical and translational research through innovative multidisciplinary projects, who respects the criteria of being integrated in the strategic objectives and in the 4 research lines of the Institute, while answering the need to promote discovery and innovation.

CALLS BY THE NATIONAL RECOVERY AND RESILIENCE PLAN (PNRR)

In 2022, the Italian Ministry of Health, within the NextGenerationEU framework, funded 2 INT-coordinated projects and 3 projects where INT researchers are partners. The aim of PNRR calls is to strengthen the biomedical research system in Italy thanks to the implementation of EU guidelines on recovery and resilience of post-COVID 19 healthcare system.

FOCUS ON MAJOR EVENTS

100 CAR-T

On June 17th the meeting "100 CAR-T: A beautiful story of the Italian healthcare system" celebrated the milestone of 100 adult patients treated with CAR-T cells in the Institute, with excellent results. In 2017, INT was the first Institute in Italy to deploy clinical protocols for this therapy that represents a revolutionary step for the treatment of certain types of hematological malignancies such as aggressive non Hodgkin B-cell lymphomas and multiple myeloma and a life-saving treatment for patients who have exhausted all other treatment options.

KICK-OFF MEETING I3LUNG

The project aims at creating a set of artificial intelligence (AI)-based personalized decision-making tools to aid both clinicians and patients in selecting the best lung cancer treatment plan. On July 1st and 2nd the 16 international multidisciplinary partners of the EU-funded project "I3LUNG" met in INT to share information, align objectives and getting to know each other to mark the start of the project, that INT coordinates with a funding of 10M€.

KICK-OFF MEETING IDEA4RC

The project, coordinated by INT (total funding 8.2M€), aims to develop a European data ecosystem for rare cancers, where scientific and clinical questions can be addressed by training suitable machine learning models on an ensemble of data sets contributed by several clinical centers across Europe. This ecosystem will be tested by 11 clinical centers of the European Reference Network on rare adult solid cancers, EURACAN, established in European countries. The test will focus on 2 among the 12 rare cancers domains: head and neck cancers and sarcomas. The kick-off meeting took place on September 28th.

KICK-OFF MEETING ACCELERATOR AWARD

The project aims to accelerate the whole research against the Pseudomyxoma Peritonei to improve the prognostic stratification, to guide treatment, and to define new-targeted therapies. On September 15th and 16th, the "1st Meeting: Accelerator Award on Appendiceal Mucinous Neoplasms and Pseudomyxoma Peritonei Building, a European Multicentric Cohort to Accelerate New Therapeutic Perspectives" was organized in INT.

INTERNATIONAL

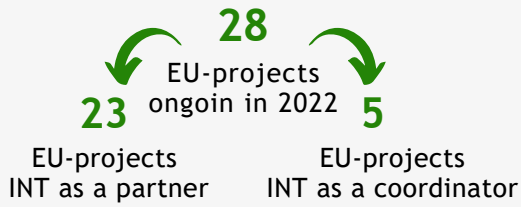
To strengthen the institutional presence on the European scenario, grant applications to the new Horizon Europe framework program calls have been successfully supported.

Within the HE-Health call, in 2022 INT was granted by 6 projects, 2 of them coordinated by INT researchers.

INT is the coordinator of the Joint Action on Network Expertise (JANE), funded under the EU4HEALTH –JA, whose purpose is the creation of 7 networks of expertise in the oncology area: personalized primary prevention, survival, palliative care, omic technologies, technological innovation, complex tumors with a negative prognosis, and the care of adolescent and young adult cancer patients.

An important role has been taken within Mission Cancer. INT coordinates 1 project on the assessment of quality of life in cancer patients (EuonQoL) involving more than 40 centers and organizations at European level. INT is also involved in 3 projects aimed at the creation of transational networks and infrastructures for cancer research, Comprehensive Cancer Infrastructures (CCI4EU) and National Hubs for the promotion of EU's Mission on Cancer (ECHOS) and wide-ranging clinical studies on high-impact oncological pathologies.

INT international visibility is consolidated by the presence of the Scientific Director and INT researchers in several boards and decision-making groups of the Cancer Mission, of Europe's Beating Cancer Plan, in the Board of Directors of Cancer Core Europe (CCE), as well as in the General Assembly of DIGICORE. Notably, in 2022 the Scientific Director was appointed by the Ministry of Universities and Research (MUR) as national representative of the "Cancer" subgroup in the Mission Board and in the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (SGPP).



Main European Liasons:

•***European Organization of Cancer Institutes - OECI***: *an International non-profit organization, that brings together the major international cancer institutions. INT obtained the accreditation as "Comprehensive Cancer Center" in accordance with OECI quality standards in 2015; Giovanni Apolone is the elected president since 2022.*

•***Cancer Core Europe - CCE***: *Alliance of seven leading European cancer centers that combine scientific research with patient care. INT is active in every pillar of Cancer Core Europe: for example, in the field of clinical and transalzionale research, INT is an enrolling center in two of the modules of the "Basket of Baskets trial", and it can count on an active participation of groups of pathologists, genomics specialists and medical physicists fron the Institue as part of CCE's dedicated task forces.*

DIGICORE: *Pan-European research network built to accelerate the implementation of precision oncology in Europe*.

STRATEGIC RESEARCH PLAN 2022 - 2024

The Strategic Research Plan (SRP) is the programmatic tool defining research strategies and objectives, maintaining a development perspective of 3-years period. The overall aim is to maintain and improve the current level of excellence of the INT Foundation.
The SRP 2022-2024 has been implemented through the 4 research lines, and it has been associated with a new Strategic and Operational Program (POAS), agreed with the Lombardy Region, aimed at organizational innovations to enhance the interdisciplinary and translational research.
In line with the previous plan, research projects will provide particular attention to principles of precision medicine, primary, secondary, tertiary, and quaternary prevention and to personalization of care.

OBJECTIVES

To support and strengthen the leading role of INT in regional and national landscapes (i.e. IRCCS, Pathology Networks and the Health Care System) with respect to research and assistance activities;

To increase INT's presence and leadership at European level, improving participation of researchers in the EU's different decision-making boards and working groups, with particular care to activities related to the Cancer Mission and the Europe's Beating Cancer Plan;

To safeguard and strengthen INT's wealth of knowledge and expertise, in order to improve the current level of research excellence and assistance and to stimulate the recruitment of new junior human resources;

To optimize the use of existing resources and the ability to attract further public and private, national and international fundings through the pooling of skills, services and technologies, in order to strengthen institutional leadership;

To put forward and apply novel and innovative organizational models in support of excellence and commitment to health research, aimed at obtaining evidence of the effectiveness of care interventions and assessing the impact of prevention activities, diagnosis, treatment and rehabilitation in terms of utility and cost-effectiveness.

PRIORITIES FOR ACTION

Research governance

Organization of the Research area and its dedicated staff

Promoting national and international partnerships

Design and implementation of research projects focusing on organizational and innovation technology

Development of a coordinated plan for science communication and dissemination.

INSTITUTIONAL RESEARCH LINES

INT's research is aimed at improving prevention, early diagnosis and treatment of cancer and the quality of life of cancer patients. Its multidisciplinary research activity hinges on the integration and synergy among preclinical and basic research, clinical, translational, epidemiological research, and quality-of-life and outcome research.
The 4 institutional research lines have been identified since 2018 as priorities to achieve INT's vision of health research imagined as the integration between different research areas.
Starting from 2019, the Scientific Directorate has been allocating resources from the Institutional Research Fund (€1.5M for each research line for the three-year period) to a strategic program related to the 4 lines of research.

For the new 3-year IRCCS research plan, approved by the Ministry of Health for 2022- 2024, INT addressed its research on the following lines, in continuity with the previous plan and in accordance to priorities of the Strategic Research Plan's section on "Research programming and governance". Effort, organizational and financial instruments are thus driven by these research priorities, considered as the main programming element to bring together old and new projects.

The following paragraph describes research lines issues and highlights selected projects funded by the Scientific Directorate with 5X1000 funds.

LINE 1
PRIMARY, SECONDARY PREVENTION AND EARLY DIAGNOSIS

LINE 2
PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

LINE 3
DIAGNOSTIC, THERAPEUTIC AND REHABILITATIVE APPROACH TO THE COMPLEXITY OF RARE CANCERS AND FRAGILE ONCOLOGICAL PATIENTS

LINE 4
CLINICAL, HEALTH CARE AND OUTCOME RESEARCH

PRIMARY, SECONDARY PREVENTION AND EARLY DIAGNOSIS

LINE 1

COORDINATOR:
GABRIELLA SOZZI

This line concerns the activity of cancer prevention with a focus on precision in cancer prevention:
1) Primary prevention: evaluates environment, diet, lifestyle, endocrine-metabolic factors and genetic factors that affect the risk of developing cancer and to correct them with intervention studies to reduce the onset.
2) Secondary prevention: develops highly sensitive molecular tests for screening programs and early diagnosis in individuals at risk. Moreover, it investigates altered molecular mechanisms and host-tumor interactions to guide the most effective interventions intended to reduce the incidence and progression of the disease.
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.

PRIMARY, SECONDARY PREVENTION AND EARLY DIAGNOSIS

LINE 1

FOCUS ON:

ORGAN MICROBIOME: IDENTIFICATION OF THE ENDOGENOUS (COMMENSAL) 'NON-HUMAN' COMPONENT WITH TRANSLATIONAL, DIAGNOSTIC, PROGNOSTIC & THERAPEUTIC POTENTIAL

The study is aimed to investigate the role of organ microbiome in 6 different human (pre)tumor malignancies (lung cancer, high-grade serous ovarian cancer, breast cancer, pseudomyxoma peritonei, prostate cancer, metabolic syndrome) in order to define new prognostic markers of dysbiosis able to detect and compartment early diseases with worse prognosis from less aggressive ones. Understanding of the mechanisms by which tumor microbiome influences tumor progression and prognosis could open the way to new therapeutic opportunities based on the modification of the microbiome.

The feasibility of the project was demonstrated by obtaining taxonomic profiles of the microbiota of various tissues and organs through sequencing of the variable regions of the bacterial 16S rRNA gene by utilizing different sample types. Selected communities of microbes will be identified as associated with tumor progression, and in-depth studies will investigate possible mechanisms involved, immune microenvironment and transcriptomic profiles, and will define the efficacy and safety of targeting bacteria as a new therapeutic strategy.

PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

LINE 2

COORDINATOR:
GIANCARLO PRUNERI

This line aims to study the new frontiers of precision medicine on multidisciplinary level and innovative diagnostic-therapeutic technologies through a reverse translational approach, in a seamless circular process in which clinical observation stimulates new testable hypotheses for benchtop research which in turn leads ideally to the next clinical trial.
Research of this line is oriented towards application of biomarkers for precision medicine: a cancer genomics approach, trascriptomics and miRNA analysis are functional to investigate tissue biomarkers and liquid biopsy for cancer progression and disease monitoring. Biomarker discovery and validation are also investigated in immunotherapy, metabolism, tumor microenvironment. Particular focus is directed towards the study of tumor/host/environment interactions to modulate the immune response and epigenetics.
Moreover, application of both pharmacological (clinical trials) and non pharmacological tecnological innovation (diagnostic, imaging, surgery).
Of note, projects of this line address radiomics, radiogenomics and artificial intelligence as innovative approach for cancer research.

PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

LINE 2

FOCUS ON:

BRCA AND HOMOLOGOUS RECOMBINATION DEFICIENCY ASSESSMENT AT THE BEDSIDE: IMPLEMENTATION OF DIAGNOSTIC ALGORITHMS FOR TAILORING TREATMENT

The cutting-edge NGS analysis has revealed promising results, uncovering BRCA mutations in 9% of pancreatic, 15% of breast, and 3.5% of prostate metastatic cancers. Moreover, pathogenic variants, including a rare BRCA2 reverse mutation in a treated breast case were found, hinting at novel treatment possibilities.

Building on this momentum, a custom NGS panel exclusively for liquid biopsy was designed, a potential game-changer in early detection. Received in September 2022, the panel is now undergoing rigorous studies to ascertain its specificity and sensitivity, utilizing Seraseq ctDNA reference materials.

In collaboration with dedicated oncologists, vital steps in establishing a defined procedure for blood sample collection from ovarian cancer patients with BRCA mutations detected in their tissues have been taken. This key development opens doors to personalized treatment approaches and offers hope for improved patient outcomes.

DIAGNOSTIC, THERAPEUTIC AND REHABILITATIVE APPROACH TO THE COMPLEXITY OF RARE CANCERS AND FRAGILE ONCOLOGICAL PATIENTS

LINE 3

COORDINATOR:
ANNALISA TRAMA

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 adolescent and young adult population), 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 access to treatment, inequalities, and requirements of 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 European and worldwide reference center 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.

DIAGNOSTIC, THERAPEUTIC AND REHABILITATIVE APPROACH TO THE COMPLEXITY OF RARE CANCERS AND FRAGILE ONCOLOGICAL PATIENTS

LINE 3

FOCUS ON:

A MULTICENTER REGISTRY FOR TRANSLATION RESEARCH AND CLINICAL SUPPORT OF EXTRA RARE TUMORS IN ITALY (RETI)

Our Institute has a long-standing experience on rare cancers and is in a privileged position to work even on ultra-rare cancers. Thus, INT has large population databases (the result of international collaborations with Asia, South America and the United States), clinical databases, high institutional expertise and multi-centre collaborations deriving from networking with other national and international centres of expertise for rare cancers.

Line 3 has decided to launch a research project on extra rare cancers to remodel the knowledge available into a better understanding of the biology and natural history of these diseases.

Starting from clinical databases that are already available but not systematically structured and standardised, the project aims to define a multi-centre registry with a virtual bio-bank on extra rare cancers leveraging also on artificial intelligence for data analyses and data sharing. The goal is to provide an infrastructure to maximize the information available and on which to develop clinical and translational studies.

The project is currently focusing on: a) sarcomas of the retroperitoneum; b) epithelial tumors of the thymus; c) nasopharyngeal carcinomas.

CLINICAL, HEALTH CARE AND OUTCOME RESEARCH

LINE

4

COORDINATOR:
UGO PASTORINO

This line of research is intended for observational, interventional and organizational activities to obtain evidence of effectiveness of health interventions, collect evidence and organize clinical, biological and outcome data in databases that can be consulted and harmonized with other sources, such as electronic health records (to create “big data” sets). An impact assessment of prevention activities, diagnosis, treatment and rehabilitation, their value in terms of utility and cost-effectiveness in clinical practice is also carried out.

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).

CLINICAL, HEALTH CARE AND OUTCOME RESEARCH

LINE

4

FOCUS ON:

SCREENING AND MULTIPLE INTERVENTION ON LUNG EPIDEMICS (SMILE)

The SMILE trial was a prospective randomized controlled trial conducted from July 2019 to March 2020, with the aim of evaluating a multiple intervention program for lifelong smokers. The program included several components: early lung cancer detection using ultra low-dose computed tomography (CT), reduction of chronic inflammation through low-dose aspirin (ASA) treatment, smoking cessation using cytisine, and modifications to diet and physical activity.

A total of 1.114 volunteers were enrolled in the study. The objectives of the trial were to assess the effectiveness of the interventions in achieving early lung cancer detection, reducing chronic inflammation, promoting smoking cessation, and improving diet and physical activity.

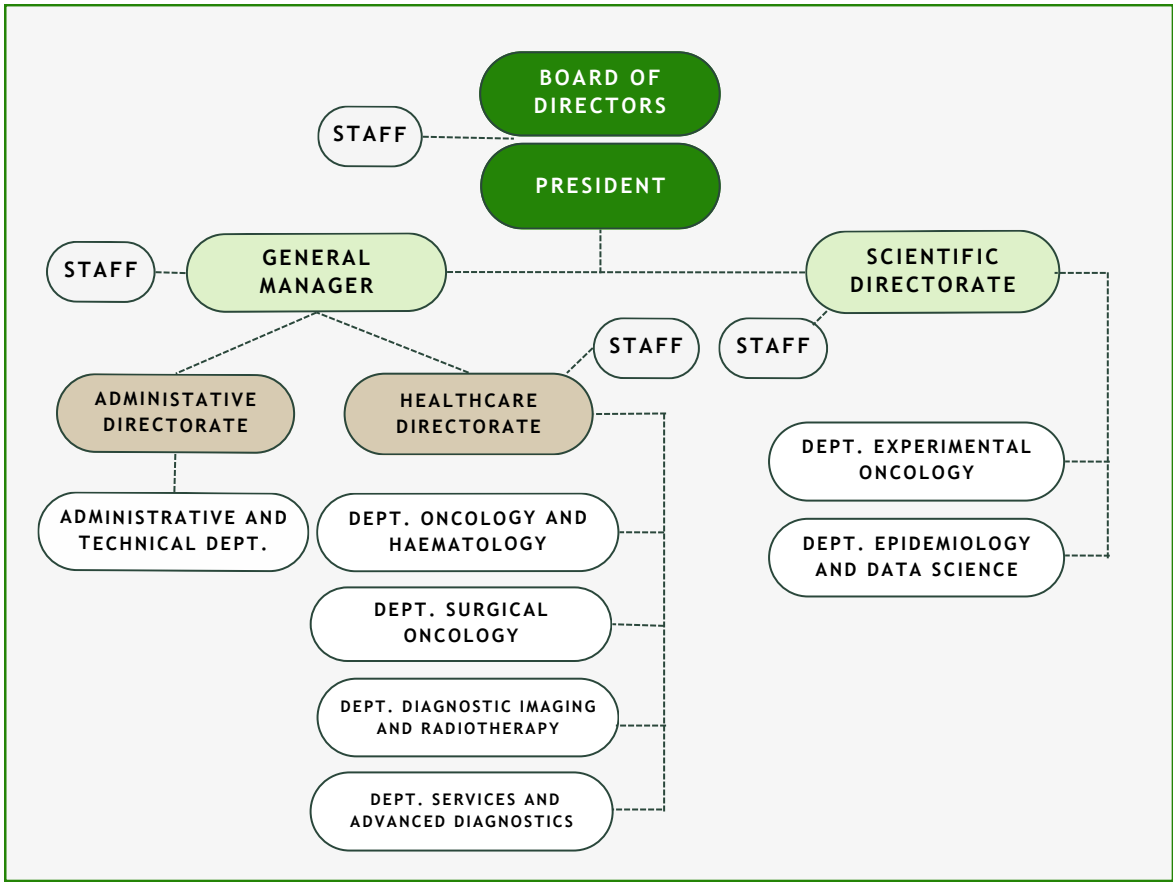
The results of the study were as follows: the 2-year follow-up was completed according to the protocol. Active surveillance was performed for sub-solid nodules, and vital status was determined for all participants. The main results obtained during the first year of follow-up were published.

At the 12-month follow-up, the intervention arm had a quit rate of 32.1% (151 participants), while the control arm had a quit rate of 7.3% (29 participants). The adjusted odds ratio of continuous abstinence was 7.2 (95% confidence interval: 4.6-11.2). Adverse events were more frequent in the intervention arm, with gastrointestinal symptoms being the most common.

Preliminary results from the analysis of 938 baseline chest CT scans using AI software showed an association between higher amounts of subcutaneous fat, higher BMI values, and elevated CRP levels.

Overall, the SMILE trial demonstrated the potential benefits of the multiple intervention program for lifelong smokers in terms of smoking cessation, early lung cancer detection, and reduction of chronic inflammation.

STRATEGIC AND OPERATIONAL PROGRAM



The institutional **Strategic and Operational Program (POAS)**, adopted by a Resolution of the Board of Directors, represents the programming tool defining INT's mission and vision, as well as its organizational structure.
The operating model identifies **the Strategic Directorate** as the backbone of the entire INT organizational system. The Strategic Directorate guarantees the effective and efficient governance of the Institute, through the identification of the objectives and the human, economic and technical resources necessary for their achievement. The Strategic Directorate is composed by the **General Manager**, **Scientific Director**, **Administrative Director** and **Healthcare Director**.

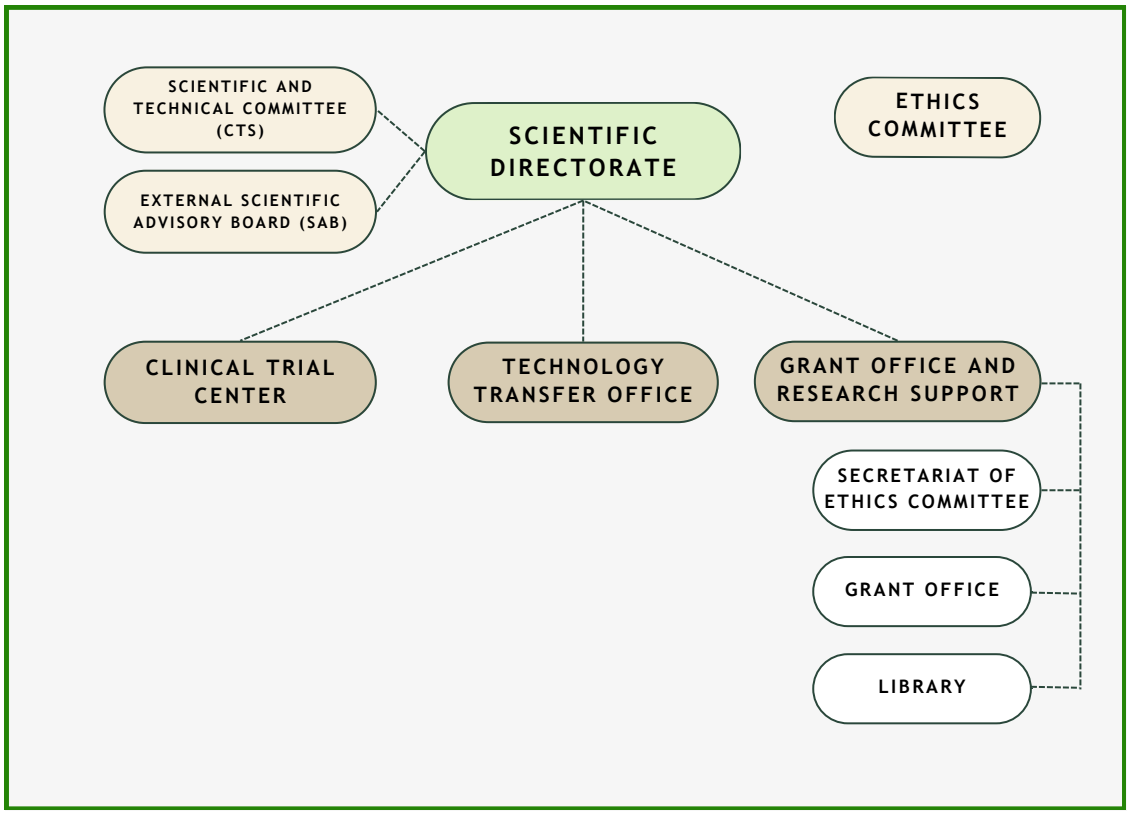
The organization of the **Research Area** envisaged for the new POAS attempts to optimize and streamline the distribution of human resources and scientific skills, in a management structure that supports homogeneous research areas.

STRATEGIC AND OPERATIONAL PROGRAM

The Scientific Directorate coordinates the research area, which now includes the **Department of Experimental Oncology** and **Department of Epidemiology and Data Science**. Their missions are, respectively, to integrate genetic, immunological, pharmacological and biological research skills into a coordinated and synergistic activity and to integrate epidemiological and biostatistics research with new bioinformatics approaches, able to interpret the "big data" generated by omics studies through computational models.

The Scientific Directorate organizes its activities within three formally appointed units: the **Clinical Trials Center**, the **Technology Transfer Office (TTO)** (formerly pertaining to administrative area), and the new **Grant Office and Research Support** unit, which will merge the functions of the **Grant Office**, **the Secretariat of the Ethics Committee** and the **Scientific Library**. **The Scientific Directorate's office** and the **Secretariat of the Scientific Directorate** complete the organization to manage the administrative and coordination functions.

The plan has been approved in October 2022, with the organization and activities structured as described in the following sections.



DEPARTMENT OF EXPERIMENTAL ONCOLOGY

MOLECULAR PHARMACOLOGY

EPIGENOMIC AND BIOMARKERS OF SOLID TUMORS

MOLECULAR EPIGENOMICS

MOLECULAR IMMUNOLOGY

MICROENVIRONMENT AND BIOMARKERS SOLID TUMOR

TRANSLATIONAL IMMUNOLOGY

RESEARCH IN NUTRITION AND METABOLOMICS

MOLECULAR BASES OF GENETIC RISK

INTEGRATED BIOLOGY OF RARE TUMORS

ANIMAL FACILITY

HEAD:

MARIO PAOLO COLOMBO
GABRIELLA SOZZI
(since October 2022)

DEPARTMENT OF EXPERIMENTAL ONCOLOGY

The research carried out by the Department of Experimental Oncology in collaboration with the clinical departments aims to develop knowledge and insights in the following areas:

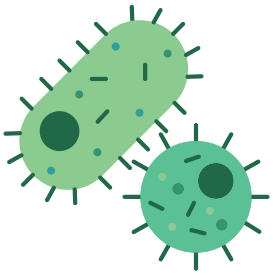
- precision prevention, which takes in consideration individuals' differences in lifestyle, environment and biology;
- risk identification, screening and early diagnosis in healthy individuals, integrating biomic and radiomic technologies with artificial intelligence approaches;
- precision medicine for personalized patient care;
- sensitivity or resistance to therapies;
- survival and quality of life.

By institutional "mission", each unit of the Experimental Oncology Department, with their own expertise and specific skills, is called to participate in joint activities of multidisciplinary and transversal oncology research within which basic research can enhance and provide the best translational research approach.

These research projects, which arise from unmet clinical needs and/or original experimental observations, are implemented in laboratories, utilizing clinical samples of patients and ad hoc pre-clinical experimental models such as homo-heterotypic cell cultures, 3D organoid-structures, in vivo models (xenografts, xenopatients, transgenic models) for the studied malignancies. The observations generated return to the clinician, with a bi-directional approach between patient and the research laboratory. This trend will allow pre-clinical research results to be transfered into current clinical practice.

The main research areas carried out in the Experimental Oncology Department include:

- Genomic, epigenetic, metabolic biomarkers of risk, diagnosis, prognosis, response prediction ("Biomics");
- Molecular and translational immunology - Immunotherapy ("Immunomics");
- Sensitivity or Resistance to Therapy ("Pharmacomics").



HIGHLIGHT

Intracellular osteopontin protects from autoimmunity-driven lymphoma development inhibiting TLR9-MYD88-STAT3 signaling.

Rizzello C, et al. MOLECULAR CANCER. 2022 Dec. DOI: 10.1186/s12943-022-01687-6

Autoimmune disorders, including Systemic Lupus Erythematosus (SLE), are associated with increased incidence of hematological malignancies. This study demonstrates that in the setting of Systemic Lupus Erythematosus-like syndrome, in which double strand-DNA chronically circulates and activates Toll-like receptors, B cell intracellular osteopontin exerts a protective role in the development of autoimmunity-driven B-cell lymphoma, mainly acting as a brake in the TLR9-MYD88-STAT3 signaling pathway.

Landscape of immune-related signatures induced by targeting of different epigenetic regulators in melanoma: implications for immunotherapy.

Anichini A., et al. JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH. 2022 Nov. DOI: 10.1186/s13046-022-02529-5 DOS

Through the analysis of transcriptional programs induced in neoplastic cells by distinct classes of epigenetic drugs, the DNMT inhibitor guadecitabine emerged as the most promising immunomodulatory agent among those tested, supporting the rationale for usage of this class of epigenetic drugs in combinatorial immunotherapy approaches.

Single-Cell Phenotypic and Molecular Characterization of Circulating Tumor Cells Isolated from Cryopreserved Peripheral Blood Mononuclear Cells of Patients with Lung Cancer and Sarcoma.

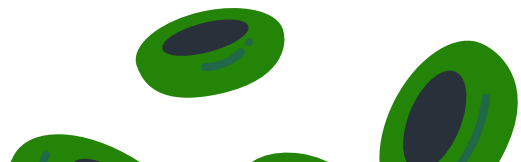
Vismara M, et al. CLINICAL CHEMISTRY. 2022 May. DOI: 10.1093/clinchem/hvac019

This study demonstrates the feasibility of the retrospective enumeration of circulating tumor cells (CTC) and their molecular characterization using an unbiased selection strategy in cryopreserved PBMCs from cancer patients. These results represent an advance in blood sample management for CTC studies, offering a wider range of retrospective genomic/phenotypic analyses to guide patients' personalized therapy, paving the way for sample sharing in multicenter studies.

The TRAR gene classifier to predict response to neoadjuvant therapy in HER2-positive and ER-positive breast cancer patients: an explorative analysis from the NeoSphere trial.

Triulzi T., et al. MOL ONCOL. 2022 Jun. DOI: 10.1002/1878-0261.13141

This study evaluated the 41-gene classifier trastuzumab advantage risk model (TRAR) as a predictive marker for patients enrolled in the NeoSphere trial. In HER2-positive/ER-positive BC, TRAR is an independent predictor of pCR and represents a promising tool to select patients responsive to anti-HER2-based neoadjuvant therapy and to assist treatment escalation and de-escalation strategies in this setting.



HIGHLIGHT

Validation of MiROvaR, a microRNA-based predictor of early relapse in early stage epithelial ovarian cancer as a new strategy to optimise patients' prognostic assessment.

Ditto A., et al. EUROPEAN JOURNAL OF CANCER. 2022 Jan. DOI: 10.1016/j.ejca.2021.11.003

In this study, the tissue-based miRNA signature named MiROvaR, previously demonstrated to be prognostic in advanced stage epithelial ovarian cancer (EOC) patients, was validated to have good prognostic performance also in early-stage EOC patients. MiROvaR emerges as a promising new tool for a more effective therapeutic approach and management of EOC patients and warrants further investigation for the development of a clinical-grade prognostic assay.

Teloxantron inhibits the processivity of telomerase with preferential DNA damage on telomeres.

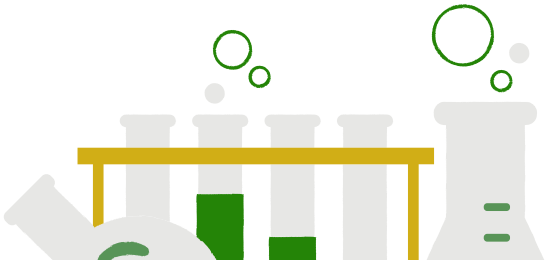
Maciejewska N., et al. CELL DEATH & DISEASE. Nov 2022. DOI: 10.1038/s41419-022-05443-y

The results of this study represent the first evidence of telomerase inhibition by anthraquinone derivatives that do not exhibit G-quadruplex-stabilizing properties. The compounds triggered DSBs in TERT-positive but not in TERT-negative cell lines, which indicates that the induction of DSBs was dependent on telomerase inhibition. The observed DNA damage activated DNA damage response pathways involving ATM/Chk2 and ATR/Chk1 cascades. Additionally, the compounds induced apoptotic cell death through extrinsic and intrinsic pathways in lung cancer cells. Taken together, our study demonstrated that anthraquinone derivatives can be further developed into novel telomerase-related anticancer agents.

Circulating CD81-expressing extracellular vesicles as biomarkers of response for immune-checkpoint inhibitors in advanced NSCLC.

Signorelli D., et al. FRONT IMMUNOL. 2022 Sep. DOI: 10.3389/fimmu.2022. 987639

We evaluated circulating EVs as possible biomarkers for ICI in advanced NSCLC patients with low tumoral PD-L1. EVs were isolated from plasma of 64 PD-L1 low, ICI-treated NSCLC patients, classified either as responders or non-responders. T cells from healthy donors were triggered in vitro using patients' EVs. In unsupervised statistical approach, R-EVs showed higher levels of tetraspanins than NR-EVs, significantly associated to better overall response rate (ORR). In multivariable analysis CD81-EVs correlated with ORR. Unsupervised analysis revealed a cluster of variables on EVs, including tetraspanins, significantly associated with ORR and improved survival. R-EVs expressed more costimulatory molecules than NR-EVs although both increased T cell proliferation and partially, activation. Tetraspanins levels on EVs could represent promising biomarkers for ICI response in NSCLC.



DEPARTMENT OF EPIDEMIOLOGY AND DATA SCIENCE

- DATA SCIENCE
- *BIOSTATISTICS FOR CLINICAL RESEARCH*
- *BIOINFORMATICS AND BIOSTATISTICS*
- EPIDEMIOLOGY AND PREVENTION
- *CANCER REGISTRY*
- *ENVIRONMENTAL EPIDEMIOLOGY*
- EVALUATIVE EPIDEMIOLOGY
- ANALYTICAL EPIDEMIOLOGY AND HEALTH IMPACT

HEAD:

VITTORIO KROGH
GIOVANNI APOLONE (INTERIM)
(since January 2023)

DEPARTMENT OF EPIDEMIOLOGY AND DATA SCIENCE

The mission of the department is the implementation of studies aimed both at guiding cancer prevention and control programs and policies and at supporting clinical decisions and therapeutic strategies, through methods and data based on a solid, scientific and innovative approach. There are two areas within the department.

EPIDEMIOLOGICAL AREA

Integrates traditional and molecular epidemiology, exploiting the growing availability of different data. In particular the availability of exposomic data encompassing internal factors (e.g. metabolomic, lipidomic, metallomics), lifestyle (e.g. diet, exercise, drinking and smoking habits), physical conditions (e.g. anthropometry, metabolic syndrome, health status), social factors (family structure, demography, migration) allows to clarify how multiple exposures associate with etiology and progression of cancer.

In addition, the epidemiological area exploits administrative data and the secondary use of medical and electronic health records aiming at methodological innovation (data interoperability solutions, innovative mathematical models, use of artificial intelligence etc). This area that represents a landmark both in Italy and in Europe, refers to the European Health Data Space to strengthen collaborations and promote studies on:

- cancer etiology, risk and prevention;
- natural history, prognostic and predictive factors, also to guide clinical decision making;
- cancer burden and organization of health services.

STATISTICS / DATA SCIENCE AREA

It promotes the use of multidisciplinary methodologies and techniques suitable for extracting information from data based on biomedical, computer and mathematical-statistical skills. These activities are carried out collaborating with the researchers of the Institute or in the context of national and international studies in the areas of cancer diagnosis, therapy and prognosis, as well as in vitro and in vivo experiments in the context of experimental research.

The researchers of this area are also involved in the application of statistical methodologies to develop innovative technologies and provide training in these fields for researchers with a clinical/biological or statistical/bioinformatic profile.

HIGHLIGHT

Long-term survival and cure fraction estimates for childhood cancer in Europe (EUROCARE-6): results from a population-based study.

Botta L., et al. LANCET ONCOLOGY. 2022 Dec. DOI: 10.1016/S1470-2045(22)00637-4

The EUROCARE-6 study, aimed to update survival progress of the European paediatric population, shows progress in survival for childhood cancer cases diagnosed during the period 2000–13. We estimate 3% points increase of 5-year survival for all childhood cancer combined in Europe in 2010-14 compared with that of 2004-2006, although some differences among countries are still present.

Excess risk of subsequent malignant neoplasms in adolescent and young adult cancer survivors: Results from the first Italian population-based cohort.

Trama A., et al. CANCER. 2022 Jen. DOI:10.1002/cncr.33931

Evidence about late effects in adolescent and young adult (AYA) cancer survivors is scarce. This study assessed the risk of subsequent malignant neoplasms (SMNs) to identify the most common ones to be considered in follow-up care. Based on a study cohort of 67692 AYA cancer survivors we estimate a cumulative incidence of all SMNs in AYA cancer survivors within 25 years of their first cancer diagnosis of ~10%. These results highlight the need to personalize follow-up strategies for AYA cancer survivors.

Prediagnostic Levels of Copper and Zinc and Breast Cancer Risk in the ORDET Cohort.

Pala V., et al. CANCER EPIDEMIOL BIOMARKERS PREV. 2022 Jun. DOI: 10.1158/1055-9965.EPI-21-1252

Case-control studies show that copper (Cu) is high and zinc (Zn) low in blood and urine of women with breast cancer (BC) compared with controls. To assess whether prediagnostic Cu and Zn are associated with BC risk, we implemented a nested case-control study within the ORDET cohort. Our prospective findings suggest that increased Cu/Zn ratio in plasma and urine may be both an early marker of, and a risk factor for, breast cancer development.

High weekly integral dose and larger fraction size increase risk of fatigue and worsening of functional outcomes following radiotherapy for localized prostate cancer.

Joseph N., et al. FRONT ONCOL. 2022 Oct. DOI: 10.3389/fonc.2022.937934

We hypothesized that increasing the pelvic integral dose (ID) and a higher dose per fraction correlate with worsening fatigue and functional outcomes in localized prostate cancer (PCa) patients treated with external beam radiotherapy (EBRT). By retrospective analysis of two prospective observational cohorts, REQUITE (development, n=543) and DUE-01 (validation, n=228), we showed that increasing the weekly ID and the dose per fraction lead to the worsening of fatigue and functional outcomes in patients with localized PCa treated with EBRT.

HIGHLIGHT

Association of Sentinel Node Biopsy and Pathological Report Completeness with Survival Benefit for Cutaneous Melanoma and Factors Influencing Their Different Uses in European Populations.

Sant M., et al. CANCERS (BASEL). 2022 Sep. DOI: 10.3390/cancers14184379.

Standard care for cutaneous melanoma includes an accurate pathology report (PR) and sentinel lymph node biopsy (SLNB) for staging clinically node-negative >1 mm melanomas. We aimed at investigating the frequency of these indicators across European countries, also assessing consequences for survival. We analyzed 4245 melanoma cases diagnosed in six European countries in 2009–2013. Accurate pathology profiling and SLNB carried survival benefit. Narrowing down between-countries differences in adhesion to guidelines might achieve better outcomes.

External Quality Assurance programs for processing methods provide evidence on impact of preanalytical variables.

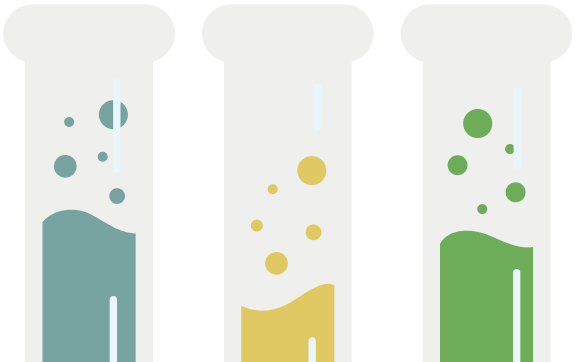
Verderio P., et al., NEW BIOTECHNOLOGY. 2022 Dec. DOI: 10.1016/j.nbt.2022.08.006.

The present global analysis, within the SPIDIA4P H2020 project, was an extensive External Quality Assurance (EQA) analysis with 10 processing schemes, over 6 years, with 997 participant/scheme attendances. Results highlighted and confirmed the critical role of some pre-analytical factors (i.e. nucleic acid extraction method and kit and the storage temperature) during nucleic acid extraction. This information is informative, not only in the context of method development and laboratory validation, but also in development of templates for biobank-standardized reports (i.e., ISO requirements).

Plasma Profile of Immune Determinants Predicts Pathological Complete Response in Locally Advanced Breast Cancer Patients: A Pilot Study.

Miceli R, et al., CLIN BREAST CANCEL. Oct 2022. Doi: 10.1016/j.clbc.2022.05.007.

To evaluate the role of circulating immune-related determinants with respect to pathological complete response (pCR) in patients with locally advanced breast cancer (LABC) subjected to neoadjuvant chemotherapy (NACT), 151 plasma samples were profile. Results of this explorative study provide the conceptual and practical foundation that a distinctive pattern of the immune determinant blood signature at diagnosis of LABC correlates with the patient's response to NACT and provides the groundwork for larger studies that could lead to a minimally invasive tool for personalized medicine.



DEPARTMENT OF SERVICES AND ADVANCED DIAGNOSTICS

- PATHOLOGICAL ANATOMY 1
  - *DIGITAL PATHOLOGY*
- PATHOLOGICAL ANATOMY 2
  - *SOFT TISSUES TUMORS*
  - *DIAGNOSTICS AND MOLECULAR RESEARCH*
  - *MOLECULAR HEMOPATHOLOGY*

- GASTROENTEROLOGY - DIAGNOSTIC ENDOSCOPY
- LABORATORY MEDICINE
- CARDIOLOGY
- IMMUNOHEMATOLOGY AND TRANSFUSION MEDICINE - SIMT
- PNEUMOLOGY
- CLINICAL PSYCHOLOGY
- BIOBANK

HEAD:

GIANCARLO PRUNERI

DEPARTMENT OF SERVICES AND ADVANCED DIAGNOSTICS

In the era of "evidence-based medicine", the Department of Advanced Diagnostics represents a transversal entity, available to support any clinical and surgical procedure. Its principles are:

- the central role played by patients;
- the continuous improvement of quality in the assistance and care;
- the multidisciplinary diagnostic approaches;
- the development of clinical and translational research to be applied in the clinical practice;
- the development of educational programs;
- the consolidation of both national and international partnerships.

The Department works on several fields of the diagnostic and research practice, including:

- laboratory diagnostics: cytological, histological, immunological, genetic-molecular, bacteriological, virological, mycological and parasitological;
- histopathological and cytological diagnostics;
- molecular diagnostics;
- transfusion medicine;
- diagnosis and treatment of cardiovascular diseases;
- prevention, diagnosis and treatment of benign and malignant diseases;
- psychological support for patients;
- diagnosis, management of comorbidity and respiratory complications in cancer patients;
- prevention and treatment of chronic respiratory diseases, such as COPD.

Moreover, the workflow in a cancer-oriented Biobank is directed on connecting different sub-specialities, focusing on both the researchers' needs and treatment opportunities for patients.

The Department promotes many research activities in healthcare, also encouraging synergistic integration with dedicated facilities.

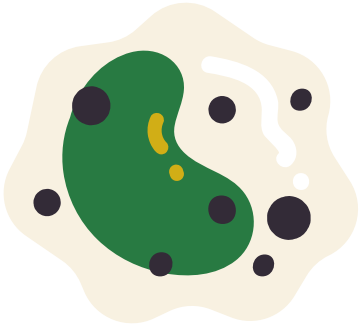
The Department of Services and Advanced Diagnostics aims at providing the best diagnostic support also oriented at treatment and prevention programs of both cardiovascular and respiratory complications in patients, ensuring medical expertise, timeliness, technology and integration.

HIGHLIGHT

Association of Upfront Peptide Receptor Radionuclide Therapy With Progression-Free Survival Among Patients With Enteropancreatic Neuroendocrine Tumors.
Pusceddu S., et al. JAMA NETW OPEN. 2022 Feb. DOI:10.1001/jamanetworkopen.2022.0290.
The paper was designed as a multicenter retrospective analysis aiming at dissecting the role played by the upfront peptide receptor radionuclide therapy (PRRT) in the entero-pancreatic neuroendocrine tumors, as compared to upfront chemotherapy or target therapy. Overall, the present study highlighted that upfront PRRT significantly improves survival outcomes, also contributing in broadening the therapeutic algorithm in patients suffering from advanced entero-pancreatic neuroendocrine malignancies.

Platinum sensitivity in patients with IDH1/2 mutated vs wild-type intrahepatic cholangiocarcinoma: A propensity score-based study.
Niger M., et al. INT. J. CANCER. 2022 Oct. DOI: 10.1002/ijc.34182.
By a retrospective multicenter analysis in 120 intrahepatic cholangiocarcinoma (iCCA) patients, recruited in six Italian Cancer Centers, the authors provide first clinical evidence that IDH1/2 mutations are not associated with increased efficacy of platinum salts in iCCA patients, nor with higher homologous recombination deficiency in Cancer Genome Atlas cholangiocarcinoma cases. The findings suggest that future trials targeting homologous recombination deficiency in IDH1/2-mutant tumors should harness new therapeutic combinations rather than PARP-targeting monotherapies.

Predictive Role of CD36 Expression in HER2-Positive Breast Cancer Patients Receiving Neoadjuvant Trastuzumab.
Ligorio F., et al. J NATL CANCER INST. 2022 Dec. DOI: 10.1093/jnci/djac126.
No reliable predictors have been identified so far for long-term clinical outcomes in patients with early-stage HER2-positive breast cancer (HER2+ BC). By investigated the association between baseline intratumor CD36 gene expression and event-free survival in 180 patients enrolled in the phase III NeoALTTO trial we showed that high intratumor CD36 expression was independently associated with worse event-free survival in patients treated with trastuzumab-based therapy but not with lapatinib-based or trastuzumab-lapatinib.



HIGHLIGHT

Gene signatures of circulating breast cancer cell models are a source of novel molecular determinants of metastasis and improve circulating tumor cell detection in patients.

Fina, et al., J. Exp. Clin. Cancer Res. Feb 2022. DOI: 10.1186/s13046-022-02259-8.

On the hypothesis that the distinguishing molecular features of Circulating Tumor Cells (CTCs) reveal useful information on metastasisbiology and disease outcome, we compared the transcriptome of CTCs, primary tumors, lymph-node and lung metastases of the MDA-MB-231 xenograft model, and assessed the biological role of a panel of selected genes, by in vitro and in vivo functional assays, and their clinical significance in M0 and M+ breast cancer patients.Our findings provide evidence on the potential of a CTC-specific molecular profile as source of metastasis-relevant genes in breast cancer experimental models and in patients. Thanks to transcriptome analysis we generated a novel CTC signature in the MDA-MB-231 xenograft model, adding a new piece to the current knowledge on the key players that orchestrate tumor cell hematogenous dissemination and breast cancer metastasis, and expanding the list of CTC-related biomarkers for future validation studies.

Integrative molecular analysis of combined small-cell lung carcinomas identifies major subtypes with different therapeutic opportunities.

Simbolo M., et al., ESMO OPEN., Feb 2022. DOI: 10.1016/j.esmoop.2021.100308.

To deepen the knowledge about the large cell neuroendocrine carcinomas (CoLCNECs) rare histotype and to clarify their relationship with lung cancers, an integrated molecular analysis of 44 patients shows that CoLCNECs constitute a standalone group of neuroendocrine neoplasm, with three different molecular profiles, two of which overlap with pure LCNEC or adenocarcinoma. CoLCNECs can be considered an independent histologic category with specific genomic and transcriptomic features, different and therefore not comparable to other lung cancers. Indeed, in addition to a histological re-evaluation of lung cancer classification, our study may help to develop a new diagnostic approach for novel and personalized treatments in CoLCNECs.

DEPARTMENT OF SURGICAL ONCOLOGY

- GENERAL SURGICAL ONCOLOGY 1 - HEPATO-PANCREATO-BILIARY SURGERY
  - *LIVER TRANSPLANTS*
- GENERAL SURGICAL ONCOLOGY 2 - COLORECTAL SURGERY
  - *PERITONEAL SURFACE MALIGNANCIES*
  - *HEREDITARY TUMORS OF THE GASTROINTESTINAL TRACT*
- GENERAL SURGICAL ONCOLOGY 3 - BREAST SURGERY
  - *INTEGRATED BREAST SURGERY*
- GENERAL SURGICAL ONCOLOGY 4 - MELANOMA SURGERY
  - *SURGICAL OPHTHALMIC ONCOLOGY*
- GENERAL SURGICAL ONCOLOGY 7 - SARCOMA SURGERY
- THORACIC SURGERY
- PLASTIC SURGERY
- GYNECOLOGIC ONCOLOGY
- OTOLARYNGOLOGIC ONCOLOGY
  - *MAXILLOFACIAL SURGERY*
- UROLOGIC ONCOLOGY
  - *TESTICULAR AND PENILE TUMORS*
- ANESTHESIA AND RESUSCITATION
  - *INTENSIVE CARE*
  - *ANESTHESIA AND SURGICAL BLOCK*
- GENERAL SURGICAL ONCOLOGY 6 - PEDIATRIC ONCOLOGY
- ONCOLOGICAL DAY SURGERY
- LASER THERAPY

DEPARTMENT OF SURGICAL ONCOLOGY

HEAD:

ANTONIO TRIARICO (INTERIM)
ALESSANDRO GRONCHI
(since October 2022)

The Department of Surgical Oncology conjugates a long-lasting tradition in surgical treatment of solid tumors with an internationally-recognized clinical and translational research focused on cancer, accordingly to the two main aspects of Fondazione IRCCS Istituto Nazionale dei Tumori: patients' care and scientific discovery. In the last decades, the Department of Surgical Oncology played a role in improving surgical outcome in the vast majority of human cancers including rare tumors with the aim to preserve quality of life and to maintain a high-quality standard of cure. The main focuses of these advancements in the last years have been:

1. the introduction of more tailored, less extensive, minimally-invasive procedures;
2. a wise, evidence-based escalation of the multimodal approach to metastatic cancer even including surgery of both primary tumors and distant lesions;
3. the development of nomograms and classificators to personalize surgery in particular settings such as rare cancers and locally recurrent diseases.

The mission of the Department of Surgical Oncology is to pursue the excellence of complex cancer surgery with the highest quality of care and using updated and evidence-based technologies and approaches, in the challenging and rapidly evolving field of surgical oncology. The main activities of the Department are:

- surgical treatment of advanced cancers in complex settings requiring a multidisciplinary approach (i.e. metastatic disease, locally advanced and/or recurrent tumors, specific disease such as sarcoma, etc);
- integration of peculiar locoregional treatments within surgery (isolated limb perfusion for sarcoma or locally metastatic melanoma, hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies);
- diagnosis, prophylactic surgery and personalized follow up for hereditary cancers (breast and/or ovarian tumors in BRCA-mutated patients, colorectal cancer in patients affected by familial adenomatous polyposis or Lynch syndrome, etc.);
- surgical and multidisciplinary treatment of rare cancers (soft tissue sarcomas, penile cancer, head and neck squamocellular tumors, peritoneal malignancies, etc);
- surgical treatment of solid tumors in pediatric patients;
- tailored, de-escalated surgery for early solid tumors with preservation of the quality of life;
- development of shared internal guidelines for cancers requiring different surgical specialties and expertises (complex surgery with resection/reconstruction of bony structures, major vessels, gynecological or urological procedures within abdominal surgery, etc);
- advanced laparoscopic/minimally invasive surgery for both early and complex solid tumors;
- continuous education and training is ensured by the organization of a monthly Journal Club in which each specific unit presents new advances in their specific field including their contributions to clinical research.

HIGHLIGHT

Long-term outcomes of resection versus transplantation for neuroendocrine liver metastases meeting the Milan criteria.

Maspero M., et al. AM J TRANSPLANT. 2022 Nov. DOI: 10.1111/ajt.17156.

The data from 104 consecutive patients undergoing either curative resection or transplantation for liver-only NELM meeting Milan criteria at a single center were retrospectively collected. 48 patients fit Milan criteria (transplantation group), 56 did not (resection group). After a median follow-up of 158 months for the transplantation group and 126 for the resection group, the 10-year survival rate was 93% for transplantation and 75% for resection. The 10-year disease-free survival rate was 52% for transplantation and 18% for resection. Transplantation was associated with improved survival at univariate analysis. The median disease-free interval between surgery and recurrence was 78 months for transplantation vs. 24 months for resection. The transplantation group had more multisite recurrences (48% vs.12%), while most recurrences in the resection group were intra-hepatic (88% vs 8%). The authors concluded that LT was associated with improved survival outcomes in NELM meeting the Milan criteria compared with LR.

Sentinel Node Biopsy Alone or With Axillary Dissection in Breast Cancer Patients After Primary Chemotherapy: Long-Term Results of a Prospective Interventional Study.

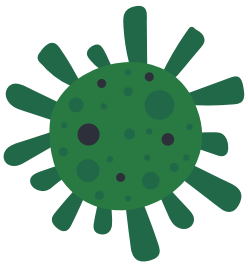
Martelli G.et al. ANNALS OF SURGERY. 2022 Nov; DOI: 10.1097/SLA.0000000000004562.

2020 guidelines do not recommend sentinel node biopsy (SNB) in most cN1 patients with clear SNs after primary chemotherapy (CT). In collaboration with the Surgery Department, we prospectively assigned SNB after primary chemotherapy to 353 consecutive cT2 cN0/1 patients to SNB only (if SNs were pN0) or completion axillary dissection (AD) (if SNs were pN1). Overall Survival (OS) and Disease-Free Survival (DFS) did not differ significantly between the groups by propensity score-weighted comparison.

Residual Adrenal Function after Multivisceral Resection with Adrenalectomy in Adult Patients.

Fiore M., et al. JAMA SURGERY. 2022 May. DOI: 10.1001/jamasurg.2021.7588.

The aim of the work was to evaluate the incidence of adrenal insufficiency (AI) in patients undergoing multivisceral resection (MVR) with en bloc adrenalectomy for retroperitoneal sarcoma. The authors concluded that AI after MVR with en bloc adrenalectomy was frequent, even in patients with adequate preoperative adrenal function. Despite this, adrenalectomy can be safely performed. Patients at risk should be monitored in the long term to exclude underrated impairment of adrenal function.

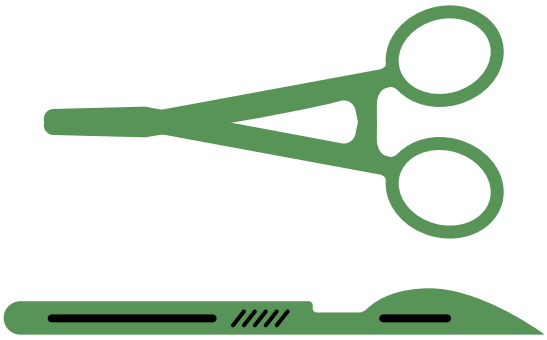


HIGHLIGHT

Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial.
Pastorino U., et al. ANNALS OF ONCOLOGY. 2022 Apr; DOI: 10.1016/j.annonc.2022.01.008.
The aim of this prospective study was to assess the additional value of the blood microRNA (miRNA) signature classifier (MSC) assay at the time of baseline low-dose computed tomography (LDCT) with the goal of personalizing lung cancer (LC) screening intervals. The authors found out that the combined use of LDCT and blood miRNAs at baseline predicts individual LC incidence and mortality, with a major effect of MSC for LDCT-positive individuals. These findings may have important implications in personalizing screening intervals.

Cytisine Therapy Improved Smoking Cessation in the Randomized Screening and Multiple Intervention on Lung Epidemics Lung Cancer Screening Trial.
Pastorino U., et al. JOURNAL OF THORACIC ONCOLOGY. 2022 Nov. DOI: 10.1016/j.jtho.2022.07.007.
The Screening and Multiple Intervention on Lung Epidemics randomized, controlled trial showed the efficacy and safety of cytisine, a very low-cost medication, for smoking cessation making it a useful treatment option for smoking cessation and a feasible strategy to improve low-dose computed tomography-screening outcomes with a potential benefit for all-cause mortality.

What is the best way to treat patients with stage IIA or IIB seminoma?
Giannatempo P., et al. LANCET ONCOLOGY. 2022 Nov. DOI: 10.1016/S1470-2045(22)00625-8.
The authors commented on the best way to treat patients with metastatic seminoma stage II. They presented the standard of care and future prospective. De-escalation strategies in stage IIA and IIB seminoma are a current unmet clinical need and could be implemented in the coming years. Available experimental data—which include reduced fields of radiotherapy, combinations of carboplatin plus radiotherapy, treatment reduction according to response, and use of surgery—provide inspiration for further improvement. Possible treatment options for stage IIA and IIB seminoma could be expanded to the use of proton therapy and improved by the implementation of more precise biomarkers, such as miRNA clusters. Patient preference has arisen as a fundamental criterion in the discussion of treatment options.



DEPARTMENT OF ONCOLOGY AND HAEMATOLOGY

- PEDIATRIC ONCOLOGY
- MEDICAL ONCOLOGY 1
  - *THORACO-PULMONARY MEDICAL ONCOLOGY*
  - *CLINICAL CANCER IMMUNOTHERAPY AND INNOVATIVE THERAPIES*
  - *GASTROENTEROLOGICAL MEDICAL ONCOLOGY*
  - *MEDICAL ONCOLOGY OF MELANOMA*
  - *MEDICAL BREAST ONCOLOGY*
- MEDICAL ONCOLOGY 2 - MESENCHYMAL AND RARE TUMORS
- MEDICAL ONCOLOGY 3 - HEAD AND NECK TUMORS
- HAEMATOLOGY
- PALLIATIVE CARE - HOSPICE, PAIN THERAPY AND REHABILITATION
- MEDICAL ONCOLOGY 4 - INTERNAL MEDICINE AND GERIATRIC CARE
- GENITOURINARY MEDICAL ONCOLOGY
- ONCOLOGICAL DAY HOSPITAL
- MEDICAL GENETICS
- CLINICAL PHARMACOLOGY

HEAD:

FILIPPO DE BRAUD

DEPARTMENT OF ONCOLOGY AND HAEMATOLOGY

The Department of Oncology and Haematology coordinates patient care and clinical research related to all solid, including rare, and haematological cancers, both in the adult and pediatric settings. The Department includes inpatient and outpatient services covering the entire spectrum from the early disease to end-of-life care, with trasversal services as the day hospital, pain and supportive care units, hemopoietic stem cell manipulation and cryopreservation laboratories and the blood unit, with its donors and apheresis centres, HLA typing and virology laboratories.

Its organizational structure, founded on units with a high level of specific commitment and expertise, allows the best quality of care for patients along with favouring comparisons and opportunities for professional and cultural growth for its physicians, nurses and biologists.

The continuous and rapid evolution of knowledge requires, in fact, that doctors dedicated to specific diseases keep up to date as to guarantee constant high quality and clinical appropriateness to their patients. Collaboration within the various units allows a process of continuous sharing and innovation in therapeutic strategies.

All decisions on diagnostic and therapeutic pathways are made within the framework of multidisciplinary meetings. The concept of "therapeutic strategy" guides clinical decisions and therefore our Department actively collaborates with the others. A strong cooperation with the Departments of Experimental Oncology and Molecular Medicine and the Department of Predictive Medicine and Prevention is in place for research purpose.

The Department is particularly engaged and competitive in the research and development of new anti-cancer drugs, including cell-therapies, both at national and international level. In this sense, exploiting clinical and translational research plays a fundamental role, and ensures that our patients are offered the best treatment strategy and/or access to cutting-edge, innovative drugs.

HIGHLIGHT

Adolescents and young adults with rhabdomyosarcoma treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) protocols: a cohort study.
Ferrari A., et al. LANCET CHILD ADOLESC HEALTH. 2022 June. DOI: 10.1016/S2352-4642(22)00121-3.
In this retrospective observational analysis, better outcomes for adolescent and young adult patients with rhabdomyosarcoma than those reported in epidemiological studies was found, supporting the inclusion of these patients in paediatric trials. However, the inferior outcomes in adolescent and young adult patients compared with those in children, enrolled in the same clinical trials and receiving similar therapy suggest that a tailored and intensive treatment strategy might be warranted for these patients.

Ibrutinib improves survival compared with chemotherapy in mantle cell lymphoma with central nervous system relapse.
Rusconi C., et al. BLOOD. 2022 Oct. DOI: 10.1182/blood.2022015560.
In this retrospective observational study, it was confirmed the role of ibrutinib, a bruton tyrosine kinase inhibitor able to overcame the blood-brain barrier, in mantle cell lymphoma patients with central nervous system recurrence; in this retrospective analysis, patients treated according to clinical practice with ibrutinib had a superior survival compared with patients treated with standard blood-brain barrier-penetrating chemotherapy.

Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up.
Casali PG., et al. ANN ONCOL. 2022 Jan. DOI: 10.1016/j.annonc.2021.09.005.
INT coordinates the sarcoma and the head & neck cancer domain in EURACAN, the European Reference Network (ERN) covering all rare solid cancer of the adult. INT covers 9 of the 10 domains of EURACAN, i.e. sarcoma, rare gynecological and genitourinary cancer, neuroendocrine tumours, rare digestive tract cancer, endocrine tumours, head & neck cancer, rare thoracic tumours, and rare skin cancer & eye melanoma. Within, EURACAN, INT coordinated the update of the clinical practice guidelines for gastrointestinal stromal tumours, alongside with soft tissue and bone sarcomas, in a joint effort with ESMO and GENTURIS (i.e. the ERN of genetic cancer risk syndromes).

Fasting-Mimicking Diet Is Safe and Reshapes Metabolism and Antitumor Immunity in Patients with Cancer.
Vernieri C., et al., CANCER DISCOV. 22 Jan. DOI: 10.1158/2159-8290.CD-21-0030.
Evidence suggests that in tumor-bearing mice, cyclic fasting or fasting-mimicking diets (FMD) enhance the activity of antineoplastic treatments by modulating systemic metabolism and boosting antitumor immunity. INT conducted a clinical trial to investigate the safety and biological effects of cyclic FMD in combination with standard antitumor therapies. In 101 patients, the FMD was safe, feasible, and resulted in a consistent decrease of blood glucose and growth factor concentration, similarly to preclinical experiments. Integrated transcriptomic and deep-phenotyping analyses revealed a reshaping of anticancer and other immune signatures associated with better clinical outcomes in patients with cancer. These findings lay the foundations for phase II/III clinical trials aimed at investigating FMD antitumor efficacy in combination with standard antineoplastic treatments.

Temozolomide Followed by Combination With Low-Dose Ipilimumab and Nivolumab in Patients With Microsatellite-Stable, O6-Methylguanine-DNA Methyltransferase-Silenced Metastatic Colorectal Cancer: The MAYA Trial.
Morano F., et al. J CLIN ONCOL. 2022 May. doi: 10.1200/JCO.21.02583.
This paper reports the results of a multicenter, single-arm phase II trial (MAYA) evaluating the efficacy and safety of an immune-sensitizing strategy with temozolomide priming followed by a combination of low-dose ipilimumab and nivolumab in patients with microsatellite-stable (MSS) and O6-methylguanine-DNA methyltransferase (MGMT)-silenced metastatic colorectal cancer (mCRC).
The MAYA study provided proof-of-concept that a sequence of priming temozolomide followed by a combination of low-dose ipilimumab and nivolumab may induce durable clinical benefit in MSS and MGMT-silenced mCRC.

HIGHLIGHT

Cabozantinib as First-line Treatment in Patients With Metastatic Collecting Duct Renal Cell Carcinoma: Results of the BONSAI Trial for the Italian Network for Research in Urologic-Oncology (Meet-URO 2 Study).

Procopio G., et al., JAMA Oncol. 2022 Jun. DOI: 10.1001/jamaoncol.2022.0238.

This article reports the results of a trial (BONSAI) specifically designed to evaluate prospectively the efficacy of cabozantinib in metastatic collecting duct carcinoma (mCDC), a rare type of non-clear cell renal cell carcinoma (ncRCC) with poor prognosis and no standard treatments.

Of the 23 patients with a confirmed mCDC diagnosis who started the treatment, 3 patients presented stable disease, 1 patient achieved a complete response, and 7 a partial response (ORR was 35%). The median progression-free survival was 4 months, the median OS was 7 months.

The trial showed encouraging efficacy of cabozantinib in untreated patients with mCDC, and gnited further investigations to advance the molecular understanding of this rare cancer histotype.

Machine Learning Using Real-World and Translational Data to Improve Treatment Selection for NSCLC Patients Treated with Immunotherapy.

Prelaj A., et al., CANCERS (BASEL). 2022 Jan. DOI: 10.3390/cancers14020435.

In advanced non-small cell lung cancer, programmed death ligand 1 (PD-L1) remains the only predictive biomarker for immunotherapy (IO). This study aimed at using artificial intelligence (AI) and machine learning (ML) tools to improve biomarkers predictivity in aNSCLC patients treated with IO. Real world data and the blood microRNA signature classifier (MSC) were used. Patients were divided into responders (R) and non-responders (NR) to determine if the overall survival of the patients was likely to be shorter or longer than 24 months from baseline IO. The results suggest that the integration of multifactorial data provided by ML techniques is a useful tool to select NSCLC patients as candidates for IO.

Phenotypic Composition of Commercial Anti-CD19 CAR T Cells Affects In Vivo Expansion and Disease Response in Patients with Large B-cell Lymphoma.

Monfrini C., et al., CLIN CANCER RES. 2022 Aug. DOI: 10.1158/1078-0432.CCR-22-0164.

We investigated the role of CAR T bag content in a real-life setting. Residual cells obtained after washing 61 anti-CD19 CAR T product bags were investigated to identify tisagenlecleucel/Tisa-cel and axicabtagene ciloleucel/Axi-cel phenotypic features associated with postinfusion CAR T-cell in vivo expansion and with response and survival. While Tisa-cel was characterized by a significant enrichment in CAR+CD4+ T cells with central memory and effector phenotypes and lower rates of CAR+CD8+ with effector memory and naïve-like phenotypes as compared with Axi-cel, the two products displayed similar expansion kinetics. In vivo CAR T-cell expansion was influenced by the presence of CAR T with a CD8+ T central memory signature in both Tisa-cel and Axi-cel infusion products and was significantly and positively associated with response and progression-free survival. These data indicate that despite the great heterogeneity of Tisa-cel and Axi-cel products, the differentiation status of the infused cells mediates CAR T-cell in vivo proliferation necessary for antitumor response.

Knowledge, use and attitudes of healthcare professionals towards patient-reported outcome measures (PROMs) at a comprehensive cancer center.

Brunelli C., et al. BMC Cancer. 2022 Feb. DOI: 10.1186/s12885-022-09269-x.

Despite evidence of the positive impact of routine assessment of patient-reported outcome measures (PROMs), their systematic collection is not widely implemented in cancer care. This study aimed at assessing the knowledge, use and attitudes of healthcare professionals (HCPs) in clinical practice and research and to explore respondent-related factors associated with the above dimensions, by the administration of an ad hoc online survey to all HCPs at INT. The survey indicated an acceptable level of knowledge of common PROM tools but low usage in practice. Based on the generally positive attitude of HCPs, routine implementation of ePROMs and adequate resources and training are in setting.

DEPARTMENT OF DIAGNOSTIC IMAGING AND RADIOTHERAPY

- NUCLEAR MEDICINE
  - *NUCLEAR MEDICINE THERAPY*
  - *PET DIAGNOSTICS*
- RADIOTHERAPY
  - *RADIOTHERAPY OF GENITOURINARY TUMORS*
  - *RADIOTHERAPY OF BREAST CANCERS*
  - *PEDIATRIC RADIOTHERAPY*
- MEDICAL PHYSICS
  - *RADIOLOGICAL PROTECTION*
- DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY
  - *INTERVENTIONAL ULTRASOUND*
  - *INTERVENTIONAL ONCOLOGY*
  - *PEDIATRIC ONCOLOGY DIAGNOSTICS*
  - *BREAST RADIOLOGY*
  - *MUSCULOSKELETAL ONCOLOGY DIAGNOSTICS*

DEPARTMENT OF DIAGNOSTIC IMAGING AND RADIOTHERAPY

HEAD:

ALFONSO MARCHIANÒ

In the Department of Diagnostic Imaging and Radiotherapy equipment, resources and structures in which different professional profiles, such as radiologists, nuclear doctors, radiation therapists, oncologists, physicists, chemists, radiochemists, biologists, engineers, biometrists operate with close interdisciplinary.

The Department is oriented towards the implementation of biological imaging and the use of imaging to optimize radiotherapy and development of new radiopharmaceuticals, which allow both the selective visualization of neoplasms and their treatment, and approaches of metabolic radiotherapy.

The Radiodiagnostic Facilities are dedicated to the diagnosis, staging and monitoring of neoplastic diseases. Conventional and tomographic radiographs, magnetic resonance imaging (MRI), mammography, ultrasound and radioguided biopsies are performed. Computed tomography (CT), angiography, general interventional radiology and intralesional treatments, as well as radiological examinations for the evaluation of the gastro-enteric apparatus are also routinely performed.

The Nuclear Medicine Structure makes use of single photon emission tomography (SPECT) gamma cameras and positron emission tomography (PET) scans to diagnose most oncological pathology. Modern SPECT/CT and PET/TC hybrid machines operate in this sector, which ensures the fusion of morphological and functional images, allowing better diagnostic accuracy.
The radiopharmaceuticals needed for diagnosis are produced in the Radiochemistry Laboratories, A Section equipped with protected chambers are dedicated to patients undergoing radiometabolic treatments.
External beam radiotherapy (3D conformational radiotherapy, Intensity Modulated Radiation Therapy - Volumetric Modulated Arc Therapy - VMAT, and Image-Guided Radiotherapy - IGRT) represents the main activity of the Radiotherapy Unit, also dedicated to treatments with high dose brachytherapy (HDR-BT) as well as combined chemo-radiotherapy which take place in a small hospital ward for a total of 8 beds. Medical Physics Unit supports the Radiotherapy Unit for treatment planning and dosimetric estimates.

Research activities are carried out in collaboration with medical oncologists and surgeons, both in the field of diagnosis and therapy. In addition, researchers are involved in both methodological and technological research (such as the development of new methods of investigation and application of new procedures), as well as translational research (i.e. development and study of new radiopharmaceuticals for diagnostics and therapy). Activities also require collaboration with Information Technologies to network all systems, develop customized programs and the implement software for better patient management and data use.

HIGHLIGHT

The Department of of Diagnostic Imaging and Radiotherapy is equipped with a large number of high-tech instruments, and has a renewed fleet of machines of great technical value (3 Magnetic Resonances, 2 Multilayer CT, 2 PET/CT, 2 Digital Mammographs, 2 Angiographs, 2 SPECT/CT gamma cameras, 1 SPECT gamma camera, 4 Traditional Radiological Devices, 2 Orthocline, 9 Ultrasound Instruments, 5 Accelerators for RT, various portable ultrasound and radiological instruments for the patient's bedside needs).

Treatment time and circadian genotype interact to influence radiotherapy side effects. A prospective European validation study using the REQUITE cohort.

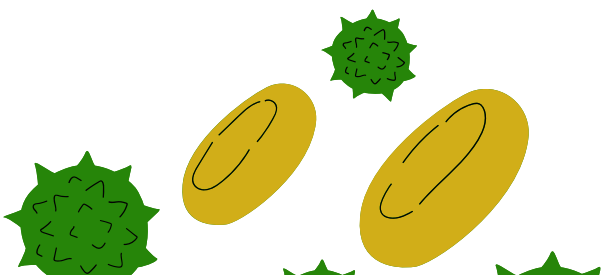
Webb AJ., et al. EBIOMEDICINE. 2022 Oct. DOI: 10.1016/j.ebiom.2022.104269.

Treatment time and circadian genotype interact to influence radiotherapy side-effects. A prospective European validation study using the REQUITE cohort of patients with breast cancer was conducted to evaluate a time-of-day effect upon the incidence of acute and late radiation toxicity and to validate the association of genetic circadian variants with late toxicity. The results showed that radiation toxicity, particularly late atrophy, can be sensitive to treatment time dependant on circadian genotypes.

A global evaluation of advanced dosimetry in transarterial radioembolization of hepatocellular carcinoma with Yttrium-90: the TARGET study.

Lam M., et al. EUR J NUCL MED MOL IMAGING. 2022 Aug. DOI: 10.1007/s00259-022-05774-0.

TARGET is an international, multi-center, retrospective study to investigate the relationships between tumor absorbed dose (TAD) or normal tissue absorbed dose (NTAD) and clinical outcomes in a large group of real-world patients with hepatocellular carcinoma treated with yttrium-90 glass microspheres. The results show a significant association between TAD and overall survival. The lack of relationship between grade 3 or higher hyperbilirubinemia and NTAD suggests the possibility to safely deliver higher absorbed dose within the tumor.



HIGHLIGHT

Relapsing pediatric non-rhabdomyosarcoma soft tissue sarcomas: The impact of routine imaging surveillance on early detection and post-relapse survival.

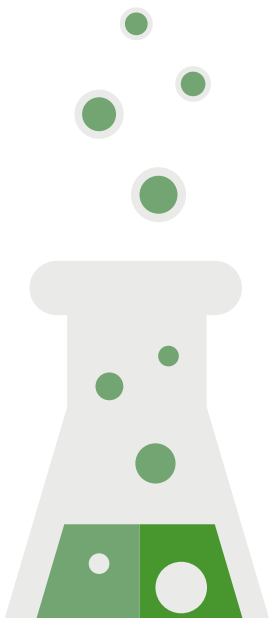
Morosi C., et al. EUR J CANCER. 2022 Nov. DOI: 10.1016/j.ejca.2022.08.028.

This retrospective single-institutional study investigates the potential role of routine surveillance imaging for detecting recurrent tumor, and its impact on post-relapse survival in patients with relapsing pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). The present analysis concerned 86 patients. Our analysis show that surveillance imaging do not result in recurrences being detected earlier. Conversely, routine imaging is extremely important for identifying lung involvement.

Occurrence of breast-cancer-related lymphedema after reverse lymphatic mapping and selective axillary dissection versus standard surgical treatment of axilla: A two-arm randomized clinical trial.

Gennaro M., et al. CANCER. 2022 Dec. DOI: 10.1002/cncr.34498.

The present two-arm prospective randomized clinical trial aims to ascertain whether axillary reverse mapping and selective axillary dissection (ARM-SAD) can reduce the risk of breast-cancer-related lymphedema (BCRL), compared with standard axillary dissection (AD), in patients with node-positive breast cancer. A significantly lower rate of BCRL after ARM-SAD is being emerged and confirmed by a multimodal analysis that included the physiatrist's findings, excess arm volume, and lymphoscintigraphic findings. Our results encourage a change of surgical approach when AD is still warranted.



RESEARCH CORE

TECHNICAL RESOURCES AND FACILITIES

MOLECULAR ANALYSIS PLATFORMS

Technology innovation and next-generation sequencing (NGS) play a fundamental role in precision medicine. INT is at the forefront for applying NGS technologies in diagnosis and translational research in order to identify novel biomarkers and therapeutic targets, as well as for patient stratification by mutational analysis. Thanks to last generation instrumentation, INT promotes basic and translational research in the field of precision medicine, and supports therapeutic decisions and diagnosis.
The following technologies are available at the Department of Advanced Diagnostics:

- DNA and RNA extraction from fresh/fresh-frozen/FFPE tissue samples, as well as from cell lines and plasma (liquid biopsy) (QIAcube and QIASymphonySP, Qiagen);
- quantification and quality assessment of nucleic acids (4200 Tapestation, Agilent; Nanodrop and Qubit, Thermo Fisher);
- library preparation, quantification and sequencing for NGS approaches on FFPE/fresh-frozen tumor and plasma samples (liquid biopsy), both with ThermoFisher and Illumina solutions;
- Gene expression profiling analysis, with microarray-based technologies (Gene Chip System 3000, Affymetrix, Thermo Fisher), RNAseq (Illumina, Takara and Lexogen libraries preparations kits) and NanoString technologies (nCounter, Nanostring);
- Spatial transcriptomic and proteomic experiments on tumor FFPE and frozen sections (GeoMx DSP, NanoString);
- Single cell RNAseq profiling (ChromiumX, 10X Genomics)
- M220 Focused-ultrasonicator (Covaris) for DNA shearing;
- QuantStudio 12K Flex Real-Time PCR System with Twister Automation Robot for quantitative real-time PCR (Thermo Fisher);
- Ion Chef Instrument, Ion PGM and Ion S5XL (Thermo Fisher) and NextSeq 500 (Illumina) for NGS applications;
- Hamilton Microlab STARlet for liquid handling.

RESEARCH CORE

TECHNICAL RESOURCES AND FACILITIES

BIOINFORMATICS

The team utilizes advanced computational tools and algorithms to extract insights from complex biological data. The team works closely with researchers across various disciplines, providing support and guidance at every stage of their projects - from experimental design to data analysis (data quality control and pre-processing, sequence alignment, variant calling, functional annotation, and downstream analysis) and interpretation. Our activities include data processing and management, developing and implementing algorithms for data analysis, designing and deploying bioinformatics pipelines, developing and maintaining databases and web interfaces for data retrieval, as well as providing training and support to researchers on bioinformatics tools and methodologies.

IMAGING

The Department of Experimental Oncology is equipped with the BioRad Radiance 2000 and Leica SP8 AFC AOBS WLL HyD laser confocal microscopes for live cell imaging, sequential and simultaneous bright field image collection of up to 8 channels and employment of a wide range of fluorescent dyes. Moreover, the INCUCYTE SX5 HD/3CLR SYS PKG allows the acquisition of images in High Definition, providing an automated workflow platform for live cell imaging and integrated analysis of cell phenotypes and kinetics. The Azure 600 (Biosystems) imaging workstation allows to digitally acquire western blot images developed by chemiluminescence, exploiting NIR, RGB, UV and BLUE fluorescence, imaging of colorimetric and silver stain gels, cell-culture plates and other clear and colorimetric samples.

FLOW CYTOMETRY AND CELL SORTING

In the Department of Experimental Oncology the facility provides support and advanced equipment to the researchers 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™ IIu cell sorter and 2 BD FACSCelesta™ flow cytometers. A MALDI imaging is also available. Moreover, several Cytoflex are dislocated in the laboratories Department of Experimental Oncology. One MACSQuant Tyto cell sorter is also available at Medical Oncology Department.

RESEARCH CORE

TECHNICAL RESOURCES AND FACILITIES

CIRCULATING TUMOR CELLS (CTC) CAPTURE

The DEPArray platform (Silicon Biosystem) combines imaging technologies with manipulation and recover of individual, rare cells from a heterogeneous sample. The DEPArray also offers applications at tissue level allowing digital sorting of pure cells derived from FFPE sections that can be used for high resolution molecular analyses. Parsortix (Angle) is a flexible micro-fluidic technology for the enrichment of CTC from whole blood or PBMC, also allowing isolation of CTC clusters for studies of the interaction between CTCs and microenvironment. Samples recovered from Parsortix can be used for subsequent molecular/*in vitro*/*in vivo* analyses or in association with DEPArray for isolation of pure CTC. RareCyte provides multiplexed fluorescent imaging systems, and reagents to investigate the spatial context and liquid biopsies.

IMMUNOHISTOCHEMISTRY

Histological and cytological processing through a wide range of histological techniques, immunohistochemistry, *in situ* hybridization, and autoradiography. The Vectra 3 automated quantitative pathology imaging system performs immuno-profiling and phenotyping of multiple immune cell subsets in situ in FFPE tissue sections (Phenoptics), to increase knowledge in prognostic and predicting value of immune contexture in neoplastic regions.

LABORATORY ANIMAL FACILITY

Authorized by the Italian Ministry of Health for housing of transgenic and immunodeficient mice under specific pathogen-free conditions (SPF). It is composed by 9 independent rooms that host 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 the veterinarian specialized in laboratory animals. The animal house is equipped with IVIS Spectrum (bioluminescence, fluorescence, 3D images), RS 2000 Small Animal and Cell Irradiator, X-RAD SmART Small Animal Image Guided Irradiator and dedicated micro-PET scanner (GE Healthcare eXplore VISTA).

RESEARCH CORE

TECHNICAL RESOURCES AND FACILITIES

PROTEOMICS/METABOLOMICS

A fully equipped laboratory (NuMeLab) is dedicated to process biological material and perform analyses in clinical biochemistry, high resolution mass spectrometry for lipidomics, HPLC/mass spectrometry for hormonal and pharmacological analyses, gas chromatography/mass spectrometry for metabolomics analyses, LC Orbitrap, ICP mass spectrometry for elemental analyses. The availability of the dedicated software LipidSearch, together with the skills of laboratory staff, allows for lipidomics data processing to help identify etiological, early detection or drug response biomarkers. The NuMeLab also offers innovative applications of mass spectrometry-based breath analysis for a non-invasive early diagnosis of head/neck and breast cancers. The NuMeLab also includes a blood bank (about 175.000 samples) of the participants into lifestyle intervention randomized trials (the MeMeMe, DIANA-5, and BRCA trials).

TISSUE AND CELL REPOSITORY

The Departments have access to a large bank of frozen and FFPE of normal and 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. Samples are provided to studies after approval by the Internal Review Board and the Ethical Committee.

MISCELLANEOUS

In the field of diagnostics and therapy, INT stands out for its latest generation equipment which, in addition to their daily clinical use, is also used for research purposes. Favored by an adequate hardware and software infrastructure, in INT diagnostic and therapy work in complete synergy, both in the clinical and research fields. In some specific cases, INT contributes in a research context also to the technological evolution and optimization of peculiar equipment, and to the implementation of new applications.

RESEARCH CORE

SUPPORTING STRUCTURES AND OFFICES

ANIMAL WELFARE BODY

The Animal Welfare Body (Organismo per il benessere animale, OPBA) is the committee responsible to monitor *in vivo* experiments. OPBA aims to support the scientific activity of researchers by allowing them to carry out *in vivo* research in compliance with current legislation, according to the international standards of Good Laboratory Practice and in full compliance with the 3Rs principle: Replacement, Reduction, Refinement. The OPBA of our Institute has 5 members: the Animal Welfare Manager, one Veterinarian specialized in laboratory animals, two Scientific Members and a Biostatistician.

DATA WAREHOUSE

The Institutional Data Warehouse is used for both research and strategic-management purposes, such as monitoring the Operating Theatre performance and the Oncological Outpatient Service performance with a panel of indicators (KPIs). DWH is used also to identify potential patients for clinical trials, to count retrospectively the potential number of patients for new prospective studies, understand the feasibility of retrospective observational studies, extract data for monitoring and bench marking as well as for accreditation to national and international networks.

INTERNAL REVIEW BOARD

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

MOLECULAR TUMOR BOARD

The Molecular Tumor Board (MTB) is a board with a strong multidisciplinary focus, integrating the knowledge and experience of professionals from different fields. 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 the most suitable and cost-effective panel of genes. It also deals with 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 discussed patients' clinical-genomic data to define the optimal treatment.
In May 2020, the first institutional MTB was established at INT.

RESEARCH CORE

SUPPORTING STRUCTURES AND OFFICES

GRANT OFFICE

The INT Grant Office (GO) 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.

CLINICAL TRIALS CENTER

The Clinical Trials Center (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 phases. The organization of the CTC and the presence of dedicated and trained staff (clinical study coordinators and research nurses) allow to conduct the clinical trials in compliance with the good clinical practice (GCP). A special team joining expertise from the Grant Office ad the CTC is dedicated to trials with Advanced Therapy Medicinal Products (ATMP), such as gene, cell and CAR-T therapies.

TECHNOLOGY TRANSFER OFFICE

INT Technology Transfer Office (TTO) was created in 2009 to value research results from a scientific and economic viewpoint, to optimize technology transfer and intellectual property right management. The TTO offers support 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.

ETHICS COMMITTEE

The institutional Ethics Committee reviews all new clinical studies submitted by investigators and approved by the scientific Institutional Review Board.

In 2022, 218 new studies were submitted to the Ethics Committee for approval: 92 were interventional trials, 76 of which were sponsored by pharmaceutical companies and 142 were investigator-driven; 126 were observational, among which a total of 7 were sponsored by pharmaceutical companies and 119 were investigator-driven. The number of clinical trials submitted according to the EU Directive 2001/20/EC in 2022 was 78.

The clinical trial evaluation system in Europe has been facing a radical change starting from 31 January 2022, with the full application of the new EU Regulation no. 536/2014. From that date, a one-year transition period begun.
During this period, applications for clinical trial authorization under the past EU Directive could still be submitted.
A dedicated portal has been developed for the management of all clinical trials in Europe, the Clinical Trials Information System (CTIS), which will be crucial to enhance transparency and strengthen collaboration, exchange information and know how for decision-making among, or within, Member States. The Secretariat of the Ethics Committee made all steps to fully adopt CTIS and evaluate clinical trials according to the new legislation.

ETHICS COMMITTEE

In 2022, 6 clinical trials were submitted according to the new EU Regulation. The transition period ended on June 6th 2023. From then on, new CETs (Territorial Ethics Committees) are operating in Italy. Italian Regions appointed a total of 40 CETs, 6 of which by the Lombardy Region:

- Lombardia 1 - IRCCS Ospedale San Raffaele, Milano
- Lombardia 2 - IRCCS Istituto Europeo di Oncologia - IRCCS Centro Cardiologico Monzino, Milano
- Lombardia 3 - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano - ASST Grande Ospedale Metropolitano Niguarda, Milano - Fondazione IRCCS San Gerardo dei Tintori, Monza
- Lombardia 4 - Fondazione IRCCS Istituto Neurologico Carlo Besta - Fondazione IRCCS Istituto Nazionale dei Tumori – Milano
- Lombardia 5 - IRCCS Istituto Clinico Humanitas – Rozzano, Milano
- Lombardia 6 - Fondazione IRCCS Policlinico San Matteo di Pavia - ASST Ospedale Papa Giovanni XXIII di Bergamo - ASST degli Spedali Civili di Brescia

MEMBERS OF THE ETHICS COMMITTEE EVALUATING CLINICAL STUDIES IN 2022

Giovanni Apolone, Emilio Bombardieri, Carlo Celentano, Emanuele Cereda, Francesca Crippa Floriani, Maurizio D'Incalci, Paolo Foa, Momcilo Jankovic, Vito Ladisa, Renato Mantovani, Antonio Miadonna, Agostino Migone de Amicis, Monica R. Miozzo, Roberta E. Pavesi, Tullio Proserpio, Antonio G. Rampoldi, Francesco Scaglione, Marta Scorsetti, Serena Togni, Valter Torri, Antonio Triarico, Rita Vetere

EDUCATION

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

The Open University's Affiliated Research Centre (ARC) Programme supports the provision of doctoral training in the UK, Europe and worldwide, making possible to pursue a research degree from Open University in a centre of research excellence. Students are enrolled to join ongoing projects in different fields of cancer supervised both by INT's Principal Investigators and by external experts.

28 Students in total enrolled enrolled in INT's PhD Programme in 2022: **22** candidates applied to the spring selection and **6** additional candidates applied to the autumn's selection

2 Students awarded their PhD upon defense of their work in front of an examination panel, including internal and international examiners (with a specific competence in their project's field)

The INT-OU PhD Programme offers a variety of activities dedicated to support PhD students career development. Indeed, courses dedicated to PhD Programme participants are organized every year on cross-cutting themes, both scientific and on "soft skills". Moreover, many scientific seminars and workshops relating to professional advancement (paper and grant writing, scientific dissemination), and other scientific seminars of particular interest are organized throughout the year. Importantly, OU-PhD Students have a program of journal clubs and data sessions which gives the opportunity to every student to discuss recent scientific papers with peers with different expertise and present their project data to all researchers from the Institute.

EDUCATION

INT is a partner of the Università degli Studi di Milano and several professors from the University Department of Oncology and Haematoncology work here as heads of departments, physicians and researchers. INT offers postgraduate medical training in a wide range of disciplines connected with oncology, and medical students and students from the biology and nursing faculties train at INT for their degrees.

246 Postgraduate students from Università degli Studi di Milano hoted by INT in 2022.

48 Students doing the intership.

Over the past 4 years, INT has been actively engaged in a close partnership with Politecnico di Milano, particularly in the realm of education and training. Joint PhD projects have been conducted, enabling medical oncologists from INT to enroll as PhD students at Politecnico's DEIB (Department of Electronics, Informatics, and Bioengineering). These projects focus on the application of AI methods in clinical and translational cancer research. In addition, it is worth noting that several INT-led European and national projects in the field of AI and Oncology were funded in recent years (I3LUNG, IDEA4RC, BD4QOL, etc.), successful endeavors that further validate the significance and impact of these collaborative partnerships between INT and technological partners such as the Politecnico.

This successful collaboration has paved the way for further steps forward, and in particular the activation of new joint PhDs planned for 2023 through which the institutions will continue their close collaboration, particularly in data science and AI-related research projects. This collaborative effort will foster the development of future leaders in the field of AI in oncology, nurturing a new generation of experts who possess a deep understanding of both medical and technological aspects.

PROJECTS GRANTED IN 2022

INTERNATIONAL CALLS: INT-COORDINATED GRANTED PROJECTS

PI	TITLE	TOTAL FUNDING	BUDGET FOR INT	CALL
A. Prelaj	I3LUNG: Integrative science, Intelligent data platform for Individualized LUNG cancer care with Immunotherapy	€ 9.996.695,00	€ 1.607.247,00	HE - HEALTH
A. Trama	IDEA4RC: Intelligent Ecosystem to improve the governance, the sharing and the re-use of health Data for Rare Cancers	€ 8.190.468,13	€ 849.280,00	HE - HEALTH
G. Apolone	EUOnQoL: Quality of Life in Oncology: measuring what matters for cancer patients and survivors in Europe	€ 10.607.311,00	€ 1.913.271,00	CANCER MISSION
P. Casali	JANE: Joint Action on Networks of Expertise	€ 3.629.146,39	€ 685.553,28	EU4HEALTH - JA

TOTAL BUDGET FOR INT: € 5.055.351,28

PROJECTS GRANTED IN 2022

INTERNATIONAL CALLS: INT GRANTED AS PARTNER

PI	TITLE	BUDGET FOR INT	CALL
A. Caraceni	MYPATH: Developing and implementing innovative Patient-Centred Care Pathways for cancer patients	€ 323.935,00	HE - HEALTH
A. Caraceni	INSPIRE: INtegrated Short-term Palllative REhabilitation to improve quality of life and equitable care access in incurable cancer	€ 184.068,00	HE - HEALTH
A. Ferrari	STRONG-AYA Initiative: improving the future of young adults with cancer	€ 318.750,00	HE - HEALTH
L. Gangeri	EU-NAVIGATE: Implementation and evaluation of a navigation intervention for people with cancer in old age and their family caregivers	€ 268.750,00	HE - HEALTH
A. Ferrari	MELCAYA: Novel health care strategies for melanoma in children, adolescents and young adults	€ 200.003,00	CANCER MISSION
S. Di Cosimo	CAN.HEAL: Building the EU Cancer and Public Healths Genomics Platform	€ 19.260,00	EU4HEALTH
A. Ferrari, M. Terenziani	EU-CAYAS-NE: EU Network of Youth Cancer Survivors	-	EU4HEALTH
F. De Braud	CCI4EU: Comprehensive Cancer Infrastructures for Europe	€ 351.875,00	CANCER MISSION
G. Apolone	ECHoS: Establishing of Cancer Mission Hubs: Networks and Synergies	€ 127.000,00	CANCER MISSION
G. Procopio	CARE1: First line randomized study platform to optimize treatment in patients with metastatic renal cell carcinoma	€ 371.250,00	CANCER MISSION
A. Gronchi	STREXIT2: A pragmatic clinical study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with high risk retroperitoneal sarcoma	€ 108.750,00	CANCER MISSION
D. Mezzanzanica	DISRUPT: On-chip tomographic microscopy: a paraDIgm Shift for RevolUtionizing lab-on-a-chiP bioimaging technology	€ 285.000,00	EIC PATHFINDER
R. Lanocita	IMAGIO: Imaging and Advanced Guidance for Workflow Optimization in Interventional Oncology	€ 100.000,00	IHI
U. Pastorino	LEAP: The Lung EArly Proteins Project	€ 53.784,00	NIH NCI (USA CALLS)

TOTAL BUDGET FOR INT: € 2.427.425,00

PROJECTS GRANTED IN 2022

NATIONAL CALLS: INT-COORDINATED GRANTED PROJECTS

PI	TITLE	BUDGET FOR INT	CALL
P. Perego	Dissecting the role of tau in ovarian carcinoma pathogenesis and drug resistance	€ 225.000,00	PNRR
S. Sieri	Beyond BMI: external exposome, dysbiosis and systemic inflammation in the development of overweightrelated chronic diseases in women	€ 323.585,00	PNRR
E. Jachetti	Alternative functions of mast cells foster castration resistance but inhibit neuroendocrine prostate cancer	€ 629.000,00	AIRC - IG
S. Kusamura	Unfolding the interactions between cancer cells and immunity in the tumor microenvironment of Pseudomyxoma Peritonei	€ 820.000,00	AIRC - IG
M. Moro	The “LKB1 connection”: role of LKB1 loss in promoting NSCLC aggressiveness through tumor microenvironment corruption	€ 733.000,00	AIRC - IG
L. Rivoltini	Persisting myeloid dysfunctions after curative surgery: effect on cancer recurrence and impact of dietary intervention	€ 867.000,00	AIRC - IG
A. Cicchetti	Improving the success rate for thoracic radiotherapy through specific cardiac substructure dosimetry: location matters	€ 499.991,25	AIRC - MFAG
U. Pastorino	Artificial Intelligence tools integrating blood biomarkers and radiomics to define lung cancer risk in computed tomography screening programs	€ 377.000,00	Ricerca Finalizzata
L. Roz	Tackling immunomodulatory properties of stromal cells to improve therapeutic strategies in lung cancer	€ 262.500,00	Ricerca Finalizzata
M. Di Modica	Role of gut miCrobiotA in the Recurrence of HER2-positive breaSt cancer (CARES)	€ 30.000,00	Berlucchi
C. Ghidoli	Studio multicentrico randomizzato di screening del tumore polmonare con CT del torace a basse dosi (LDCT) associato a prevenzione primaria e riduzione delle co-morbidita’ in forti fumatori ad alto rischio.	€ 30.000,00	Roche

TOTAL BUDGET FOR INT: € 4.767.076,25

PROJECTS GRANTED IN 2022

NATIONAL CALLS: INT GRANTED AS PARTNER

PI	TITLE	BUDGET FOR INT	CALL
P. Corradini	A multiomics approach to identify signatures of response and resistance to immunotherapy in R/R Diffuse Large B-cell Lymphoma	€ 200.000,00	PNRR
D. Mezzanzanica	Overcoming PARPi resistance in ovarian cancer: from biology to clinical application	€ 260.000,00	PNRR
L. Roz	From diagnostic to theranostic CXCR4-targeting PET probe. Proof of concept in Non Small Cell Lung Cancer (NSCLC)-PDX model	€ 362.000,00	PNRR
P. Corradini	LSH-TA Initiative	€ 1.600.000,00	PNC
A. Cannarozzo, A. Turi	PNC TT NETWORK Initiative	€ 72.225,00	PNC

TOTAL BUDGET FOR INT: € 2.494.225,00

SELECTED CLINICAL TRIALS

Clinical trials have been selected according to the following characteristics: i) INT as a promoter ii) no-profit clinical trials iii) interventional or prospective studies.

A MULTICENTER PROSPECTIVE OBSERVATIONAL STUDY ON CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR LYMPHOMA: MONITORING FEASIBILITY, EFFICACY, TOXICITY AND BIOMARKERS IN A REAL-LIFE SETTING

Promoter: INT
Principal Investigator: Paolo Corradini
Centers: all Italian hematological centers approved by regulatory authorities for CAR T- cell therapy administration
Accrual: ongoing
Primary objectives: Feasibility and efficacy of the treatment in the real life practice
Secondary objectives: evaluation of Outcome [Response rate (ORR), Overall survival (OS), Progression free survival (PFS), duration of response (DoR) non-relapse mortality (NRM)]; Evaluation of safety (CRS, neurotoxicity, infections, cytopenias, B cell aplasia); Comparison of the different CAR T-cell products (time from patient screening to infusion, disease response and safety); Characterization of biomarkers of early response (circulating tumor cell free DNA versus PET and CT scans); Characterization of toxicity biomarkers; Analysis of immune reconstitution.

PILOT PHASE II STUDY OF SELINEXOR IN COMBINATION WITH IFOSFAMIDE, ETOPOSIDE AND DEXAMETHASONE (S-IDE) IN PATIENTS WITH RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMAS

Promoter: INT
Principal Investigator: Paolo Corradini
Centers: nine Italian hematological centers
Accrual: ongoing
Primary objectives: to define the overall response rate (ORR) (complete response plus partial response) after 4 courses of selinexor when combined to ifosfamide, etoposide and dexamethasone (S-IDE)
Secondary objectives: duration of response, DOR; 18-months Progression Free Survival, PFS; 18-months Overall Survival, OS; Treatment Related Mortality, TRM; Complete Response rate (CR) by histotypes [angioimmunoblastic T cell lymphoma (AITL), anaplastic ALK negative lymphoma (ALK neg), peripheral T cell lymphoma not otherwise specified (PTCL-NOS), T helper follicular lymphoma (TFH)]; Proportion of patients able to undergo allogeneic SCT; Adverse events (grading/onset/severity) according to SOC and within the CTCAE v.5.0 category.

SELECTED CLINICAL TRIALS

APOLLO 11 CONSORTIUM IN ADVANCED LUNG CANCER PATIENTS TREATED WITH INNOVATIVE THERAPIES: INTEGRATION OF REAL WORLD DATA AND TRANSLATIONAL RESEARCH.

Promoter: INT
Principal Investigator: Arsela Prelaj
Centers: 48 Italian centres
Accrual: ongoing
Primary objectives: to build a strong long-lasting Italian lung cancer network (in 48 Italian centres) by creating a long-term, decentralized (settled locally in each centre) but standardized national database on real world data with an associated multilevel biobank.
Secondary objectives: i) to establish the consortium by activating at least 20 of the 48 centres involved in data collection within the database, and by activating at least 10 biobanks capable of collecting samples (tumor tissue, blood, stool and urine), according to shared procedures and appropriately annotated in the database; ii) to develop a "software" biomarker that can predict IO efficacy and selection more accurately than the single standard-of-care biomarker (e.g., PD-L1) answering a key scientific question for aNSCLC patients treated with immunotherapy.

PROACT 2.0, A NEW MOBILE APP TO ENHANCE ENGAGEMENT AND COMMUNICATION WITH PATIENTS PARTICIPATING IN EARLY ONCOLOGY STUDIES: A FEASIBILITY STUDY

Promoter: INT, developed as part of the "UpSMART" Accelerator Award
Principal Investigator: Silvia Damian
Co-Investigator: Luca Agnelli
Accrual: ongoing
Primary objectives: to improve the communication between patients and the medical team, involved in the clinical trial, such as physicians, nurses and researchers
Secondary objectives: the main objectives of the Feasibility Study were the following: to assess the attitude of cancer patients of participating in clinical trials using a Mobile App PROACT 2.0 that allow to interact with the health care provider (HCP); to assess compliance, acceptability and usability of PROACT 2.0; to identify those features which will require future refinement; to study those elements that might help to improve the communication between patients and physicians/research nurses, thanks to the analysis of patients' feedback; to study an AI (Artificial Intelligence) algorithm able to unravel adverse events severity from the messages content in order to prioritise communications between patient and healthcare providers.

TUMORI JOURNAL

Tumori Journal is an international peer-reviewed journal focused on cancer research, that is committed to provide a swift review by its expert editorial board.
Tumori Journal is indexed in all major databases and altmetrics data available for all articles.

Tumori Journal aims to convey outstanding scientific reports covering all the facets of cancer science, and encourages submissions of original data in cancer biology and therapy, and technology innovation for precision oncology and clinical trials.
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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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