Sistema Socio Sanitario

Fondazione IRCCS
Istituto Nazionale dei Tumori

Regione
Lombardia

SCIENTIFIC REPORT 2023

Fondazione
IRCCS
Istituto
Nazionale dei
Tumori

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 **57 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).*

AMADEOLAB
Via G.A. Amadeo 42

27

research labs

~700

personnel devoted to research

CAMPUS CASCINA ROSA
Via A. Vanzetti 5

3600

SQM surface

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 2023.

In accordance to its IRCCS nature, INT has the 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.

During 2023 INT research activity resulted in 835 published papers with a total IF of 7.916; the 446 experimental studies ongoing (399 of which are pharmacological clinical trials) offer the best possible treatment while also giving access to innovative drugs and other health technologies to patients. It is also worth mentioning that INT preclinical and clinical researchers are involved in 304 observational studies and 156 ongoing granted projects, 37 of which granted by international funding agencies.

Once more, according to the evaluation of the Ministry of Health, INT has been confirmed as the first ranked oncology specific 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.

Research staff includes 700 professional figures and in 2023 was implemented with 23 researchers in the preclinical, translational and epidemiological fields; 16 researchers in the statistical-computational field and one research psychologist, following competitions held pursuant to Law No. 205/2017 dedicated to career pathway of Health Researchers and Health Research Support staff.

The 4 reasearch lines, endorsed by the Ministry of Health, focus on translational research, linking research activities and healthcare through multidisciplinary programs by scientific teams made up of researchers from various clinical and scientific backgrounds.

In 2023, the Scientific Director proposed the turnover of the Coordinators for the 4 research lines and appointed eight researchers, two for each research line, one with clinical expertise and one with experimental and pre-clinical expertise.

The new coordinators have been tasked with selecting the projects to be funded for the 2023-2025 triennium and with overseeing the monitoring of institutional projects within each research area.

An internal competitive call was launched at the end 2023 and a total of 46 projects were financed following evaluation by the Scientific Director and the research line coordinators.

INTRODUCTION

Moreover, the Scientific Director appointed a Deputy Scientific Director for the Preclinical and Clinical Research area to support the Scientific Directorate in identifying translational research areas and activities and a Deputy Scientific Director for the Operational Management area.
In 2023, several actions have been taken to comply with the requirements of the Legislative Decree 200/2022. Among these, the update of the Foundation's Bylaws and the development of the Code of conduct on research integrity have been approved by Board of Directors and adopted (respectively on July and June).
Finally, during this year further steps have been taken for the “Città della Salute e della Ricerca” project, born from the ambitious idea of bringing together in a single large complex infrastructure two great public IRCCS of Milan, Istituto Nazionale dei Tumori and Istituto Neurologico Carlo Besta. The final goal will be the sharing of organizational models in order to meet patients clinical needs, psychological and physical well-being. This will result in a new healthcare complex of research, clinical, and teaching, capable of responding readily to present and future needs of the two IRCCS. The construction works started in 2021, and the relocation is scheduled for 2028.
Our outstanding results have been possible thanks to the synergic committment of the Presidency and Strategic Directorate (General Manager, Scientific, Healthcare and Administrative Directors) and the strong effort of all researchers, clinicians and the administrative staff.

PRESIDENT

Gustavo Galmozzi

GENERAL MANAGER

Carlo Nicora

SCIENTIFIC DIRECTOR

Giovanni Apolone

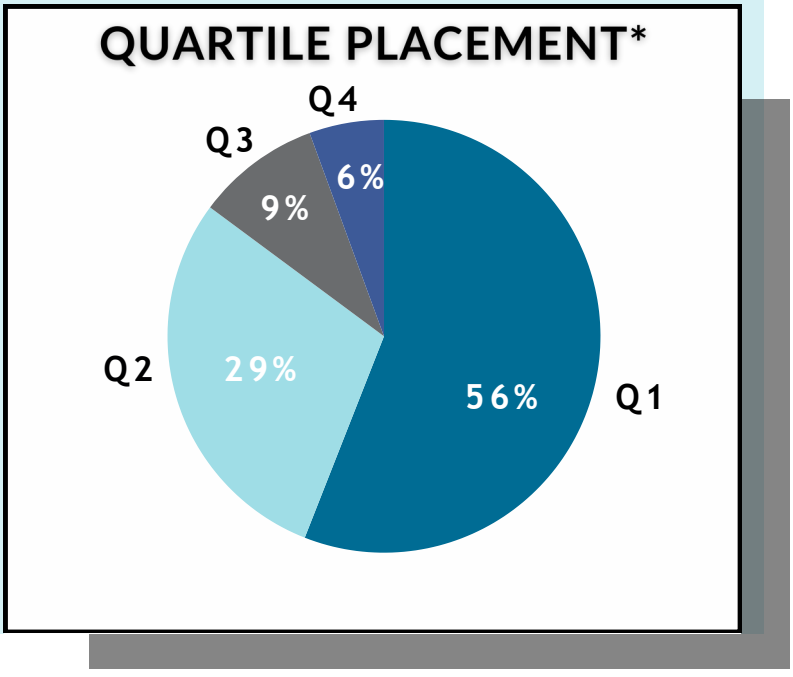
FACTS AND FIGURES

THE ESSENTIAL ABOUT INT 2023

PUBLICATIONS

TOTAL NUMBER	835
FIRST/LAST/ CORRESPONDING AUTHOR	43%
IMPACT FACTOR	7.916,00
FIELD WEIGHTED CITATION IMPACT	2,76
INTERNATIONAL COLLABORATIONS	54% (+ 14% COMPARED TO THE ITALIAN AVERAGE)

H-INDEX INT RESEARCHERS	
H-INDEX > 10	241
H-INDEX > 50	40
RANGE	1- 100
MEDIAN	13



*47 publications without impact factor are excluded from the chart

GRANTS

ONGOING PROJECTS IN 2023	
NATIONAL	119
INTERNATIONAL	37
TOTAL	156

INTERNATIONAL PROJECTS: INT AS...	
COORDINATOR	5
PARTNER	32
TOTAL	37

INTERNATIONAL CALLS: FUNDED BY...	
CANCER MISSION	6
EU4HEALTH	5
HORIZON	21
ERANET	5
TOTAL	37

GRANTS

NATIONAL PROJECTS: INT AS...	
COORDINATOR	99
PARTNER	20
TOTAL	**119**

NATIONAL CALLS: FUNDED BY...	
Associazione Italiana per la Ricerca sul Cancro - AIRC	43
MoH* - Ricerca Finalizzata	21
MoH*- National Recovery and Resilience Plan (PNNR)	5
Regione Lombardia, FRRB	4
FUV Fellowships**	14
Associazione Bianca Garavaglia	6
Other Grants	26
TOTAL	**119**

*Ministry of Health
** Fondazione Umberto Veronesi

CLINICAL RESEARCH DATA

ONGOING CLINICAL STUDIES

	STUDIES			PATIENTS	
	PROFIT	NO PROFIT	TOTAL	ENROLLED IN 2023	TOTAL
Experimental	259	187	446	2.979	14.238
Observational	14	290	304	63.533	453.147*
Registries	-	14	14	721	49.240
TOTAL	**273**	**491**	**764**	**67.233**	**516.623**

CLINICAL STUDIES LAUNCHED IN 2023

	PROFIT	NO PROFIT	TOTAL
Experimental	49	21	70
Observational	5	55	60
TOTAL	**54**	**76**	**130**

PROGRESS OF CLINICAL STUDIES

	PROFIT	NO PROFIT	TOTAL
Concluded	49	60	109
In enrolment	99	289	388
Follow-up	124	141	265
Interrupted	1	1	2
TOTAL	**273**	**491**	**764**

*The high number of patients enrolled in observational studies is partly due to studies that use large databases and screening projects.

CLINICAL RESEARCH DATA

CLINICAL STUDIES PROMOTED BY INT

	TOTAL	LAUNCHED IN 2023
Experimental	69	10
Observational	174	37
Registries	6	-
TOTAL	**249**	**47**

CLINICAL STUDIES BY NUMBER OF CENTERS

	PROFIT	NO PROFIT	TOTAL
Monocentric	14	193	207
Multicentric	259	298	557
TOTAL	**273**	**491**	**764**

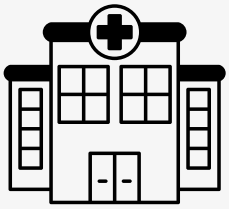
PHARMACOLOGICAL CLINICAL TRIALS

PHASE	STUDIES	PATIENTS ENROLLED IN 2023	TOTAL PATIENTS ENROLLED
I	23	52	236
I/II	48	116	466
I/III	3	13	63
II	148	399	3.643
II/III	10	59	154
III	162	331	2.443
IV	5	1	16
TOTAL	**399**	**971**	**7.020**

OTHER DATA

HEALTHCARE DATA

482	BEDS
11.449	ORDINARY ADMISSIONS
5.034	DAY HOSPITAL ADMISSIONS
1.264.102	CONSULTATIONS



NETWORKING PARTECIPATION

SCIENTIFIC SOCIETIES/ASSOCIATIONS AND ORGANIZATIONS/PROFESSIONAL ORDERS	126
COMMITTEES/BOARDS	38
NETWORKS	29
TECHNICAL PANELS/WORKING GROUPS/ MINISTRIES	19

INT MOLECULAR TUMOR BOARD

1.781	PATIENTS ANALYZED
2.343	MOLECULAR TESTS
256	CASE REPORTS DISCUSSED

PATENTS PORTFOLIO

16	PATENTS FAMILIES
8	OF WHICH INT OWNER
8	OF WHICH INT CO-OWNER

EDUCATION

301	EVENTS/TRAINING COURSES
10.018	PARTICIPANTS
57.847	OVERALL FORMATIVE HOURS

RESEARCH FUNDING

RESEARCH BALANCE

74.168.904,00 €

RESEARCH REVENUE

57.324.001,00 €

MAIN RESEARCH FUNDINGS

8.419.940,00 €	Structural Research Funds (Ricerca Corrente)
7.684.112,00 €	MoH* Funding for Researchers' Careers
2.823.932,00 €	National grants
12.416.300,00 €	International grants
5.634.314,00 €	Income from Clinical Trials
2.486.217,00 €	Donations and Bequests
3.616.668,00 €	5xMille**
4.242.518,00 €	Other income

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

PERSONNEL

The total number of INT employees accounts for about 2.100 people, including administrative staff, human resources, ICT, accounting, clinical engineering, researchers, physicians, nurses, technicians, fellows, etc.
A staff consisting of approximately 700 people is dedicated to research activities, distributed in 3 different categories:

1. researchers who are dedicated full time to research activities (bench side);
2. researchers who are dedicated both to research and healthcare activities (bed side);
3. personnel full time supporting research activities (i.e. technicians, project managers, clinical study coordinators, data managers, research nurses…).

Cost for the approximately 700 units of research personnel is covered by several sources. Bed researchers costs are covered by Institutional funding from Lombardy Region, whereas bench researchers costs are mainly covered by Ministry of Health (Ricerca Corrente and "Piramide", staff salaries) or grants (fellowships). Both pay full time personnel supporting research activities.

"Bench" (**research only**) and "Bed" (**research and healthcare**) research activities are carried out by permanent and temporary staff (including fixed term research taff - so called Piramide), corresponding to the staffing level. In addition to these personnel, activities are also carried out by fellows and personnel hired with different forms of contracts. The sum of these categories represents the total wokforce required to maintain the institutional performance level.
The table below describes the distribution of research staff.

TOTAL RESEARCH WORKFORCE

BENCH	BED	TOTAL
415	312	727

PERSONNEL

PERMANENT RESEARCH STAFF

	BENCH	BED	TOTAL
Researchers	40	214	254
University	2	14	16
Support to research	80	10	90
SUBTOTAL	**122**	**238**	**360**

RESEARCH STAFF SUPPORTED BY MOH

	BENCH	BED	TOTAL
Researchers	103	0	103
Support to research	96	0	96
SUBTOTAL	**199**	**0**	**199**

TEMPORARY RESEARCH STAFF

	BENCH	BED	TOTAL
Researchers	5	27	32
Support to research	1	0	1
SUBTOTAL	**6**	**27**	**33**

OTHER - INDEPENDENT PROFESSIONALS

	BENCH	BED	TOTAL
Researchers	9	36	45
Support to research	10	3	13
SUBTOTAL	**19**	**39**	**58**

OTHER - FELLOWSHIPS

	BENCH	BED	TOTAL
Researchers	60	7	67
University	4	1	5
Voluntary staff	5	0	5
SUBTOTAL	**69**	**8**	**77**

HIGHLIGHTS

NEW COORDINATORS FOR THE 4 RESEARCH LINES

In 2023, there was a turnover of the Coordinators for the 4 research areas: eight new researchers were appointed, two for each research line, one with clinical expertise and one with experimental and pre-clinical expertise. The new coordinators have been tasked with selecting the projects to be funded for the 2023-2025 triennium and with overseeing the monitoring of institutional projects within each research area.

INSTITUTIONAL RESEARCH CALL

The Institutional Call for Research Projects initiative in 2023 merged into the competitive selection of projects within the 4 research areas. The preparation of the 4 calls took place from June to September and were published in September 2023. From November onward, the peer review of submitted projects began, culminating in the final publication of the funded projects' ranking in December 2023. Since 2019, projects have been funded with budget autonomy by the coordinators.

CODE OF CONDUCT FOR RESEARCH INTEGRITY

On June 26th, INT adopted a new code of conduct for research integrity, which outlines the fundamental rules for personnel to conduct research activities through proper practices inspired by the principles of integrity. In accordance with the law of May 31, 2022, the Institutes ensure that research and care activities adhere to the principles of fairness, transparency, equity, responsibility, reliability, and comprehensiveness recognized at the international level.

HIGHLIGHTS

INSTITUTIONAL HIGH PERFORMANCE COMPUTING (HPC)

Available at INT since June 2023, the HPC platform is intended for the processing of BigData produced by the "-omics" platforms, the use of biostatistical and bioinformatic applications, the implementation of artificial intelligence models, or more generally, all computational activities that can benefit from the use of a high number of parallel computing nodes and a considerable amount of operational memory.

YOUNG RESEARCHER AWARD

On April 23th, 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 2023. Respectively Alessandro Cicchetti, Alessandra Raimondi, Alice Bernasconi and Federico Nichetti have been awarded for the excellence of their research activities.

INTERACTION

In November the Scientific Directorate launched INTeraction, the website dedicated to INT researchers. It offers a wide range of services and resources, including the ability to search for publications, publish blog articles, manage and view research groups and their members, as well as book and schedule the equipment available for research.

THE BIG R.EVOLUTION

On December 13th, the oncology exhibition 'The Big R.evolution' was inaugurated, with the aim of retracing the 98-year history of the Institute, from its foundation to the present day, highlighting the major achievements the Institute has reached in cancer research and treatment.

NETWORKING

INT's visibility is consolidated by the presence of the Scientific Director and INT researchers in ministerial boardss, regional planning boards, and pathology networks, as well as through the creation of stable networks and continous collaboration with important Universities, Institutes and Research Bodies.
At the national level, INT is a member and founding partner of the largest national oncological network **Alliance Against Cancer**, whose "mission" is to promote the transfer of scientific-technological innovation to clinical practice, thus enabling more effective and sustainable treatment in oncology. INT's leadership is enhanced by the presence of two of its leading figures (Scientific Director and a clinical researcher) on the ACC Board of Directors and in the role of Scientific Coordinator.
Moreover, INT formally collaborates and is one of the founding members of cutting-edge research organisations such as **IFOM** (the Institute of Molecular Oncology, funded by FIRC, a center specialized in the study of molecular mechanisms underlying tumor formation and development), and **CNAO** (The National Center for Oncology Hadrontherapy is a major research and development center established for the purpose of treating cancer using protons and carbon ions, whose Scientific Director is a clinical researcher at the Institute).
Networking activity is also pursued through a **Joint platform** with UNIMI - Università degli Studi di Milano for the integrated planning and synergetic implementation of joint research projects or programmes, as well as enhancing the excellence of training activities.

At the international level, the Institute has a presence 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, since 2022 the Scientific Director is 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). The Main European liasons are:

- **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 president since July 2023.
- **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 translational 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 Institute as part of CCE's dedicated task forces.
- **DIGICORE**: is a pan-European research network built to accelerate the implementation of precision oncology in Europe. It promotes and equips cancer centres in their use of routine electronic health records (EHR) and molecular diagnostic information (MDX) for trial automation, real world outcomes research, digital diagnostics and care quality management.

INTERNATIONAL

To strengthen the institutional presence on the European scenario, grant applications to Horizon Europe Framework Program calls and EU4Health calls for proposals have been successfully supported.

Within the Mission on Cancer (Horizon Europe), 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 other 5 projects. "CCI4EU" is aimed at the creation of transational networks and infrastructures for cancer research, Comprehensive Cancer Infrastructures; "ECHOS" is aimed at the creation of National Hubs for the promotion of EU's Mission on Cancer; "CARE1" is focused on pragmatic clinical trials and it aims to improve the first-line treatment for patients with metastatic kidney cancer by implementing a routine biomarker, leveraging a unique academic network in Europe; "MELCAYA" (started in 2022) aims to understand risk factors and determinants of melanoma to improve the prevention, diagnosis and prognosis of melanomas in childhood, adolescence and young adults; "STREXIT 2" will investigate the added value of neoadjuvant chemotherapy before surgery for high-risk retroperitoneal sarcoma.
Within the Programme Horizon Europe/Innovative Health Initiative (IHI), INT is Partner in the project "IMAGIO": Imaging and Advanced Guidance for Workflow Optimization in Interventional Oncology (started in 2023).

In 2023 INT received a 2 European Direct Grants to support the European Reference Network "PAEDCAN" and "EURACAN"; it was involved in a European Research Council (ERC) Consolidator Grant as Collaborating Institution (Deciphering the exposome by metabolomic technology in breast cancer- EXPOMET); and joined a MSCA partnership (Fellowship programme for talented researchers in cancer Talent- AECC Talent).
INT is also involved in 4 EU4Health Projects. INT is Coordinator of "ELISAH": European Linkage of Initiative from Science to Action in Health (funded in 2023, the project will start in 2024) and is Partner in 3 projects "EU CAYAS NET": EU Network of Youth Cancer Survivors (started in 2022); "SOLACE": Strengthening the screening of Lung Cancer in Europe (started in 2023) and "CAN.HEAL": Building the EU Cancer and Public Health Genomics platform (started in 2022).

INT is the coordinator of the Joint Action on Network Expertise (JANE) started in 2022, 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.

In 2023 INT was also involved in an international consortium financed by the National Cancer Institute USA (NCI) with the Project "LEAP" (The Lung EArly Proteins project: A LEAP towards implementing biomarkers in lung cancer screening).

INSTITUTIONAL RESEARCH LINES

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

INSTITUTIONAL RESEARCH LINES

According to the 3-year IRCCS research plan for 2022-2024, approved by the Ministry of Health, research in INT is organized in 4 Institutional Research Lines, representing the main planning element to blend old and new projects.

The 4 research lines integrate all the research areas, as multidisciplinary research activity hinges on the integration and synergy among preclinical, basic research, clinical, translational, epidemiological research, and quality-of-life and outcome research. Moreover these lines represent priorities for INT health research, driving research efforts as well as the set up of organizational and financial tools.

Since 2019, the Scientific Directorate has been allocating resources from 5x1000 funds (€1.5 M for each research line, for the three-year period) to a strategic program related to the 4 lines of research. Due to the success of this initiative, in 2023 the Scientific Director decided to promote a rotation in the Lines' governance, appointing 8 new Coordinators, two for each research line, one with clinical expertise and one with experimental and pre-clinical expertise.

In July 2023, the coordinators promoted an internal competitive thematic project call. Following a peer review process, 22 3-year projects and 23 18-months proof-of-concept projects have been selected, with a total expenditure commitment of around € 3.8 M. Multidisciplinarity and synergy between research groups, clear clinical impact, aims and feasibility represent major strengths of the funded projects, which span both ongoing and novel research topics.

The 45 projects funded in the 2023 call (whose activities formally started in 2024) are listed for each line.

PRIMARY, SECONDARY PREVENTION AND EARLY DIAGNOSIS

LINE 1

COORDINATORS:
SABINA SANGALETTI
MATTIA BOERI

This line is focused on cancer prevention activities achieved through primary, secondary, and tertiary processes.
Primary prevention represents the promotion of health and well-being and the reduction of risks known to contribute to the development of cancer. Once the pathogenic role of pollutants and erroneous lifestyles is identified, primary prevention aims to correct them through intervention studies, in order to reduce risk of onset. Secondary cancer prevention includes screening of at-risk populations and early diagnosis in the absence of overt symptoms, when the disease is more susceptible to treatment.
Tertiary prevention concerns individuals already diagnosed with malignant neoplasia and is aimed at increasing survival by reducing the risk of recurrence and toxicity and provide patients with a better quality of life, in order to choose the most effective intervention, and monitoring its effects on the tumor.
Projects focus on several topics:

- Epidemiological and registry studies;
- Impact of metabolic alterations and lifestyle on cancer development;
- Epidemiology of cancer and increased risk among individuals under 65;
- Understanding cancer development mechanisms for devising new preventive strategies, with an emphasis on discovering biomarkers, identifying high-risk patients, and studying the tumor microenvironment.
- Biomarker validation and technological innovations for targeted diagnosis., spanning from basic to clinical research, in order to expedite the discovery of early diagnosis and recurrence systems,

PRIMARY, SECONDARY PREVENTION AND EARLY DIAGNOSIS

LINE 1

FUNDED PROJECTS

PI	TITLE
G. Procopio N. Nicolai	RISP-VUR: Prospective Single-center Pilot Study for Screening Urinary Tract Tumors in Subjects Enrolled in Lung Cancer Screening
C. Chiodoni	Circulating Myeloid Cells, Coupled with ATF3 Expression by CD14+ Monocytes, Discriminate Malignant from Benign Mammographic Lesions: Validation Cohort and Technical Refinement
S. Signoroni S. Lauricella	Collection of Body Fluids, Diet and Lifestyle Information for the Identification of Risk Factors and Potential Biomarkers in Early Onset Colorectal Cancer Patients
P.Pasanisi	A Prospective Web-based Cohort and Biobank of Women Carriers of BRCA Mutations
O. Fortunato L. Roz	Extracellular Vesicles as Markers and Mediators of Increased Lung Cancer Risk in COPD
E. Bruno E. Venturelli	Exploring Mechanism Linking Diet, Dysbiosis And Breast Cancer Recurrences: The Discoveromics Study
M. Colombo L. Caleca	Clinical Classification of Variants of Uncertain Significance in BRCA1/2 Genes by Functional Approches
S. Bhoori L. Rivoltini	Tracing Anti-cancer Immunity in Patients Undergoing Liver Transplantation for HCC After Downstaging with Immunotherapy
T. Beninato A. Fabbri	Epigenetics In SCLC to Early Detect Treatment Resistance and Discovery New Druggable Pathways

PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

LINE 2

COORDINATORS:
TIZIANA TRIULZI
LUCA AGNELLI

This line is focused on research activities aimed at optimizing and personalizing oncological care considering all its aspects, such as diagnostics, surgery, therapy, and monitoring. This line promotes the identification, development, and validation of (i) tissue and/or circulating biomarkers for patient stratification and monitoring, (ii) new therapeutic targets and strategies, and (iii) new approaches/technologies in the context of personalized medicine. Since personalized therapy requires a holistic understanding of the disease - including all of the characteristics that, in addition to genetics, influence tumor phenotype, treatment response, and resulting toxicity - the research line pays particular attention to the study of the tumor, the host, and their interaction to identify factors relevant to patient care. For example, the line supports projects aimed at identifying and/or validating new biomarkers for prognostic, predictive, and/or personalized treatments; characterizing the tumor/patient using -omics technologies (including pilot studies on prospective cohorts); integrating -omics variables/methodologies and artificial intelligence into diagnostic/prognostic/predictive models; studying the molecular mechanisms underlying therapy resistance; studying the role of the tumor microenvironment and tumor-host interaction in various stages of care; implementing "functional precision medicine".
Moreover, this line is dedicated to the application of both pharmacological (clinical trials) and non-pharmacological technological innovation (diagnostic, imaging, surgery). Of note, projects of this line address radiomics, radiogenomics and artificial intelligence as innovative approaches for cancer research.
Precision medicine is thus implemented in projects with a strong basic-to-translational discovery component, to generate innovation and develop new techniques, methodologies, models, or applications and in projects from bench to clinical research to accelerate the discovery and validation of new biomarkers, potential therapeutic targets, and new treatment approaches.

PRECISION MEDICINE AND TECHNOLOGICAL INNOVATION

LINE 2

FUNDED PROJECTS

PI	TITLE
G. Bertolini G. Lo Russo	Trapping Circulating Tumor Cells to Develop Prognostic Biomarkers and Novel Anti-metastatic Strategies in Lung Cancer (TRAP-2-CURE)
E. Jachetti E. Verzoni	CDK4/6 plus PARP Inhibitors in Prostate Cancer: a Matter of Synthetic Lethality and Immune Modulation – the PROPARCY Study
L. Possenti A. Beretta	PANORAMA – PANcreatic Cancer On-chip: a Breakthrough Technology to Reshape Preclinical Analyses of TreatMent Strategies
F. Ligorio A. Vingiani	Unveiling the Intratumor Heterogeneity of Immunometabolic Modulations During Chemoimmunotherapy Plus Caloric Restriction in Early-stage TNBC Patients
D. Lecis	Targeting Nonsense-mediated mRNA Decay as a Novel Strategy to Enhance Immune Checkpoint Therapy Efficacy
M. Brambilla C. Proto	ZEB1 Defines Suppressive Neutrophils and Neutrophil Extracellular Traps in Non-small Cell Lung Cancer
M. Figini M. Montermini	Roadmap for a Successful Clinic Development of a Bispecific Antibody and a CAR-T:What we Need to Know
M. Magni	Dissecting the Interplay Between Tumor Genotypes, Systemic Immune Environment and Circulating CAR T Cells in Large B-cell Lymphoma Patients to Identify Determinants of CAR T Therapy Failure
J. Iacovacci	MicMark-HNC: Defining a Microbiota-based Salivary Biomarker to Predict Treatment Outcomin Head and Neck Cancer
V. Vallacchi M. Rodolfo	Dissecting Translational Correlates of Response to Anti-PD1 and Anti-EGFR in Patients with Advanced Cutaneous Squamous Cell Cancer Enrolled in the Prospective Phase II INT-Sponsored Trial I-Tackle (NCT03666325) by an Ex-vivo 3D Culture Platform of Patient Derived Tumor Explants
L. Sfondrini M. Sommariva	The Evil Trio: S. Epidermidis, Tregs and Macrophages Cross-talk in Promoting Immunosuppression in Breast Cancer
S. Nazzani A. Busico	Clinical Validation of MicroRNA 371 Use in Small Testicular Masses, in Stage II, Low-volume Germ Cell Tumors and in Seminoma With a Residual Mass After-chemotherapy
M. Iorio	miR-9 Inhibition as a Strategy to Disrupt Tumor-MDSC (Myeloid-Derived Suppressor Cell) Communication
C. Sposito V. Mazzaferro	The Prognostic Performance of Liquid Biopsy in Peritoneal Lavage of Patients with Locally Advanced Gastric Cancer (Liquid Study - Peritoneal)
S. Iadecola F. Barretta	A Step Towards Inclusive Medicine: Implementation of Gender-Related Indicators (PANDORA)

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

LINE 3

COORDINATORS:
ANDREA FERRARI
SANDRO PASQUALI

This line is aimed at at the diagnostic, therapeutic, or rehabilitative approach to complexity, understood as rare tumors and fragile patients. Our Institute is characterized by a recognized expertise regarding rare tumors, with a national and international leadership role, being reference center for a number of rare cancers. The theme of "rare tumors" can be connected to that of "fragile oncological patients," and certainly, this latter can also be developed in patients with common tumors.
These issues are tackled with a multi- and interdisciplinary approach from the genetic, molecular, clinical and social care point of views, taking into account inequalities in access to treatment, and specific 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. In this respect, line 3 has focused on the creation of infrastructure projects as well as the generation of preliminary data aimed at creating networks of clinical and pre-clinical researchers in the field of rare tumors/fragile oncological patients.

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

LINE 3

FUNDED PROJECTS

PI	TITLE
A. Gronchi M. Fiore	Retroperitoneal Sarcoma Registry (RESAR)
M. Ganzinelli D. Miliziano	Gene Expression Profiling in Advanced Thymic Epithelial Tumors (TETS) and Integration with Clinical Outcome in a Real World Setting
V. Doldi G. Cassinelli	Molecular and Functional Characterization of Dedifferentiated Liposarcoma-derived Extracellular Vesicles
E. Schiavello C. Dossena	An Integrative Metagenomics and Epigenomics Approach to Disclose the Biological Underpinnings in Pediatric Brain Tumors Through non Invasive Methods
A. Belfiore S. Brich	Leveraging Transcriptomics to Enhance HIPEC Performance in Patients with Epithelioid Diffuse Malignant Peritoneal Mesotheliomas
M. Mazzoni T. Dimarco	Dissecting the Role of Innervation in Thyroid Cancer
D. Lenoci S. Alfieri	Evaluating the Role of Intratumor Microbioma and Diet Exogenous MiRNAs in the Pathogenesis and Outcome of Endemic and non Endemic EBV-related NPC (MICROBE-NPC)
R.M. Leone A. Licata	The Ecology of HPV-related Cancers: Bridging Biology Between Head and Neck Cancer and Cervical Cancer to Discover Mechanisms of Response in Primarily Chemo or Chemoradio Treated Tumors (HYPER)
G. Sabella M. Gentili	Dissecting and Deciphering the Amphicrine Tumors: Genetic and Epigenetic Analyses to Improve Diagnosis, Prognosis and Therapy
E. Rausa V. Miskovic	The Application of Artificial Intelligence in Assessing Intra Abdominal Desmoid Tumors in Familial Adenomatous Polyposis Patients

CLINICAL, HEALTH CARE AND OUTCOME RESEARCH

LINE 4

COORDINATORS:
ARSELA PRELAJ
GIORGIO BOGANI

This line focuses on 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.
Clinical outcomes in oncological conditions with limited prospects are studied, aiming to improve symptom management and the discovery of biomarkers that guide more targeted therapies, important fordeveloping personalized diagnostic and therapeutic approaches that can positively influence patient prognosis. 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.
Interest is focused on the application of artificial intelligence (AI) in treatment and data analysis, integrating AI for predictive analysis and personalization of care. AI is used for big data and omic data analysis, with the aim of identifying correlations crucial for treatment personalization.
Research is also 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).
Finally, development of technological tools for the storage and analysis of clinical data, ensuring safe and efficient information management, supports knowledge sharing among professionals, essential for an integrated and multidisciplinary approach to the treatment of neoplasms.
In conclusion, Line 4 proposes advanced and integrated research, leveraging technology and innovation for a significant impact on outcomes, toxicity reduction, and healthcare systems.

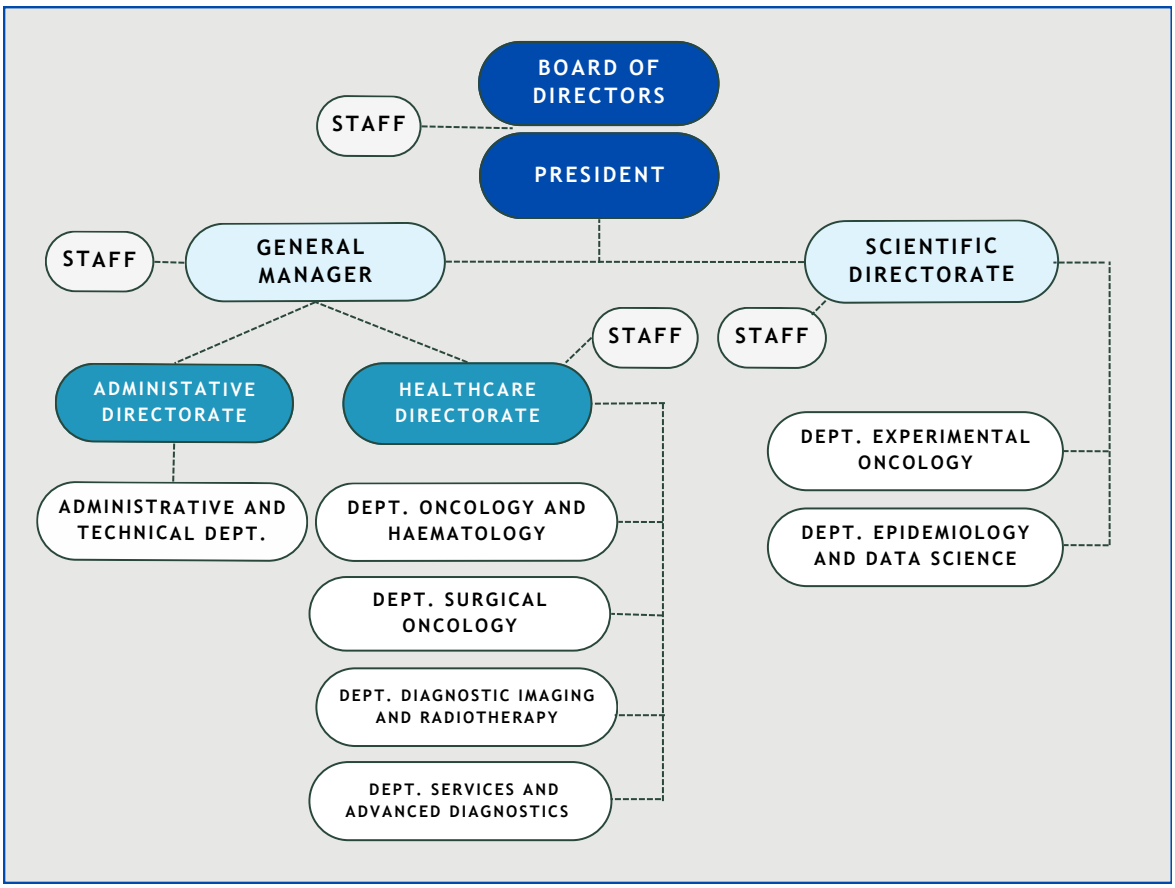
CLINICAL, HEALTH CARE AND OUTCOME RESEARCH

LINE 4

FUNDED PROJECTS

PI	TITLE
L. Provenzano C. Vernieri	Using RADIOmicS to Predict HER2 Status and T-DXd Efficacy in Metastatic Breast Cancer: the RADIOSPHER2 Study
M. Occhipinti D. Lorenzini	Discovering of Biomarkers for Immune Checkpoint Blockade in Pleural Mesothelioma
F. Raspagliesi	Artificial Intelligence Applied to Digital Pathology in Predicting Unfavorable Risk Criteria in Early-Stage Endometrial Cancer: a Machine Learning Development Process
R. Orlandi A. Polymeropoulos	Exploiting Artificial Intelligence-based Tools for Analysis of Clinical Breathomics Data
C. Marenghi B. Noris Chiorda	Mid- to Long-term Outcomes in Prostate Cancer Patients Enrolled in Active Surveillance
S. Pizzamiglio S. Di Cosimo	Integrative Multi-omic Analysis Towards Personalized Treatment of HER2-positive Early-stage Breast Cancer
E. Daveri L. Sorrentino	Exploration of MyeLoid Immunity Estimated by Radiomics to Predict Curability in Locally Recurrent Rectal Cancer (ELISABETH)
M. Guaglio R. Vigorito	Developing AI-based Predictive Molecular and Radiological Markers to Tailor Surgical Approaches for Peritoneal Metastasis from Colorectal Cancer (DAMASCO)
P. Giannatempo V. Huber	Understanding Tumor and Immune Dynamics and Predicting Poor Outcome to Intravescical Therapies (BCG) in Patients with Non-muscle-invasive Bladder Cancer that had Progressed in Locally Advance/Metastatic Disease
E. Tognoli	Exercise Training and Nutrional Interventon to Modulate Cytokine Status Before Surgery in Overweight/Obese Cancer Patents: A Pilot Study
M. Vitellaro P. Verderio	National Multicenter Network on Familial Adenomatous Polyposis

INT ORGANIZATIONAL SYSTEM



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, Healthcare Director and Administrative Director.

The organization of the Research Area attempts to optimize and streamline the distribution of human resources and scientific skills, in a management structure that supports homogeneous research areas. The Scientific Directorate coordinates the research area, which includes the Department of Experimental Oncology and Department of Epidemiology and Data Science.

SCIENTIFIC DIRECTORATE

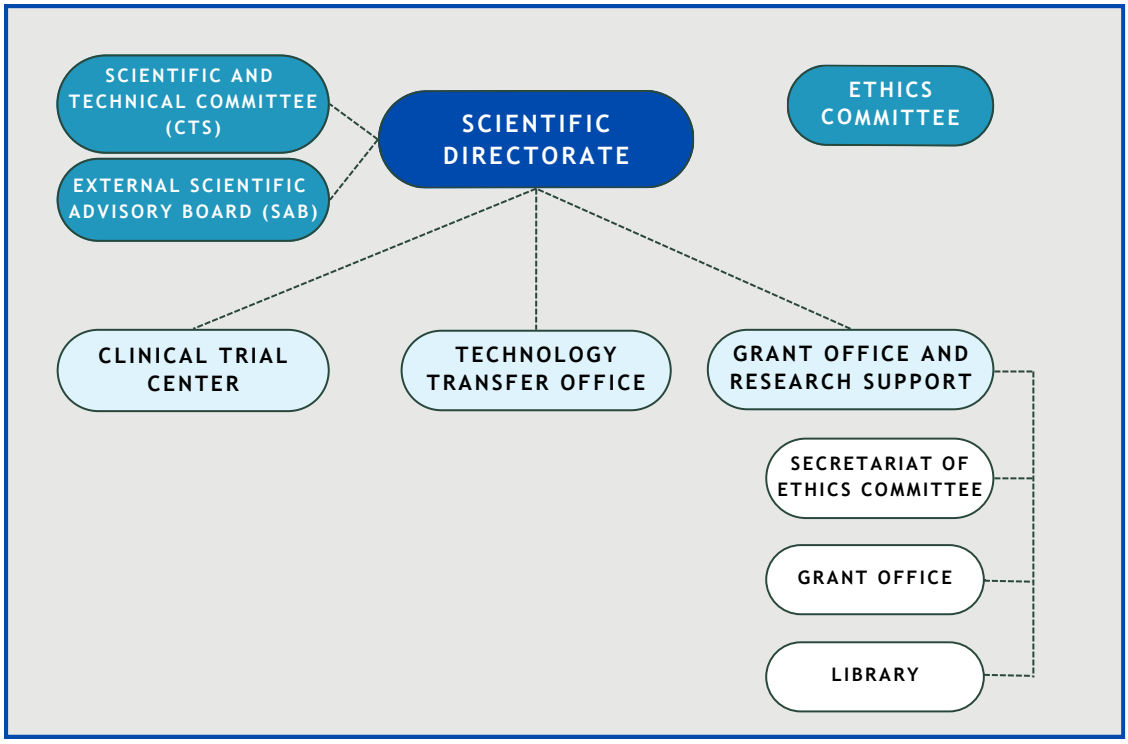
SCIENTIFIC DIRECTOR:

GIOVANNI APOLONE

The Scientific Directorate organizes its activities within three formally appointed units: the Clinical Trials Center, the Technology Transfer Office (TTO) (formerly pertaining to the administrative area), and the Grant Office and Research Support unit, which merges 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 Scientific Directorate is responsible for the following tasks:

- It is responsible for the strategic planning of institutional research and the management of related funding;
- It supports researchers in participating in research calls promoted by national and international, public and private entities;
- It conducts scouting activities for research project funding;
- It maintains relations with the Ministry of Health regarding research activities and report results about the research performance of the IRCCS;
- It supports clinical researchers in the management of clinical trials;
- it supports the Strategic Directorate regarding the legal and contractual aspects of research activities.

The Advisory Board, composed by preclinical and clinical researchers, provide support to the Scientific Directorate for its activities of communication and dissemination, review of grants applications, and organization of scientifc events.



DEPARTMENT OF EXPERIMENTAL ONCOLOGY

MOLECULAR PHARMACOLOGY

EPIGENOMIC AND BIOMARKERS OF SOLID TUMORS

MOLECULAR EPIGENOMICS

MOLECULAR IMMUNOLOGY

MICROENVIRONMENT AND BIOMARKERS OF SOLID TUMOR

TRANSLATIONAL IMMUNOLOGY

RESEARCH IN NUTRITION AND METABOLOMICS

MOLECULAR BASES OF GENETIC RISK

INTEGRATED BIOLOGY OF RARE TUMORS

ANIMAL FACILITY

HEAD:

GABRIELLA SOZZI

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 individual 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 and 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 asked to participate to joint multidisciplinary and transversal oncology research activities. In this environment, basic research can enhance and provide the best translational research approach.

The research projects, which arise from unmet clinical needs and/or original experimental observations, are implemented in laboratories, employing 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 research laboratory. This coordination allows pre-clinical research results to be transferred 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”).

HIGHLIGHTS

Y90-radioembolisation in Hepatocellular Carcinoma Induces Immune Responses Calling for EarlyTreatment with Multiple Checkpoint Blockers

Rivoltini L, et al. GUT. 2023 Feb. DOI: 10.1136/gutjnl-2021-326869

Authors, through longitudinal blood immune monitoring in patients with intermediate-advanced hepatocellular carcinoma (HCC) who had preserved hepatic function, identified short-term (one-month) immune activation as a consequence of Y90-radioembolisation (Y90TARE). The subset of CD4+Ki67+GZB+LAG3+ T cells was higher in patients with tumor response compared to those with stable or progressing disease. These findings indicate that Y90TARE, followed by PD-1 and LAG3 inhibitors after one month, could represent a promising strategy to induce optimal immune-mediated disease control in patients with HCC.

Biological and Clinical Impact of Membrane EGFR Expression in a Subgroup of OC Patients from the Phase IV Ovarian Cancer MITO-16A/MANGO-OV2A Trial

Forlani L, et al. J EXP CLIN CANCER RES. 2023 Apr. DOI: 10.1186/s13046-023-02651-y

This study identified three ovarian cancer subgroups based on EGFR membrane expression in patients of the MITO-16A/MaNGO-OV2A trial, who received front-line chemotherapy and bevacizumab. Strong and homogeneous EGFR membrane expression was an independent negative prognostic factor for overall survival. This subgroup lacked angiogenic characteristics, but showed activation of EGFR-related networks and crosstalk with RTKs like AXL. In vitro studies suggested that co-targeting EGFR and AXL could be an effective therapeutic strategy for this subgroup of patients.

Rewiring Innate and Adaptive Immunity with TLR9 Agonist to Treat Osteosarcoma

Cascini C, et al. J EXP CLIN CANCER RES. 2023 Jun. DOI: 10.1186/s13046-023-02731-z

Authors demonstrated that the administration of TLR9 agonist in mice bearing two contralateral osteosarcoma (OS) strongly impaired the growth of locally-treated tumors and also exhibited an abscopal effect on contralateral, untreated lesion. Massive changes were observed in the OS immune microenvironment of both lesions, involving a reduction in M2-like macrophages, increased infiltration of dendritic cells and activated CD8 T cells. The expansion of specific TCR clones was observed in both lesions, providing the first evidence of the rewiring of tumor-associated T cell clonal architectures.

Extracellular Vesicles from Subjects with COPD Modulate Cancer Initiating Cells Phenotype through HIF-1α shuttling

Petraroia I., et al.CELL DEATH DIS. Oct 2023. DOI: 10.1038/s41419-023-06212-1

Authors explored how circulating extracellular vesicles (EVs) from chronic obstructive pulmonary disease (COPD) subjects might influence lung cancer development. Plasma EVs were isolated from heavy smokers with (COPD-EVs) and without (HS-EVs) COPD, and used to stimulate genetically modified human bronchial epithelial cells. COPD-EVs increased CD133+CXCR4+ metastasis-initiating cells (MICs) and enhanced 3D growth, migration, invasion, and mesenchymal traits. The findings indicate that hypoxia-inducible factor 1-alpha (HIF-1α) in COPD-EVs activates the CXCR4 pathway, promoting MICs expansion and pro-tumorigenic effects.

HIGHLIGHTS

ATF3 Reprograms the Bone Marrow Niche in Response to Early Breast Cancer Transformation

Perrone M, et al. CANCER RES. 2023 Jan. DOI: 10.1158/0008-5472.CAN-22-0651

Authors demonstrated that IL1B released by tumor-primed bone marrow (BM) mesenchymal stem cells (MSCs) induces ATF3 activation in hematopoietic stem cells and promotes the formation of myeloid progenitor clusters, a necessary step toward myeloid cell differentiation The cross-talk between distant tumors and the BM ultimately leads to the release of tumor promoting ATF3-expressing myeloid cells into the circulation, which were also detected in the peripheral blood of patients with breast cancer. The evaluation of ATF3-expressing myeloid cells is proposed as a potential circulating marker for early cancer detection in clinical settings.

Reduction of Staphylococcus Epidermidis in the Mammary Tumor Microbiota Induces Antitumor Immunity and Decreases Breast Cancer Aggressiveness

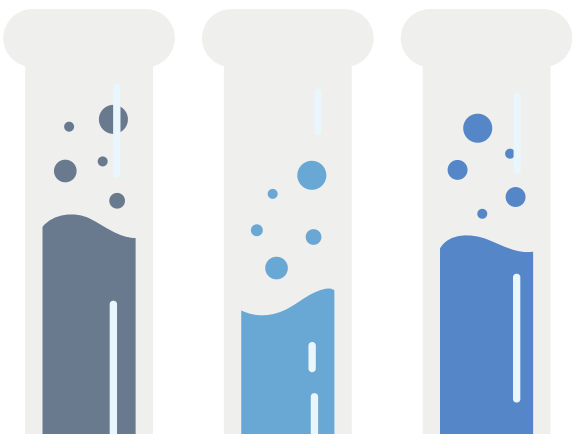
Bernardo G, et al. CANCER LETT. 2023 Feb. DOI: 10.1016/j.canlet.2022.216041

Authors demonstrated that oral treatment with absorbable antibiotics like ampicillin (Amp) reduced murine mammary tumor growth and enhanced their response to paclitaxel by disrupting tumor-associated microbiota. Mechanistically, Amp decreased Staphylococcus epidermidis levels, leading to reduced inflammation and regulatory T cells within the tumor, while increasing bacteria that promote an antitumor immune response. An Amp-like signature was also identified, which correlated with high antitumor immune infiltration and better prognosis in breast cancer patients.

Fatty Acid Synthase as a New Therapeutic Target for HER2-positive Gastric Cancer

Castagnoli L, et al. CELL ONCOL (DODR). 2023 Jun. DOI: DOI: 10.1007/s13402-023-00769-x

Authors investigated the role of fatty acid synthase (FASN) in resistance to anti-HER2 therapies in HER2+ gastric cancer (GC). They found that FASN is induced by treatment in cancer stem cells (CSCs). Inhibiting FASN reduced the proportion of CSCs and impaired HER2 activation. Combining HER2 and FASN blockade improved therapy efficacy compared to monotherapy, both in vitro and in vivo, by reducing CSCs and the growth of trastuzumab-resistant GC cells. These findings highlight FASN as a novel druggable target to overcome trastuzumab resistance in HER2+ GC.



DEPARTMENT OF EPIDEMIOLOGY AND DATA SCIENCE

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

DEPARTMENT OF EPIDEMIOLOGY AND DATA SCIENCE

HEAD:

GIOVANNI APOLONE (INTERIM)

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), environment, 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.

HIGHLIGHTS

A Comprehensive Review of Healthy Effects of Vegetarian Diets

Agnoli C, et al. NUTR METAB CARDIOVASC DIS. 2023 Jul. DOI: 10.1016/j.numecd.2023.04.005

A comprehensive review of the effect of vegetarian (V) and non-vegetarian (NV) diets on the health outcomes including risk factors for the major non-communicable diseases was performed. Eligible studies included randomized controlled trials (RCTs) and observational studies (i.e., cohort), comparing the effects of a V diet to those of a NV diet. Cohort studies showed benefits of V diets compared with NV diets on the incidence of ischaemic heart disease, overweight and obesity and/or mortality risk. In RCTs, V diets led to greater weight loss and better glycaemic control than NV diets. Further well-designed trials are needed to confirm this comprehensive review conclusions.

Causes of Death in Women with Breast Cancer: a risks and rates Study on a Population-based Cohort

Contiero P, Boffi R, et al. FRONT ONCOL. Nov 2023. DOI: 10.3389/fonc.2023.1270877

The study analysed data from 12742 women diagnosed with primary breast cancer (BC) from population-based cancer registries and followed for six years. Competing-cause analysis, cumulative incidence functions (CIFs) and cause-specific hazards (CSHs) were estimated. BC had the highest CIF while cardiovascular disease was the second leading cause of death. The contribution of BC deaths to the overall CIF varied by age group and by stage; CSH analysis showed temporal and geographic variations. These findings highlight the importance of multidisciplinary surveillance and prevention through community-based survivorship care models.

Cancer burden in adolescents and young adults in Europe

Trama A, et al. ESMO OPEN. 2023 Feb; DOI: 10.1016/j.esmoop.2022.100744

The study retrieved crude and age-standardized incidence and mortality rates for adolescents and young adults (AYAs; aged 15-39) from the Global Cancer Observatory for all cancers and the 13 most relevant cancers to AYAs in Europe. There was significant variation between countries, with the highest mortality in Eastern EU countries. Cancers of the female breast, thyroid and male testis were the most common cancers across countries followed by melanoma of skin and cancers of the cervix. Mortality disparities may stem from differences in early-stage diagnoses, public education, awareness, and access to treatment. The study emphasizes the need of AYA-specialized services to ensure uniform treatment across countries.

Sample Size and Predictive Performance of Machine Learning Methods with Survival data: A Simulation Study

Infante G., et al., STAT. MED. 2023 Dec. DOI: 10.1002/sim.9931

Prediction models are increasingly developed and the use of machine learning (ML) methods is becoming more and more popular over traditional regression techniques. While there is guidance for sample size needed for developing traditional statistical models, it is not the same for ML techniques. This work develops a time-to-event simulation framework to evaluate performances of Cox regression compared to tuned random survival forest, gradient boosting, and neural networks at varying sample sizes. Simulations were based on replications of subjects from publicly available databases, where event times were simulated according to a Cox model with nonlinearities on continuous variables and time-varying effects and on the SEER registry data.

HIGHLIGHTS

A Three-gene Signature Marks the Time to Locoregional Recurrence in Luminal-like Breast Cancer

Chiodoni C, et al. ESMO OPEN. 2023 Aug. DOI: 10.1016/j.esmoop.2023.101590

Gene expression profiling (GEP)-based prognostic signatures are increasingly used for systemic management of breast cancer (BC) patients but are less developed for locoregional risk assessment (LLR). The GEP analysis on two independent luminal-like breast cancer cohorts with early (≤5 years) or late (>5 years) LRR discover a three-gene signature, by principal component analysis, associated with early LRR. This association was retained in the two in silico datasets; in the third independent cohort, the signature resulted significantly associated with relapse-free survival. The signature represents a new exploitable tool to aid treatment choice in luminal-like BC at risk of developing early recurrence.

A Three-dimensional Method for Morphological Analysis and Flow Velocity Estimation in Microvasculature on-a-chip

Rota A, et al. BIOENG TRANSL MED. 2023 Jun. DOI: 10.1002/btm2.10557. PMID

Three-dimensional (3D) imaging techniques are commonly used to visualize in vitro models, especially microvasculature on-a-chip. Still, the 3D analysis is not the standard method to extract quantitative information from those models. The paper proposes the μVES algorithm to analyse vascularized in vitro models leveraging 3D data by estimating morphological parameters and intravascular flow velocity. Results suggest that microfluidic vascularized in vitro models successfully replicate functional features of the microvasculature in vivo in terms of intravascular fluid flow velocity, supporting its application in analyses of different in vitro vascular models and ex vivo microvasculature.

Out-of-pocket Costs Sustained in the Last 12 Months by Cancer Patients: an Italian Survey-based Study on Individual Expenses between 2017 and 2018

Lillini R, et al. EUR J HEALTH ECON. 2023 Nov. DOI: 10.1007/s10198-022-01544-9

The survey, investigating the amount and the types of Out of Pocket (OOP) costs sustained by Italian cancer patients for care services, was conducted by FAVO. Multilevel mixed-effects negative binomial regression was used to assess the combined effects of patient's characteristics on the differences in acquiring health services. Results based on 39 adhering hospitals and 1289 patients diagnosed from 1985 to 2018, estimated a yearly average OOP of 1841.81€, with the highest values for transports and for diagnostic examinations. Significantly higher OOP were found in North and Centre than South and Islands.

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

DEPARTMENT OF SERVICES AND ADVANCED DIAGNOSTICS

HEAD:

GIANCARLO PRUNERI

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.

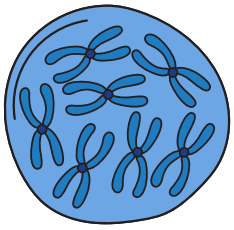
The Department works on several fields of the diagnostic and research practice, including:

- 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.



HIGHLIGHTS

Genomic and Transcriptomic Analyses of Thyroid Cancers Identify DICER1 Somatic Mutations in Adult Follicular Patterned RAS-like Tumors

Minna E., et al. FRONT. ENDOCRINOL. 2023 Oct. DOI: 10.3389/fendo.2023.1267499

The study was designed as a single-centre retrospective assessment, focusing on the molecular landscape of the follicular cell-derived thyroid cancers and included patients with both papillary and follicular thyroid tumors. In addition to already known molecular alterations, mutations in the DICER1 gene were found in BRAFV600E-negative tumors lacking RAS mutations, as well as RET and NTRK gene fusions. Three different types of DICER1 mutations have been characterised in adults in the proposed series.The study cohort recapitulated the well-established genetic background for follicular cell-derived thyroid cancer. In addition, DICER1 mutations were described in adult patients, one of which has not been previously reported in thyroid cancer. For these less common alterations and for patients with unknown drivers, we provide signaling information applying TCGA-derived classification.

Noninvasive Morpho-molecular Imaging Reveals Early Therapy-induced Senescence in Human Cancer Cells

Bresci A., et al. SCIENCE ADVANCES. 2023 Sep. DOI: 10.1126/sciadv.adg6231.

The study focuses on therapy-induced senescence (TIS) of cancer cells, which have been established to promote treatment resistance and disease recurrence, via the paracrine secretion of pro-inflammatory mediators affecting non-cancerous cells. In addition to senescence markers analysis, multimodal imaging methods can be used to investigate TIS, representing a non invasive method for the identification of general cellular traits without cell manipulation. Compared to control proliferating cancer cells, TIS cancer cells exhibited a 3-fold more shrunk pattern of NAD(P)H and FAD coenzymes in the mitochondrial network, and a 20-fold higher accumulation of bigger lipid droplets gathered in cytoplasm, together with cytoplasmic and nuclear abnormalities. Overall, the present study provide fundamental knowledge about original TIS early dynamics in human cancer cells.

Molecular Tumor Board as a Clinical Tool for Converting Molecular Data Into Real-World Patient Care

Vingiani A, et al. JCO PRECIS ONCOL. 2023 Jul. DOI: 10.1200/PO.23.00067

The advent of Next-Generation Sequencing (NGS) allowed a paradigm shift focused on mutational models for personalized treatments. Accordingly, novel drugs are currently approved in oncology based on the evidence of specific biomarkers. The Molecular Tumor Board represent a potential tool for allowing the implementation of mutational models for precision oncology in daily practice. The multidisciplinary team cooperate to generate, interpret, and match molecular data with personalized treatments. Our Institutional MTB was set on May 2020. Our real-world data provide evidence that MTB is a valuable tool for matching NGS data with targeted treatments, eventually implementing precision oncology in clinical practice.

HIGHLIGHTS

Ascl1 and OTP Tumour Expressions are Associated with Disease-free Survival in Lung Atypical Carcinoids

Centonze G, et al. HISTOPATHOLOGY. 2023 May. DOI: 10.1111/his.14873

The study aims at identifying molecular predictors of malignant behavior in lung atypical carcinoids, more aggressive tumors with a higher risk of metastasis compared to typical carcinoids. The histological analysis was performed on 370 candidate cases and 58 were included in the study, the occurrence of well-differentiated morphology, the architectural pattern; the mitotic count; necrosis; pathological tumor staging; vascular invasion; perineural invasion; the lymphocyte infiltrate; microscopic invasion of the bronchial wall or pleura; tumor spread through air spaces (STAS) were evaluated. Ascl1 and OTP expression, together with the Ki-67 proliferative index, were found to contribute to the prognostic assessment ofatypical lung carcinoids, identifying patients at high risk of post-operative relapse. The evaluation of Ascl1 and OTP expression and the Ki-67 proliferation index was suggested as a useful tool in the diagnostic work-up.

Ten-year Survival of Neoadjuvant Dual HER2 Blockade in Patients with HER2-positive Breast Cancer

Nuciforo P., et al. EUR J CANCER. 2023 Mar.DOI: 10.1016/j.ejca.2022.12.020

The study was designed as a phase III, multicentre, international trial, enrolling 455 women who had been randomised to receive lapatinib, trastuzumab or the combination of the two drugs. It was focused on the role of neoadjuvant therapy in HER2-positive breast cancer. Neoadjuvant therapy has become a routine treatment for primary resectable HER2-positive breast cancer, with trastuzumab being the first HER2-targeted agent. Dual anti-HER2 blockade with lapatinib and pertuzumab has recently been shown to achieve a higher pathological complete response (pCR) rate, compared with the trastuzumab-based strategy. The primary analysis of neoadjuvant lapatinib and/or trastuzumab treatment optimisation (NeoALTTO study) showed that patients with early-stage HER2-positive breast cancer, who received neoadjuvant dual anti-HER2 therapy with lapatinib and trastuzumab plus weekly paclitaxel, had a significant improvement in pCR compared with monotherapy. The NeoALTTO trial showed a durable disease control in the pCR group. A second anti-HER2 agent had a positive impact on survival in pCR group, as evidenced by the absence of late relapse. Overall, the long-term follow-up analysis showed that patients with pCR experience better outcomes than patients without pCR. The achievement of pCR with anti-HER2 combination therapy was associated with prolonged recurrence-free survival, representing a long-term predictor of a favorable outcome in HER2-positive breast cancer.

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:

ALESSANDRO GRONCHI

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, in line with 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.

HIGHLIGHTS

Survival Benefit of Adequate Lymphadenectomy in Patients Undergoing Liver Resection for Clinically Node-negative Intrahepatic Cholangiocarcinoma

Sposito C, et al. JOURNAL OF HEPATOLOGY. 2023 Feb. DOI: 10.1016/j.jhep.2022.10.021

The aim of this study was to determine whether adequate lymphadenectomy improves long-term outcomes in patients undergoing liver resection for cN0 iCCA. We performed a retrospective cohort study on consecutive patients who underwent radical liver resection for cN0 iCCA at five tertiary referral centers.

Our data suggest that adequate lymphadenectomy provided better survival outcomes for patients with cN0 iCCA who were found to be node-positive at pathology, supporting the routine use of adequate lymphadenectomy for cN0 iCCA.

Prophylactic Salpingo-Oophorectomy and Survival After BRCA1/2 Breast Cancer Resection

Martelli G., et al. JAMA SURGERY. 2023 Dec. DOI: 10.1001/jamasurg.2023.4770

To assess the association of PSO and prophylactic mastectomy (PM) with prognosis after quadrantectomy or mastectomy as primary treatment for patients with BRCA1 or BRCA2 breast cancer, we perfomed a single institution retrospective cohort study. Our findings suggest that PSO should be offered to all patients with BRCA1/2 breast cancer who undergo surgery with curative intent to reduce risk of death. In particular, PSO should be offered to patients with the BRCA1 variant at the time of breast surgery.

Preoperative Neutrophil-to-Lymphocyte Ratio and a New Inflammatory Biomarkers Prognostic Index for Primary Retroperitoneal Sarcomas: Retrospective Monocentric Study

Fiore M., et al. CLINICAL CANCER RESEARCH. 2023 Febr. DOI: 10.1158/1078-0432.CCR-22-2897

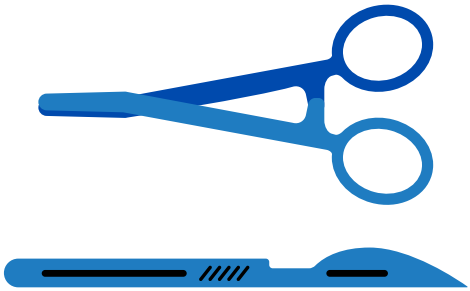
In a large study on patients with primary RPS who undergo surgery, we showed the association between serum inflammatory biomarkers and patient survival and generated a prognostic index that improved the prognostic accuracy of the nomogram included the eighth edition of the AJCC Cancer Staging Manual.

This inflammatory biomarker prognostic index has also relevance to identify patients at risk for septic complications after surgery. This information may be integrated in decision-making to personalize both multimodal treatments strategies and perioperative management for patients affected by primary RPS. NLR was an independent prognostic factor for OS in RPS. When combined into a prognostic index with hemoglobin, monocytes, and PLR, it serves as a readily available prognostic tool addressing tumor-related inflammation and helps in classifying RPS risk in addition to the Sarculator nomogram.

Safety and Efficacy of Robotic vs Open Liver Resection for Hepatocellular Carcinoma

Di Benedetto F., et al. JAMA SURGERY. 2023 Jan. DOI: 10.1001/jamasurg.2022.5697

Long-term oncologic outcomes of robotic surgery remain a hotly debated topic in surgical oncology. We performed a retrospective analysis to analyze short- and long-term outcomes of robotic liver resection (RLR) for hepatocellular carcinoma (HCC) from Western high-volume centers to assess the safety, reproducibility, and oncologic efficacy of this technique The study included 398 patients and represents the largest Western experience to date of full RLR for HCC. Our data show that compared with open liver resection (ORL), RLR performed in tertiary centers represents a safe treatment strategy for patients with HCC and those with compromised liver function while achieving oncologic efficacy.



HIGHLIGHTS

Association of Excision Margin Size with Local Recurrence and Survival in Patients with T1a Melanoma at Critical Structures

Maurichi A., et al. JAMA DERMATOLOGY. 2023 Jun. DOI:10.1001/jamadermatol.2023.0620

To compare outcomes of wide vs narrow excision in patients with T1a melanoma near critical structures, we conducted this cohort study for a retrospective comparison of 1341 consecutive patients aged 18 years or older. The study's findings suggest that local excision with 5-mm margins for T1a melanoma may not be associated with an increased risk of local recurrence.

Breslow thickness greater than 0.4 mm, mitotic rate greater than 1/mm2, and acral lentiginous melanoma and lentigo maligna melanoma subtypes were associated with a higher risk of recurrence. These findings may be useful for future melanoma treatment guidelines.

Long-term Outcomes of Lung Cancer Screening in Males and Females

Ruggirello M., et al. LUNG CANCER. 2023 Nov. DOI: 10.1016/j.lungcan.2023.107387

This study explored female and male overall mortality and survival in two LC screening (LCS) populations, focusing on the predictive value of coronary artery calcification (CAC) at baseline low-dose computed tomography (LDCT). Our findings demonstrate that female LCS participants had lower rates of all-cause mortality at 12 years and better LC survival than their male counterparts, with similar LC incidence rates and stage at diagnosis. The lower CAC burden observed in women at all ages might contribute to explain their lower rates of all-cause mortality and better LC survival.

Impact of Microscopically Positive (≤1 mm) Distal Margins on Disease Recurrence in Rectal Cancer Treated by Neoadjuvant Chemoradiotherapy

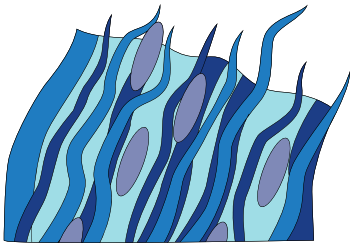
Sorrentino L., et al. CANCERS. 2023 Mar. DOI: 10.3390/cancers15061828

The adequate distal resection margin in rectal cancer patients after neoadjuvant chemoradiotherapy might be tighter than expected. Patients with a distal margin of _1 mm vs. >1 mm were compared: while a distal margin of _1 mm may be sufficient in case of major/complete response, a margin of >1 mm is still required to avoid locoregional recurrence in patients with a low response to neoadjuvant treatment. The findings of the present study might also increase the rate of sphincter-preserving rectal surgery in patients with a close/microscopically positive distal margin and a major/complete response to neoadjuvant chemoradiotherapy.

Diagnostic Accuracy of Magnetic Resonance Imaging in the Pre-Operative Staging of Cervical Cancer Patients Who Underwent Neoadjuvant Treatment: A Clinical-Surgical-Pathologic Comparison

Ditto A., et al. CANCERS. 2023 Apr. DOI: 10.3390/cancers15072061

Magnetic resonance imaging plays a key role in preoperative staging and the evaluation of treatment responses of patients affected by cervical cancer (CC). This study aimed to compare the accuracy of MRI for the preoperative staging of patients with CC who underwent neoadjuvant treatment (NAT) or direct surgery, through a retrospective data analysis of 126 patients with primary CC. Secondary objectives include accuracy comparison between magnetic resonance imaging and physical examination for detecting parametrium and vaginal involvement, and the accuracy in the evaluation of lymph node status. Our results show that the overall accuracy rate of magnetic resonance imaging in preoperative staging of cervical cancer does not seem to be satisfactory, especially when it is applied to pretreated patients.



DEPARTMENT OF ONCOLOGY AND HEMATOLOGY

- 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
- HEMATOLOGY
- 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

DEPARTMENT OF ONCOLOGY AND HEMATOLOGY

HEAD:

FILIPPO DE BRAUD

The Department of Oncology and Hematology 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 patient journey, from the early disease to end-of-life care, exploiting the close collaboration with the other departments, and its trasversal services as the day hospital, pain and supportive care units, the hospice, hemopoietic stem cell manipulation and cryopreservation laboratories, and the blood unit, with its donors and apheresis centres, HLA typing, and virology laboratories.

Its organization, founded on units with a high level of specific commitment and expertise, guarantees the best quality of care for patients and favors new opportunities for professional and cultural growth for its physicians, nurses and biologists. The continuous and rapid evolution of knowledge requires, in fact, that the healthcare professionals keep up to date as to offer constant high-quality care and clinical appropriateness to their patients.

Collaboration within the various units and departments allows a process of continuous sharing and innovation in therapeutic strategies. All decisions on patients' diagnostic and therapeutic pathways are made within the framework of multidisciplinary tumor boards. The concept of "therapeutic strategy" guides clinical decision making. A strong cooperation with the Departments of Experimental Oncology and the Department of Epidemiology and Data Science is in place for research purposes.

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, aware that exploiting clinical and translational research plays a fundamental role, and ensures that our patients are offered the best therapeutic strategy and access to cutting-edge, innovative drugs.

HIGHLIGHTS

Safety and Antitumor Activity of Metformin plus Lanreotide in Patients with Advanced Gastro-intestinal or Lung Neuroendocrine Tumors: the Phase Ib Trial MetNET2
Pusceddu S. et al. JOURNAL OF HEMATOLOGY & ONCOLOGY. 2023 Dec. DOI: 10.1186/s13045-023-01510-9
We conducted the first-in-human phase Ib MetNET2 trial to investigate safety and antitumor activity of metformin in combination with the somatostatin analog lanreotide autogel (ATG) in both diabetic and non-diabetic patients with advanced WDNETs of the gastrointestinal (GI) or thoracic tract. Our study showed that metformin plus lanreotide ATG is a safe and well tolerated combination treatment that is associated with promising antitumor activity in both populations.

STYLE (NCT03449173): A Phase 2 Trial of Sunitinib in Patients with Type B3 Thymoma orThymicCarcinoma in Second and Further Lines
Proto C., et al. JOURNAL OF THORACIC ONCOLOGY. 2023 Aug. DOI:10.1016/j.jtho.2023.04.009
The multicentric Simon 2 stages, phase 2 STYLE trial was aimed to evaluate activity and safety of sunitinib in advanced or recurrent type B3 thymoma (T) and thymic carcinoma (TC). The documented ORR (21.7%), DCR (91.7%), and PFS (8.8 months) confirmed the activity of sunitinib in patients with TC, supporting its use as a second-line treatment.

Romidepsin-CHOEP Followed by High-dose Chemotherapy and Stem-cell Ttransplantation in Untreated Peripheral T-Cell Lymphoma: Results of the PTCL13 Phase Ib/II study
Chiappella A., et al. Leukemia. DOI: 10.1038/s41375-022-01780-1
We reported on a study combining romidepsin and CHOEP as induction before HDT + auto-SCT in untreated PTCLs (PTCL-NOS, AITL/THF, ALK-ALCL). A phase Ib/II trial was conducted to define the maximum tolerated dose (MTD) of Ro-CHOEP, and to assess efficacy and safety of 6 Ro-CHOEP as induction before HDT. The study hypothesis was to achieve a 18-month PFS of 70%. No unexpected toxicities were reported. The primary endpoint was not met; therefore, the enrollment was stopped at a planned interim analysis. The addition of romidepsin to CHOEP did not improve the PFS of untreated PTCL patients.

The SINTART 1 study. A Phase II Non-randomised Controlled Trial of Induction Chemotherapy, Surgery, Photon-, Proton- and Carbon ion-based Radiotherapy Integration in Patients with Locally Advanced Resectable Sinonasal Tumours
Resteghini C., et al. EUROPEAN JOURNAL OF CANCER. 2023 Jul. DOI: 10.1016/j.ejca.2023.03.033
This study assessed activity and safety of an innovative integration of multimodality treatment modulated by histology and response to ICT for sinonasal tumours, rare diseases with poor prognosis. Our data demonstrated that treatment of advanced sinonasal cancer with histology-driven ICT followed by (CT)RT in responsive patients was feasible. Overall, these findings suggest a possible role of ICT as the primary approach in newly diagnosed, resectable sinonasal tumours—especially SNUC—to select patients with favourable prognosis.

A Multicenter Phase 2 Single arm Study of Cabozantinib in Patients With Advanced or Unresectable Renal Cell Carcinoma Pre-treated with One Immune-checkpoint Inhibitor: The BREAKPOINT Trial (Meet-Uro trial 03)
Procopio G., et al. TUMORI. 2023 Feb. DOI: 10.1177/03008916221138881
First-line therapies based on immune-checkpoint inhibitors (ICIs) significantly improved survival of metastatic renal cell carcinoma patients (mRCC). The impact of ICIs combinations in first line on subsequent TKI therapies is still unclear. This is the first trial shedding light on this issue, demonstrating the activity (ORR 38%, mPFS 8.3 months) and safety of cabozantinib in mRCC patients after receiving ICI-based therapy.

HIGHLIGHTS

Italian nivolumab Expanded Access Programme in melanoma adjuvant setting: patient outcomes and safety profile

Ascierto PA., et al. EUROPEAN JOURNAL OF CANCER. 2023 Sep. DOI: 10.1016/j.ejca.2023.113246

This paper reports the results of the Italian Nivolumab EAP in the adjuvant setting of stage III and IV melanoma patients, representing one of the largest series reported in adjuvant setting with the longest follow-up. Our results confirm in a real-life setting the efficacy and safety of nivolumab reported in the CheckMate238 registrative/pivotal trial.

Prognostic Significance of HER2-low Status in HR-positive/HER2-negative Advanced Breast Cancer Treated with CDK4/6 Inhibitors

Zattarin E., et al. NPJ BREAST CANCER. 2023 Apr. DOI: 10.1038/s41523-023-00534-1

Whether Human Epidermal growth factor Receptor 2 (HER2)-low status has prognostic significance in HR + /HER2- advanced Breast Cancer (aBC) patients treated with first-line Endocrine Therapy plus CDK 4/6 inhibitors remains unclear. In 428 patients evaluated, HER2-low status was independently associated with significantly worse PFS and OS when compared with HER2-0 status. Based on our findings, HER2-low status could become a new prognostic biomarker in this clinical setting.

Prevalence of BRCA Homopolymeric Indels in an ION Torrent-based Tumour-to-germline Testing Workflow in High-grade Ovarian Carcinoma

Azzollini J., et al. SCIENTIFIC REPORTS. 202 May. DOI: 10.1038/s41598-023-33857-x

We investigated the prevalence of indels overlooked by ion semiconductor-based sequencing techniques at the homopolymeric regions of BRCA1/2 in a retrospectively selected cohort of 157 high-risk patients affected with high-grade ovarian cancer and negative at tumour testing by ION Torrent sequencing. Our results indicated that the prevalence of homopolymeric indels overlooked by ion semiconductor techniques is seemingly low, providing evidence that tumour sequencing through ION Torrent is a reliable tool for detecting BRCA1/2 germline pathogenic variants.

Relapse After Non-metastatic Rhabdomyosarcoma: The Impact of Routine Surveillance Imaging on Early Detection and Post-relapse Survival

Casanova M., et al. PEDIATRIC BLOOD & CANCER. 2023 Feb. DOI: 10.1002/pbc.30095

This retrospective, single center study examines how well surveillance imaging identifies recurrent tumors and its impact on post-relapse survival in 79 patients <21 years old whose initially localized RMS relapsed. Our study indicates the doubtful role of surveillance imaging in RMS relapse detection and patients' post-relapse survival.

Effectiveness and Safety of Trabectedin and Radiotherapy for Patients With Myxoid Liposarcoma: A Nonrandomized Clinical Trial

Sanfilippo R. et al. JAMA ONCOL. 2023 May DOI: 10.1001/jamaoncol.2023.0056

This international, open-label, phase 2 nonrandomized clinical trial including 46 patients with myxoid liposarcoma demonstrated the activity and safety of trabectedin and radiotherapy, achieving 22% partial responses according to RECIST, with 13% of patients achieving a complete pathologic response and 51% of patients having 10% or less of a viable remaining tumor.

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

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

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 pathologies. 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 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. The 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, in the fields of diagnosis and therapy both. 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 implement software for better patient management and data use.

HIGHLIGHTS

FAP Expression in Alpha Cells of Langherhans Insulae—implications for FAPI Radiopharmaceuticals' Use

Kirienko M., et al. EUR J NUCL MED MOL IMAGING. 2023 May. DOI: 10.1007/s00259-023-06246-9

Radiopharmaceuticals targeting fibroblast activation protein (FAP) alpha are increasingly studied for diagnostic and therapeutic applications. We discovered FAP expression at immunohistochemistry (IHC) in the alpha cells of the Langerhans insulae of few patients. Therefore, we planned an investigation aimed at describing FAP expression in the pancreas and discussing the implications for radioligand applications. No difference was found among NET and adenocarcinoma , nor according to neoadjuvant chemotherapy in the adenocarcinoma cohort (received or not received). We concluded that pancreatic Langerhans islet alpha cells normally express FAP. This is not expected to influence the diagnostic accuracy of FAP-targeting tracers. In the therapeutic setting, our results suggest the need to better elucidate FAPI radioligands' effects on the Langerhans insulae function.

Utility of Detection of Breast Calcifications with Integrated Real-time Radiography System (IRRS) During Digital Breast Tomosynthesis (DBT)-guided Vacuum Assisted Biopsy (VAB): Initial Single-center Experience

Giambersio E., et al. BREAST RADIOLOGY, 2023 Jun. DOI: 10.1007/s11547-023-01636-3

The purpose of this study was to determine whether the presence of calcifications in specimens collected during stereotactic-guided vacuum-assisted breast biopsies (VABB) is sufficient to ascertain their adequacy for final diagnosis at pathology A total of 888 specimens were retrieved, 471 containing calcifications and 417 without. Although there is a statistically significative difference between calcified and non-calcified samples and the detection of cancer , our study shows that the sole presence of calcifications in the specimens is not sufficient to determine their adequacy for final diagnosis at pathology because non-calcified samples can be cancerous and vice-versa. Ending biopsies when calcifications are first detected through IRRS could lead to false negative results.

One-week External Beam Partial Breast Irradiation: Survival and Toxicity Outcomes

Colciago R.R. et al. J CANCER RES CLIN ONCOL. 2023 Jun. DOI: 10.1007/s00432-023-04973-y

According to ASTRO and ESTRO guidelines, external beam Partial Breast Irradiation (PBI) is a valid option for early-stage breast cancer patients. and consensus about the best treatment schedule is needed. We retrospectively analysed data of 344 female patients treated at our institution with adjuvant "one-week" partial breast irradiation. The aim is to report long-term survival and toxicity outcomes of 30 Gy in 5Fx delivered in one week. Based on our experience and the results of this study, "Oneweek"PBI is also effective and safe, and this schedule is a valid option for highly selected early breast cancer patients. For diabetic women, a de-escalation trial will soon start its accrual, to evaluate the effect of 26 Gy in 5Fx on fat necrosis.

HIGHLIGHTS

Stability of Multi-Parametric Prostate MRI Radiomic Features to Variations in Segmentation

Thulasi S.S., et al. J PERS MED. 2023 Jul. DOI: 10.3390/jpm13071172

Stability analysis remains a fundamental step in developing a successful imaging biomarker to personalize oncological strategies. This study proposes an in silico contour generation method for simulating segmentation variations to identify stable radiomic features. In total, we generated 15 synthetic contours for a given image-segmentation pair. 1224 unfiltered/filtered radiomic features were extracted applying Pyradiomics, followed by stability assessment using ICC(1,1). Our findings suggest that segmentation variations can significantly impact radiomic feature stability but can be mitigated by including pre-filtering strategies as part of the feature extraction pipeline.

Magnetic Localization of Breast Lesions: A Large-Scale European Evaluation in a National Cancer Institute

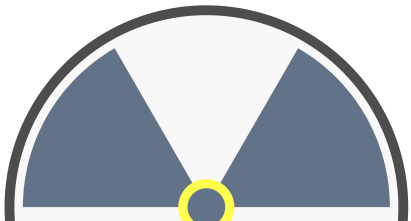
Depretto C., et al. CLINICAL BREAST CANCER. 2023 Aug. DOI: 10.1016/j.clbc.2023.08.004

IIn this study, we analysed the performance of Magseed, a preoperative localization system for nonpalpable breast lesions, based on a magnetic induction system by testing its efficacy, safety and ease of use on a wide scale of 1123 procedures. We analyzed imaging findings, histological results, and type of surgery. The primary outcome was the successful localization rate. Secondary outcomes were the successful placement rate, the ease of percutaneous positioning, the lower procedural complications and reintervention rate. Our analysis showed that image-guided localization with magnetic seeds is an easy, safe, reliable, and effective method for localizing nonpalpable breast lesions. Moreover, the technology was intuitive.

Efficacy and Safety of Vacuum-assisted Excision (VAE) of Fibroadenomas: Experience in a Tertiary Centre

Carriero S., et al. RADIOL MED. 2023 Oct. DOI: 10.1007/s11547-023-01684-9

To evaluate the technical success and efficacy rates of US-guided percutaneous vacuum-assisted excision (VAE) of breast fibroadenomas, also assessing procedural complications and long-term patient satisfaction rates, the institutional database of a tertiary breast cancer referral centre was retrospectively reviewed to retrieve all women with fibroadenomas who underwent US-guided VAE. Immediately after VAE, technical success and the occurrence of procedural complications were evaluated. Imaging follow-up was performed to evaluate technical efficacy (defined as the absence of fibroadenoma recurrence at 6-month follow-up); long-term patient satisfaction was evaluated with phone interviews. Our study showed that US-guided VAE is a safe and effective procedure for the excision of fibroadenomas, representing a viable alternative to surgery, with a low complication rate and high patient satisfaction.



TECHNICAL RESOURCES AND FACILITIES

MOLECULAR ANALYSIS PLATFORMS

Technological 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 to identify novel biomarkers and therapeutic targets, as well as for patient stratification by mutational analysis. Thanks to cutting-edge 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 library 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.

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. 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, this 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 avaiable in the laboratories of the Department of Experimental Oncology. One MACSQuant Tyto cell sorter is also available in the Medical Oncology Department.

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 is avaiable 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 of 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).

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 lipidomic 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 of 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 normal and tumor tissues, and blood/plasma/serum samples, collected and stored within a short time from collection 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 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, in both the clinical and research fields. In some specific research contexts, INT also contributes to the technological evolution and optimization of peculiar equipment, and to the implementation of new applications.

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 benchmarking 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

Since 2020, the Molecular Tumor Board (MTB) is a board with a strong multidisciplinary focus, integrating the knowledge and experience of professionals from different fields. It aims to harmonize the access to molecular analyses and help 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 of 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.

SUPPORTING STRUCTURES AND OFFICES

GRANT OFFICE

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

BIOMEDICAL LIBRARY

The 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 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 at the CTC is dedicated to trials with Advanced Therapy Medicinal Products (ATMP), such as gene, cell and CAR-T therapies.

TECHNOLOGY TRANSFER OFFICE

The Technology Transfer Office was created in 2009 to valorize research results from a scientific and economic viewpoint, to optimize technology transfer and intellectual Property rights 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 the dissemination of Intellectual Property culture among researchers.

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.

- 27 students in total actively enrolled in INT's PhD Programme as of December 31, 2023 with 3 prospective candidates awaiting approval for their registration, having applied to October 2023's selection round.

- 1 Student has been awarded their PhD upon a successful defense of their work (in front of an examination panel including internal and international examiners selected on the basis of their expertise in the project's research area).

The INT-OU PhD Programme offers a variety of activities dedicated to support PhD students career development. 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.

OU-PhD Students are given the chance to present recent scientific papers with their peers through a program of weekly journal clubs, and present their project's progress and obtained data on a yearly basis through Data Sessions opened to the broad INT research community. These occasions, both of which see them discuss with and present to an audience of peers, and senior researchers, with very varied backgrounds, strengthens their communication skills and fosters useful collaborations / exchanges from a translational research perspective. This approach is further encouraged through the program of travel grants that the PhD Programme funds, covering the registration fee and travel costs for 1 or 2 students to a series of events throughout the year: the AACR meeting, the EACR conference, and more specific conferences put forward by the Steering Committee of the program.

EDUCATION

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

- **282** Postgraduate students from UniMi
- **32** Postgraduate students from different universities

- **91** Medical students from UniMI who are doing their internship at INT
- **98** Students from different universities who are doing their internship at INT

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. Progresses throughout 2023 have led to the setup and the launch of AI-ON Lab (Artificial Intelligence for Oncology) led by Dr. Prelaj, MD and PhD from the Politecnico, with a faculty composed of both INT clinicians and researchers, and associate / full Professors from PoliMi. As of December the lab counted a dozen Master and PhD students from PoliMi cooperating with junior INT clinicians in a range of activities, from clinical data analysis to radiomics. Students from the Politecnico are also present in other units within the Data Science department. This collaboration is being formalized by a framework agreement for a joint research platform in 2024.

INT is also highly active in training and educational programs from European and national networks. One example is Cancer Core Europe’s Summer School in Translational Research, co-organized every year by the Scientific Directorate, to which 6 INT junior clinicians and researchers participated in October. Other examples are ESO courses or ESMO and OECI training courses.

THE BOARD OF DIRECTORS

The Board of Directors (CdA), is composed of seven members: the President and six councilors. Four members are appointed by the President of Regione Lombardia, one by the Ministry of Health, one by the Mayor of Milan, and one by the Participating Entities. If there are no Participating Entities, the appointment is made by the President of Regione Lombardia.
The CdA exercises the functions of overall management and control. In particular, it is responsible for approving the strategic directions of the Institute in accordance with the general guidelines of national and regional planning. It approves, upon the proposal of the General Manager, the Strategic and Operational Program and adopts the recruitment plan. It supervises and monitors that the activities are consistent with approved programs and directed toward predetermined results. It approves, upon the proposal of the General Manager, the budget and deliberates on the acquisition of inheritances, bequests, donations and estate changes.
The current Board of Directors, unless dismissed for cause, will serve until December 31, 2028.

MEMBERS

President

Gustavo Galmozzi

Councilors

Sonia Madonna

Carlo Lucchina

Stefano Bolognini

Simona Tesolin

Gianpaolo Carrafiello

Dorina Bianchini

ETHICS COMMITTEE

Since June 6th 2023 Italian Regions appointed a total of 40 CETs (Territorial Ethics Committees), 6 of which belonging to 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 Nazionale dei Tumori - Milano Fondazione IRCCS Istituto Neurologico Carlo Besta**
- 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

From then on, the Institutional Ethics Committee of IRCCS Fondazione Istituto Nazionale dei Tumori in Milan has been upgraded to **"Comitato Etico Territoriale Lombardia 4"** (covering Fondazione IRCCS Istituto Nazionale dei Tumori, Fondazione IRCCS Istituto Neurologico Carlo Besta, ASST di Cremona, ASST di Crema, ASST di Mantova, ATS della Val Padana, Fondazione Teresa Camplani, Fondazione Don Carlo Gnocchi).

The main tasks and responsabilities of the CET and the related STS (Segreteria Tecnico Scientifica) include:

1. **Organizing monthly CET meeting** to guarantee an on time evaluation of clinical trials and the subsequent release of the CET opinions and approvals
2. Evaluation, validation and monitoring of **clinical trials according with the EU CTR** (Clinical Trials Regulation 536/2014) through the european Clinical Trials Information System (CTIS)
3. Evaluation of clinical trials and amendments for **all the other non-CTR Trials (interventional, non interventional, observational, medical devices/IVD**)

In 2023, the submitted INT trials to this CET are the following:

STUDY CLASSIFICATION	NO PROFIT	PROFIT	TOTAL
Observational	125	6	131
Interventional	19	40	59
TOTAL	**144**	**46**	**190**

In addition, 50 CTR studies and 119 non-CTR CET studies has been submitted since June 2023 + 72 studies from afferent Institutions)

- Evaluation of Compassionate use requests (EAP, MAP) from IRCCS Fondazione INT (91 requests in 2023)
- Technical, scientific and regulatory support to clinical researchers and study coordinators for the start up and management of clinical trials, especially focusing on indipendent institutional research

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.
TumoursJournal.org is the website that offers the opportunity for continuous updates in oncology through the insights of opinion leaders and promising researchers featured in Tumori Journal articles, podcasts and social media content.

Listen on Apple Podcasts

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

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Editor in Chief: Giancarlo Pruneri
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Impact factor: 2.3

NATIONAL AND INTERNATIONAL RESEARCH PROJECTS

NATIONAL PROJECTS: GRANTED IN 2023

INT AS COORDINATOR

PI	TITLE	CALL
S. Pasquali	Dissecting Immunological Effects of Neoadjuvant Therapies in Primary High-risk Soft Tissue Sarcomas	AIRC - Next Gen
L. Licitra	A Multi-omics Approach to Disclose Progression and Underlying Biology of Head and Neck Adenoid Cystic Carcinoma	AIRC - IG
S. Sangaletti	Bone Marrow Stroma Cell Education Expand ZEB1+ Neutrophils that Detect Lung Cancer Early Relapse	AIRC - IG
S. Stacchiotti	Molecular Characterization and Patient-derived Models to Expand Therapeutic Options for Epithelioid Hemangioendothelioma	AIRC - IG
M. Di Modica	Role of Gut Microbiota in the Recurrence of HER2-positive Breast Cancer (CARES)	Berlucchi
L. Rivoltini	Quantify Systemic Immunosuppression to Personalize Cancer Therapy	Roche

INT AS A PARTNER

PI	TITLE	CALL
C. Vernieri	Metastasis as Mechanodisease	AIRC - Metastatic disease: the key unmet need in oncology Second edition
L. Beretta	GLYBIOSENS: Glycolipids-coated Colloidal Quantum Dots as Optical Biosensing Platform for Selective Molecular Recognition	PRIN
G. Bertolini	HIMALAYA: High throughout Microscope on a Chip for Liquid Biopsy Assisted by Artificial Intelligence	PRIN

INTERNATIONAL PROJECTS: ONGOING IN 2023

INT AS A COORDINATOR

PI	TITLE	CALL
A. Prelaj	I3LUNG: Integrative Science, Intelligent Data Platform for Individualized LUNG Cancer Care with Immunotherapy	HE - HEALTH
A. Trama	IDEA4RC: Intelligent Ecosystem to Improve the Governance, the Sharing and the Re-use of Health Data for Rare Cancers	HE - HEALTH
G. Apolone	EUOnQoL: Quality of Life in Oncology: Measuring what Matters for Cancer Patients and Survivors in Europe	CANCER MISSION
P. Casali	JANE: Joint Action on Networks of Expertise	EU4HEALTH -JA
L. Rivoltini	SERPENTINE: Quantifying Systemic Immunosuppression to Personalize Cancer Therapy	ERA PERMED

INT AS A PARTNER

PI	TITLE	CALL
I. Bongarzone	CRIMSON: Coherent Raman Imaging for the Molecular Study of the Origin of Diseases	HORIZON 2020
G. Procopio	KATY: Knowledge At the Tip of Your fingers: Clinical Knowledge for Humanity	HORIZON 2020
S. Cavalieri	BD4QOL: Big Data Models and Intelligent Tools for Quality of Life Monitoring and Participatory Empowerment of Head and Neck Cancer Survivors	HORIZON 2020
C. Brunelli	CCE-DART: Building Data Rich Clinical Trials	HORIZON 2020
A. Caraceni	MYPATH: Developing and Implementing Innovative Patient-Centred Care Pathways for Cancer Patients	HE - HEALTH
A. Caraceni	INSPIRE: Integrated Short-term Palliative Rehabilitation to Improve Quality of Life and Equitable Care Access in Incurable Cancer	HE - HEALTH
M. Gariboldi	Phys2BioMed: Biomechanics in Health and Disease: Advanced Physical Tools for Innovative Early Diagnosis	MARIE-CURIE
A. Ferrari	STRONG-AYA Initiative: Improving the Future of Young Adults with Cancer	HE - HEALTH
L. Gangeri	EU-NAVIGATE: Implementation and Evaluation of a Navigation Intervention for People with Cancer in Old Age and their Family Caregivers	HE - HEALTH
D. Mezzanzanica	DISRUPT: On-chip Tomographic Microscopy: a Paradigm Shift for Revolutionizing Lab-on-a-chip Bioimaging Technology	EIC
R. Lanocita	IMAGIO: Imaging and Advanced Guidance for Workflow Optimization in Interventional Oncology	HE - IHI
S. Sieri	EXPOMET: Deciphering the Exposome by Metabolomic Technology in Breast Cancer	ERC
L. Roz	AECC TALENT: Fellowship Programme for Talented Researchers in Cancer Talent	MARIE-CURIE

INTERNATIONAL PROJECTS: ONGOING IN 2023

INT AS A PARTNER

PI	TITLE	CALL
S. Di Cosimo	CAN.HEAL: Building the EU Cancer and Public Healths Genomics Platform	EU4HEALTH
A. Ferrari, M. Terenziani	EU-CAYAS-NE: EU Network of Youth Cancer Survivors	EU4HEALTH
U. Pastorino	SOLACE: Strengthening the Screening of Lung Cancer in Europe	EU4HEALTH
P. Casali	EURACAN23-27: European Reference Network on Rare Adult Solid Cancers	EU4HEALTH
M. Massimino	PAEDCAN Y7-Y10: European Reference Network on Paediatric Cancer- ERN	EU4HEALTH
A. Ferrari	MELCAYA: Novel Health Care Strategies for Melanoma in Children, Adolescents and Young Adults	CANCER MISSION
F. De Braud	CCI4EU: Comprehensive Cancer Infrastructures for Europe	CANCER MISSION
G. Apolone	ECHoS: Establishing of Cancer Mission Hubs: Networks and Synergies	CANCER MISSION
G. Procopio	CARE1: First Line Randomized Study Platform to Optimize Treatment in Patients with Metastatic Renal Cell Carcinoma	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	CANCER MISSION
F. Spreafico	FORTEe: Effects of Exercise Training in Paediatric Oncology	HORIZON 2020
M. Gariboldi	Oncobiome: Gut OncoMicrobiome Signatures (GOMS) Associated with Cancer Incidence, Prognosis and Prediction of Treatment Response	HORIZON 2020
U. Pastorino	4-IN-THE-LUNG-RUN: Towards Individually Tailored Invitations, Screening Intervals, and Integrated Co-morbidity Reducing Strategies in Lung Cancer Screening	HORIZON 2020

SELECTED CLINICAL TRIALS

Clinical trials have been selected according to the following characteristics:

- investigator driven, INT promoted
- first patient enrolled in 2023

SELECTED CLINICAL TRIALS

Multimodal Approach in Patients with Metastatic Hormone-sensitive Prostate Cancer. A Pragmatic Randomized Study with Apalutamide and Local Treatment (APPROACH trial)

Promoter: INT
Principal Investigator: Valentina Guadalupi
Center(s): 16
Accrual: ongoing
Primary objectives: To determine whether treatment with Apalutamide in combination with androgen deprivation therapy (ADT) for 6 months, followed by locoregional treatment with radiotherapy or radical prostatectomy, is more effective compared to medical treatment with Apalutamide + ADT alone in terms of radiographic progression-free survival (rPFS) in patients with hormone-sensitive prostate adenocarcinoma with low-volume metastatic disease
Secondary objectives: To evaluate ORR, TTTP, OS, QoL, L-EFS, safety

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Management of Patients with Early-stage Non-metastatic Breast Cancer Undergoing Antiestrogen Hormonal Treatment. Evaluation of the Feasibility of New Dedicated Pathways Through a Randomized Prospective Study on Osteopathy, Diet, Quality of Life, and Modulation of Inflammatory Status

Promoter: INT
Principal Investigator: Cristina Ferraris
Center(s): 1
Accrual: ongoing.
Primary objectives: To test the effectiveness of physiotherapy and lifestyle modifications in improving side effects from ongoing cancer treatments (menopausal syndrome, weight gain, joint pain) and the reduction of inflammatory status, with the result of improving the quality of life and prognosis of patient, and develop a clinical pathway

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SELECTED CLINICAL TRIALS

Impact of a Nursing Case Management Intervention on the Activities and Satisfaction of Healthcare Professionals in Palliative Care

Promoter: INT
Principal Investigator: Augusto Caraceni
Center(s): 1
Accrual: ongoing
Primary objectives: To study the impact of a nursing case management intervention on the activities and satisfaction of healthcare professionals in Palliative Care

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Approach of Cyclic Quasi-fasting to Enhance the Effectiveness of Chemoimmunotherapy in the Preoperative Treatment of Triple-negative Breast Cancer: the BREAKFAST 2 Study

Promoter: INT
Principal Investigator: Filippo De Braud
Center(s): 1
Accrual: ongoing.
Primary objectives: To investigate whether the quasi-fasting approach, in combination with standard chemoimmunotherapy, can increase the pCR rate compared to standard chemoimmunotherapy alone, which includes anthracyclines, taxanes, and platinum salts in combination with Pembrolizumab.
Secondary objectives: To evaluate ORR, EFS, DFS, DMFS, OS, QoL, safety

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Severe Cyclic Caloric Restriction to Enhance the Efficacy of Maintenance Immunotherapy in Advanced Small Cell Lung Cancer (aSCLC): The FASTIMMUNE Study

Promoter: INT
Principal Investigator: Filippo De Braud
Center(s): 1
Accrual: ongoing.
Primary objectives: To determine if the combination of 5-day cyclic severe caloric restriction with maintenance therapy with atezolizumab in patients with aSCLC who have not progressed after four cycles of induction chemo-immunotherapy with carboplatin, etoposide, and atezolizumab can improve the efficacy of first-line chemo-immunotherapy approach in terms of patient PFS (Progression-Free Survival).
Secondary objectives: To evaluate ORR, OS, QoL, safety

SELECTED CLINICAL TRIALS

Circulating MicroRNAs to Choose the IO Strategy in PD-L1≥50% NSCLC Patients: the Ark Clinical Trial

Promoter: INT
Principal Investigator: Claudia Proto
Center(s): 1
Accrual: ongoing
Primary objectives: To compare the efficacy of ICI +/- chemotherapy as a first-line treatment in patients with advanced PD-L1≥50% NSCLC characterized by high-risk levels
Secondary objectives: To show that a quantitative assessment of main immune cell populations in freshly isolated blood samples possibly to identify significant associations with response, PFS and OS in the two arms of the trial; to deeply characterize the effects of ICI +/- chemotherapy

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Phase II Study to Evaluate the Efficacy of CAR-T Cell Therapy with KTE-X19 in Patients with Relapsed/Refractory Mantle Cell Lymphoma who Achieved Partial Remission During Salvage Therapy with Ibrutinib

Promoter: INT
Principal Investigator: Paolo Corradini
Center(s): 1
Accrual: ongoing
Primary objectives: To estimate the CR rate at 90 days after KTE-X19 infusion in patients with PR undergoing monotherapy with Ibrutinib
Secondary objectives: To evaluate the effectiveness and safety of the treatment, survival, prognostic and predictive biomarkers

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EUGENIA Study: a Screening Protocol for Ovarian Cancer for High-risk Women with Family History or Suggestive Symptoms

Promoter: INT
Principal Investigator: Francesco Raspagliesi
Center(s): 1
Accrual: ongoing
Primary objectives: To identify early-stage ovarian cancer (FIGO I-II) in the screened population; to evaluate the long-term impact of screening on ovarian cancer mortality in the screened population
Secondary objectives: To evaluate logistical and organizational aspects useful for the implementation of the subsequent phases of the study

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SELECTED CLINICAL TRIALS

Effects of Maintaining Motor and Respiratory Performance in Patients Undergoing CAR-T Cell Therapy through Training and Incentivization to Physical Activity during Hospitalization

Promoter: INT
Principal Investigator: Chiara Piazza
Center(s): 1
Accrual: ongoing
Primary objectives: To verify if physical activity performed throughout the hospitalization for CAR-T cell therapy allows patients to maintain the same motor and respiratory performance at discharge and one month after discharge compared to admission
Secondary objectives: To make the patient self-sufficient in the long term and aware of the effectiveness of physical exercise, even after discharge

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Pilot Study on the Effectiveness of Smoking Cessation Interventions for Women Undergoing Surgery for Breast Cancer

Promoter: INT
Principal Investigator: Elena Munarini
Center(s): 1
Accrual: ongoing
Primary objectives: To compare the effectiveness of a standard treatment (4 sessions of motivational counseling) versus an intensive treatment (8 motivational phone sessions and the option to join an online support group) in promoting smoking cessation among women with a recent diagnosis of breast cancer who are candidates for surgery
Secondary objectives: To understand variations in abstinence outcomes based on subpopulations (age, level of dependence, and possible pre-surgical chemotherapy

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CREDITS

We thank the Advisory Board of the Scientific Directorate who contributed in the realization of this report.


FONDAZIONE IRCCS
ISTITUTO NAZIONALE DEI TUMORI


RICERCA ONCOLOGICA

2023

SCIENTIFIC REPORT

The Scientific Report has been published in September 2024 by the Scientific Directorate Fondazione IRCCS Istituto Nazionale dei Tumori.

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