SCIENTIFIC REPORT 2022-2023

ISTITUTO TUMORI GIOVANNI PAOLO II - IRCCS

istituto tumori

IRCCS - Bari

CONTENTS

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INTRODUCTION

The Tumor Institute 'Giovanni Paolo II' in Bari, a Scientifically Characterized Hospitalization and Treatment Institute, is involved in the diagnosis, treatment, and research in cancer care. The Tumor Institute of Bari is integrated into the SSR, the regional health service, as a regional oncology reference center with the task of guaranteeing care and research in the field of oncology and coordinating the functions of research and treatment, including through the definition of diagnostic and therapeutic care pathways for oncological diseases, monitoring their effectiveness and providing for their updating.

Specifically, the Institute carries out clinical and translational research in the biomedical field and in that of the organization and management of health services. All the operating units of the Institute carry out research activities both through internal institutional projects and through projects funded by external parties (Ministry of Health, Apulia Region, Charities, etc.).

In particular, the Institute carries out both current research activities, autonomous scientific research of the Scientific Hospitalization and Treatment Institutes in their field of recognition directed at developing knowledge in the field of biomedicine and public health, and finalized research, through specific projects and directed at achieving particular and priority objectives, biomedical and health, identified by the Regional Health Plan and the National Health Plan.

The lines on which current research activity is based are defined and approved by the Ministry of Health every three years. Targeted research, on the other hand, is developed through participation in specific regional, national, and international calls for proposals promoted by public or private entities and institutions and also in carrying out sponsored research. In a historical period in which oncology is experiencing a moment of great innovation given by the development of new therapeutic opportunities associated with new diagnostic possibilities, interventions financed by our country and aimed at improving and optimizing the cancer patient care pathway are of fundamental importance. All these interventions involve the strengthening of oncology research through the development of new procedures and innovative models, including personalized medicine, in the areas of prevention, diagnosis and treatment. In addition, all these projects involve the formation of larger or smaller research networks for sharing resources and expertise.

The year 2022 was the starting year of the three-year Current Research 2022-2024, thus marked by the definition of new lines of research that would orient the Institute toward global clinical and translational research at that time. From the perspective of finalized and translational research, moreover, 2022 was marked by the opportunity to participate in the new ministerial Finalized Research calls and to access PNRR funds aimed at strengthening the biomedical research sector of the National Health System, exploiting collaboration with the research programs of the Ministry of University and Research (MUR) and the technology transfer programs of the Ministry of Economic Development (MISE).

Brief History of the Institute

The Tumor Institute 'Giovanni Paolo II', Istituto di Ricovero e Cura a Carattere Scientifico, is located in the historic Fascist-era building of the 'Domenico Cotugno' hospital, a sanatorium dedicated to tuberculosis patients, which opened in 1939, as the date in Roman numerals at the entrance to the Institute indicates.

The building, also known in the city by the name of 'il lazzeretto', due to the presence of highly infectious patients, had been built in a then suburban area. It maintained this function until the mid-1960s, and then gradually changed its purpose and vocation. In 1976, the president of the Apulia Region declared it a Provincial Hospital Specializing in Oncology. In 1985, an interministerial decree transformed it intoInstituto di Ricovero e Cura a Carattere Scientifico.

Today, the Institute is IRCCS, a legal entity under public law, of national importance, not transformed into a foundation, confirmed by ministerial decree in 2006 in the oncology discipline specialization. The Institute began the verification process in 2010 to be accredited as a center of excellence dedicated to Oncology according to international criteria. After a visit by the International Commission of the European Organization of Cancer Institutes (OECI) in October 2014, the Institute was internationally accredited as a "Clinical Cancer Center" and received certification at the OECI General Assembly in June 2015.

Mission, Goals and Values

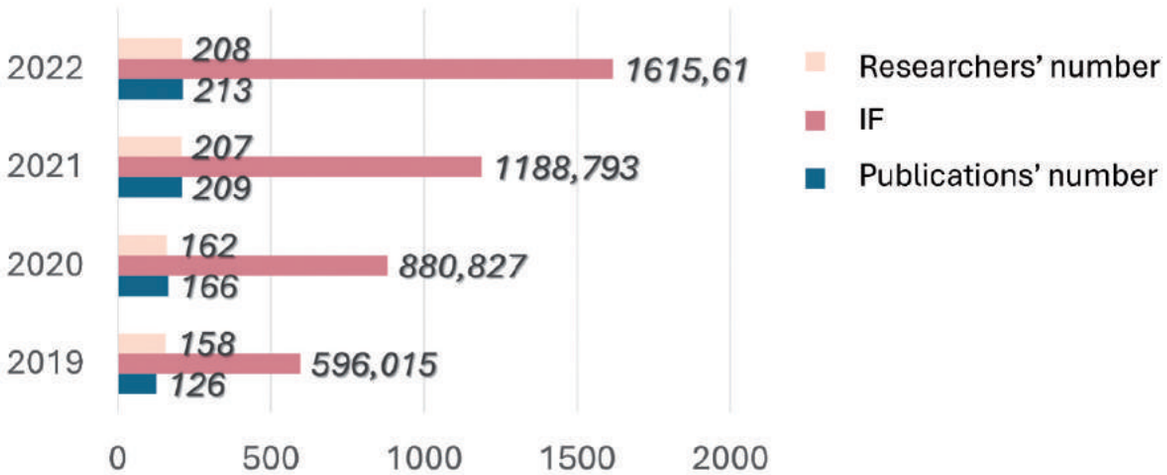
The Institute pursues goals concerning:

- The diagnosis and treatment of cancer through the application of increasingly advanced and internationally recognized diagnostic and therapeutic methods and protocols;
- Research in the field of cancer aimed at a greater understanding of biological aspects and continuous improvement of systems of diagnosis and treatment;
- Information to the public on all issues related to cancer and the continuing education of all personnel employed within the Institute.

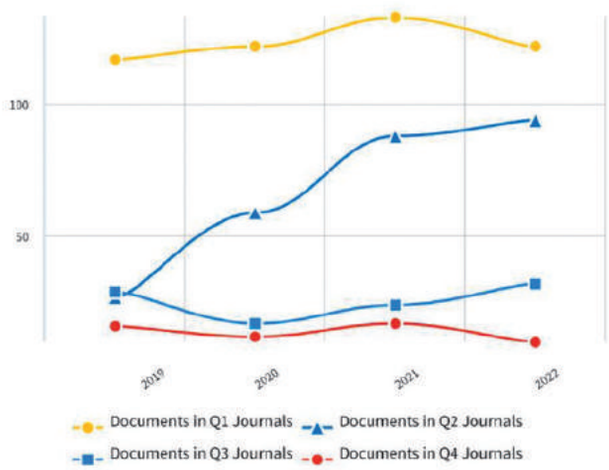
The Institute operates in three areas: clinical, research and training. Its mission is to achieve and maintain levels of excellence in cancer prevention and in the diagnosis, treatment, and rehabilitation of people with neoplastic diseases, giving priority to research in the areas of epidemiology, etiology, neoplastic transformation and progression, and experimental therapies. The Institute's activities are carried out by constantly caring for the principles of person-centeredness, effectiveness of care provision and efficiency of organizational processes. The primary strategic objective is the strengthening of translational research aimed at improving diagnosis and treatment in the field of oncology with the intention of promoting synergy between clinical and basic research and working for efficient and timely transfer of knowledge to the patient's bedside.

SCIENTIFIC ACTIVITY

PUBLICATIONS

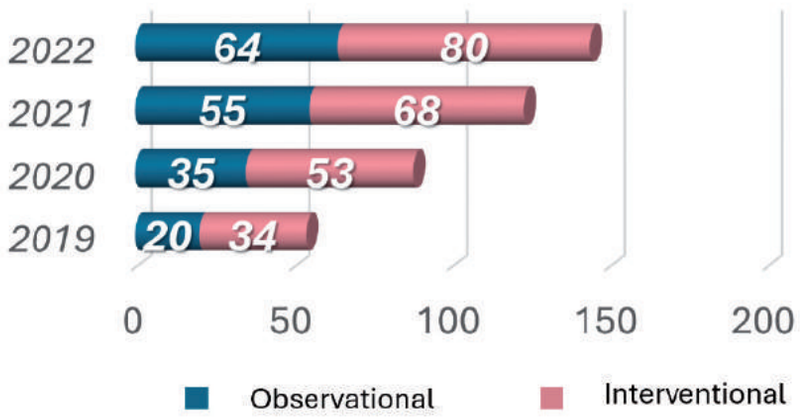


Quartile placement

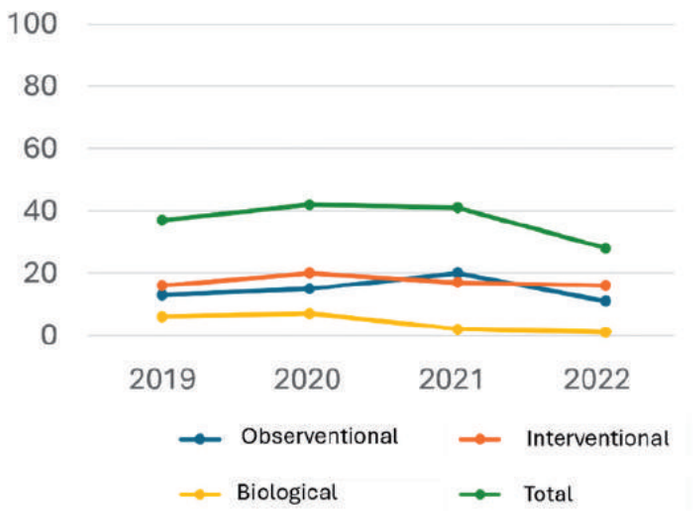


Average IF per researcher

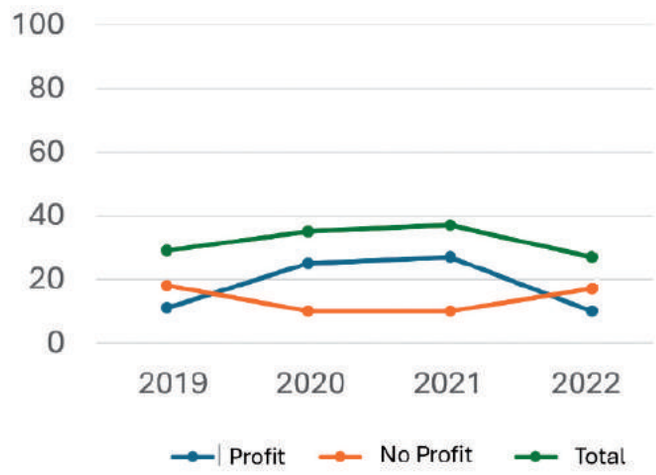
CLINICAL TRIALS



No. activated clinical trials by type

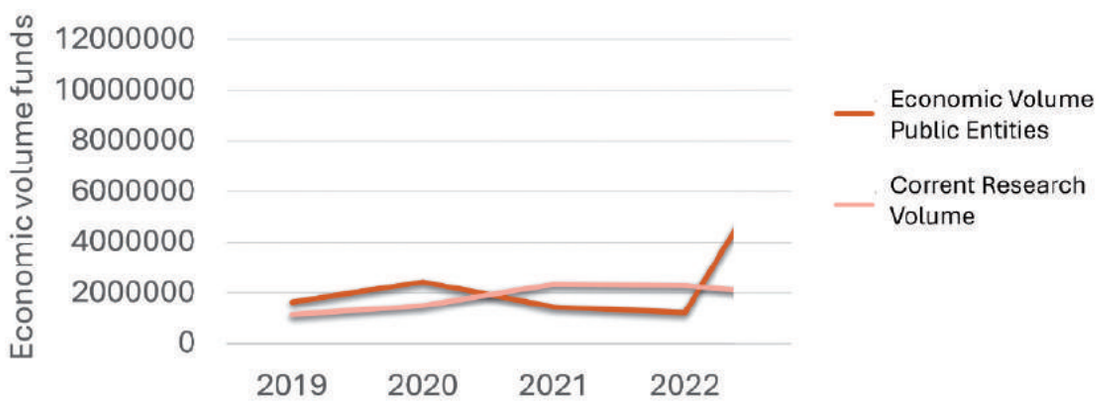


No. activated clinical trials by sponsor profile



FUNDING

Economic Volume Public Entities



Economic Volume Private Entities

PNRR	€ 2.440.400,00
PNC	€ 3.082.775,00
POS	€ 2.240.000,00
Ricerca Finalizzata	€ 346.000,00
Totale	€ 8.109.175,00

MAJOR EVENTS

The Oncology Institute stands as a pillar of excellence in the field of cancer research and treatment, distinguished by its commitment to promoting and actively participating in events of national and international scope. Founded on scientific innovation and fruitful collaboration with leading institutions, the Institute has achieved significant influence in the oncology landscape.

In addition to offering the highest level of care to patients with malignancies, the Institute is fervently committed to opening the door to sharing experience and knowledge with the global scientific community. Organizing and participating in major events thus stand as milestones in the Institute's journey, contributing tangibly to the advancement of oncology research and the dissemination of best practices in cancer treatment. The participation of luminaries in the field of oncology, along with institutional representatives and prestigious international organizations, lend the events promoted by the Institute unparalleled importance and prestige. These meetings provide fertile ground for the exchange of ideas and the establishment of fruitful collaborations, further consolidating the Institute's leadership position in the global oncology arena.

The following are the events in which the institute has participated or sponsored:

Cultural Artistic Events

- “The Enchantment of Beauty” literary prize, in collaboration with APS Bottega del Sorriso
- “Re-shoot” photo project and exhibition, in collaboration with photographer Alessandro Matassa
- Presentation of the volume “Medicaments and Other Truths”, a collection of poems by Silvia Costanzo

- Documentary “Unfiltered”, made by the Academy of Fine Arts in Rome, on the theme of fighting lung cancer
- Concert series with “The excellencies of the conservatory Niccolò Piccinni” of Bari
- Naming of the conference hall after Massimo Tommasino, former scientific director of the Institute
- Ceremony of delivery of a 50 thousand euro donation from Bank of Italy
- “Communication Oncology, the lesson of Alessio Viola”. Training course for journalists, by the Ordine dei Giornalisti di Puglia
- Presentation of the volume “Aldo Moro: the truth denied”, by Gero Grassi

Fundraisers, Charity Evenings

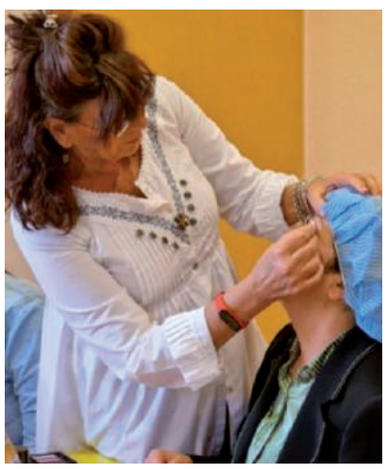
- Race for the Cure Bari, year 2022.
  Participation with running team, information booths and conferences
- Race for the Cure Bari, year 2023.
  Participation with running team, information booths and conferences
- Together for Oncology, 2022.
  Benefit evening by the Italian Women's Center Province of Bari
- Together for oncology, 2023.
  Benefit evening by the Italian Women's Center Province of Bari

Open Day and Free Checkups for Patients

- Open Weekend Prostate Cancer by Onda, year 2022, carried out in collaboration ONDA Foundation, National Observatory on Women's Health and Gender
- Gynecological Cancers Open Day, year 2022, in collaboration with ACTO Puglia
- Psychological Wellness Month, year 2022, by the psycho-oncology service
- RISP, national lung screening program for smokers and former smokers
- World Thrombosis Day, year 2022, event held in collaboration with Anmco
- Free urological examinations on the occasion of Father’s Day, year 2023
- Open Week of Cardiovascular Diseases, year 2023, carried out in collaboration ONDA Foundation, National Observatory on Women's Health and Gender
- Psychological Wellness Month, year 2023, by psycho-oncology service
- World Thrombosis Day, year 2023, event realized in collaboration with Anmco
- “Menopause. Everything you always wanted to know and never dared to ask”. Open meeting on early menopause, year 2023, by the psycho-oncology service
- Free radiological examinations for female workers in the Bari industrial zone, year 2023, an event held in collaboration with “Una stanza per un sorriso Odv”
- Training course for patients on PICC management, year 2023

Aesthetic Oncology Initiatives And Mental And Physical Well-Being

- Makeup to feel better, year 2022-2023, various dates. Make-up, hairdressing and corrective make-up sessions conducted in collaboration with local associations.
- Project “Cancer but not fear. Meetings with nutritionists and psychologists”, by APS Bottega del Sorriso, year 2023
- Project AMAti - Adapted Motor Activities, for patients with lung cancer, carried out in collaboration with Walce Onlus, year 2023
- Project “Vital Steps. Nordic walking and yoga” for patients undergoing treatment, year 2023
- Signing of protocol with Angiulli sports club for physical activity for cancer patients and healthy lifestyles for all.



Other initiatives

- Home-Work Displacement Plan of the Municipality of Bari.
- Start CUP award for innovation, organized by ARTI in collaboration with Regione Puglia, Edition 2022
- Start CUP Prize for Innovation, organized by ARTI in collaboration with Regione Puglia, Edition 2023

Scientific Dissemination Patient Awareness and Education Events

- Scientific research, three-day “retreat” for our Institute’s researchers, year 2022.
- European Researchers’ Night, edition 2022
- Beyond Dysphagia, training and awareness day, year 2022.
- CTPO with the Sylos-Fiore High School Pole in Terlizzi, year 2022
- Nutrition of patients with colorectal cancer. Insight by Ass. Gabriel OdV, year 2022

- Insight into the care of the cancer patient. Bridge The gap project, by Isheo and The Lamp of Aladdin, year 2023 Bridge The Gap. April 2023
- European Research Night, year 2023
- Notte europea della ricerca, anno 2023
- ERN 2023/Polytechnic
- Conference to present the “Breath Analysis” device, year 2023
- Conference on the role of patient associations in regional oncology networks.

ECM Conferences

- Breast cancer, what’s new from American Society of Clinical Oncology 2022?
- Oncology Day - Valencia - June 2022
- World Conference on Lung Cancer, Vienna, 2022
- The evolution of radiation protection, year 2022
- Sixth Pulmonary Oncology Conference, year2022
- “New strategies for risk assessment and risk reduction in neoplasms of the female sphere”, year 2022
- Risk Management Forum In Health Care. Year 2022
- “Therapeutic Innovations in Oncology”, Year 2022
- Pills of Cardioncology, Year 2022
- 43rd EORTC-PAMM Meeting, Year 2023
- Rare cancers, challenges and opportunities, year 2023
- Physician and healthcare facility liability in light of the law. Year 2023
- EACR-OECI Conference, Year 2023
- Single Guarantee Committee 2023
- Molecular Tumor Board. Update and optimization. Year 2023
- New frontiers in metastatic gastric cancer. Year 2023
- “Contrast media in radiodiagnostics: myths and realities”. Year 2023
- “The role of mass media in preventing and combating cancer” organized by Gabriel OdV Association, Year for the Humanization of Care in Oncology. June 2023
- European Congress of Oncology OECI, Year 2023
- Oncofertility. Year 2023.
- Cardioncology Year 2023.

- Uro-gynecologic cancers. Comparison and discussion of new therapies, treatment opportunities, research, and take-home policies. Year 2023.
- 7º Mediterranean Forum in Health Care 2023.
- ACC Annual Meeting 2023 - Genoa, Italy
- Networks of care for Breast Cancer: the role of the “Cancer Institute in patient care”. Year 2023
- Perioperative management in gynecologic oncology. Year 2023
- “Topics in women's oncology”, November 2023.
- 2nd Pathologic Anatomy Symposium “Advances in Cancer Research”, Year 2023
- 7th Pulmonary Oncology Conference. From prevention to treatment of advanced disease. Year 2023.
- Risk management in health care. November 2023.
- BRCA Related Tumors

Awards and recognitions obtained by researchers

- May 2023. Italian Clinical Engineering Association. “Artificial Intelligence for the Prediction of Lymph Node Status in Clinically Negative Breast Cancer Patients”, presented by Raffaella Massafra - medical physicist at IRCCS Giovanni Paolo II in Bari was found to be the “most popular” study.
- May 2023. “Italian Clinical Engineering Association. Validation of ARGO (Automatic Record Generator in Onco-Hematology)”, submitted by Gian Maria Zaccaria, biomedical researcher at IRCCS Giovanni Paolo II, emerged as the winner in the category “Applications of Artificial Intelligence in Healthcare”
- June 2023, IFODS Paris, Prix Poster for a study on predicting disease recurrence in patients with lung cancer, coordinated by Raffaella Massafra.
- September 2023, Best Poster at ACC Annual Meeting to Maria Colomba Comes.
- September 2023, FIL Club 2023 call for papers, awarded to Dr. Sabino Ciavarella for a research project on lymphomas in elderly patients.
- November 2023, National Congress of Psycho-oncology, best poster to Francesca Romito and Fulvia Lagattolla.

Awards Obtained By The Institute

- Three Pink Stamps for our Institute. Recognition by Onda - National Observatory on Women’s Health and Gender for cancer care reserved for women. https://bit.ly/3EIyM9n
- Prostate cancer, our Institute is from Bollino Azzurro. Onda - National Observatory on Women’s Health and Gender.

INSTITUTIONAL RESEARCH LINES 2022-2024

The mission of the Institute is to pursue and combine two fundamental aspects: research and care. To this end, the Institute promotes interaction and collaboration between clinical and translational research units, focusing efforts and tools on the four Lines of Research, approved for the three-year period 2022-2024 by the Ministry of Health.

The main objectives to be pursued are to strengthen the Institute's role in research activities at regional, national, and international levels, and to apply a new and innovative organizational model of research aimed at optimizing the use of already available resources to achieve better results in science, including through the recruitment of new and young resources.

The 4 Research Lines recognized by the Ministry of Health are continuously implemented in content with new strategies with the intent to better respond to new care, scientific and technological challenges and to encompass all new research projects.

The following section describes research lines issues and projects funded under Current Research 2022-2024.

LINE 1

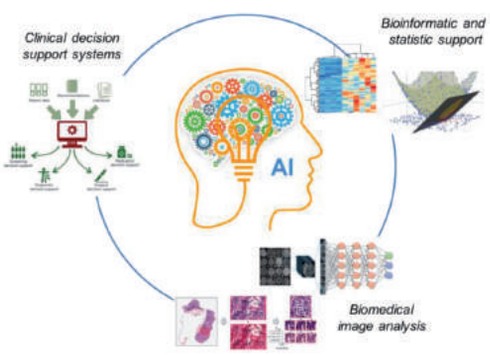
From Cancerogenesis to Tumor Progression for a Precision Oncology

LINE 2

Clinical Trials in the Age of Precision Oncology

LINE 3

Computational Science and Technology of Artificial Intelligence: Drivers for a Digital Oncology



LINE 4

New Organizational-Management Models in Oncology

LINE 1 | From Cancerogenesis to Tumor Progression for a Precision Oncology

Overview

Personalization of the approach to cancer disease requires in-depth knowledge of the genetic-molecular-cell biological characteristics underlying the development and growth of the individual tumor, knowledge that will enable future innovative clinical programs for cancer prevention/diagnosis and treatment in the individual patient. This conceptual approach enhances the role that new in vitro/ex vivo/invivo study models and especially the importance of having biological materials from patients and subjects at risk. The availability of innovative preclinical models, such as patient's derived organoids (PDOs), the study of extracellular vesicles, the ability to characterize tumors and the tumor microenvironment, and to study circulating factors, will allow for a deeper understanding of the mechanisms of tumor development and progression using omics techniques or based on innovative genetic screening and cell biology techniques. Among these will be considered projects with single-cell approaches, genetic engineering techniques such as CRISPR/Cas9, transcriptomics analysis, metabolomics, etc., performed on tumor and microenvironment cells (fibroblasts, cells of the innate and adaptive immune system, vascular and lymphatic network cells). The activity of the IRCCS Istituto Tumori di Bari in the field of prevention, and in particular in the oncological prevention of subjects at risk for socio-clinical-genetic characteristics, the presence of an excellent Biobanking activity and the cultural/technological substrate with which the Institute is endowed guarantee to said Line an important role in future project planning. This Line of Research will include all Laboratory activities that with in vitro/ex vivo/in vivo techniques will deepen the cellular mechanisms underlying the processes of disease genesis and progression up to hypothesize "biomolecular based" preclinical and clinical models of primary-secondary prevention.

Aims

Modern oncology is essentially based on the concept of personalization of various clinical approaches that exploits, for preventive/diagnostic/therapeutic purposes, the knowledge in the individual patient of cellular pathways, involved in the mechanisms of genetic/epigenetic regulation, of the genesis/transmission of intercellular tumor signals, between tumor cell and microenvironment, and between tumor cell and host. Through the use of immortal cell lines and patient biological materials (primary cultures, organoids, tumoroids, pdx, extracellular vesicles, etc.) with in vitro/ex vivo/in vivo techniques, said Line aims to identify biomolecular features of potential clinical relevance to be proposed for translational studies. Said Line will also include studies on biological matrices of xenobiotic exposure and biological damage in at-risk subjects. The intense activity of the IRCCS Istituto Tumori di Bari in the field of prevention, and in particular in the oncological prevention of subjects at risk for socio-clinical-genetic characteristics, the presence of an excellent Biobanking activity and the cultural/technological substrate it has at its disposal guarantee that the said Line will play an important role in the scientific programming of the Institute. Specifically, the Line will consider: a) biomolecular mechanisms of carcinogenesis; b) biomolecular mechanisms of progression; c) biomolecular mechanisms of metastasis; d) biomolecular mechanisms of drug resistance/sensitivity; e) new laboratory technologies; f) clinical-biomolecular bases for new models of primary/secondary prevention. The design should prefer the use of biological material from patients, pursue novel scientific hypotheses, and include new laboratory approaches to be developed up to analytical validation. "Proof of concept" studies of primary and secondary prevention based on the aforementioned biomolecular information will also be included.

Identification of circulating factors for diagnosis, prognosis, and/or prediction of response to therapy in solid tumor disease

P.I. Amalia Azzariti
Start date: 2022
End date: 2024

Background

The search for circulating factors with a role as diagnostic/prognostic/predictive biomarkers in solid tumor diseases is the focus of this project, which has 3 main objectives and involves the characterization as biomarkers of extracellular vesicles (EVs), cytokines, ncRNAs, cells of immunity, etc. The rationale for evaluating the expression of 7 lncRNAs as diagnostic/prognostic factors in prostate cancer is based on an in silico study conducted by Dr. De Summa that identified 7 lncRNAs that when over-expressed indicate a risk of having a Gleason score greater than 4+3. During laparoscopic or open surgeries, manipulation of the surgical field could change the content of extracellular vesicles in the abdominal cavity leading to an alteration of the microenvironment correlated with colorectal cancer invasiveness and/or metastasis processes; therefore, we will characterize these EVs to determine their differences. Finally, we will validate the results of an in silico study conducted on the relationship between certain circulating immune cells and pancreatic carcinoma, which showed that dendritic cells, macrophages, and T lymphocytes expressing three markers S100A8, S100A6, and S100A12 are differentially expressed in patients compared with healthy people, as a "tool" for the diagnosis of this cancer pathology in liquid biopsy.

Aims

1. Analysis of the diagnostic/prognostic/predictive role of EVs, cytokines, circulating immune cells and ncRNAs carried by EVs in biological fluids of patients with solid tumors.
2. Expansion of the case series with an additional 20 patients with peritoneal carcinosis from CRC to validate the hypothesis that certain subpopulations of EVSs released into the peritoneal lavage fluid (PLF) may be responsible for creating the premetastatic niche of tumor dissemination leading to the development of peritoneal carcinosis.
3. Analysis of the diagnostic/prognostic role of circulating circRNAs carried by EVs in the plasma of patients with NSCLC (AIRC project, PI: Prof. Storlazzi - UNIBA).
4. Analysis of the diagnostic role of a panel of genes analyzed in EVs from plasma and urine of patients with ovarian cancer (PREGO project, PI: Prof. Scillimati - UNIBA).)

Results

The experimental study to validate the diagnostic/prognostic role of the 7 lncRNAs in the tumor tissues of 24 pts with prostate cancer and 5 healthy pts with prostate cancer has been completed and data processing is in progress. It was decided to evaluate the presence of these lncRNAs in EVs from urine. Cytofluorimetric analysis of EVs from peritoneal lavage fluids of patients with colon Ca has been finished and data analysis is underway to be followed by statistical analysis.

The validation study as diagnostic factors for pancreatic ca of selected circulating immune populations is finished and the manuscript is being written in collaboration with Dr. A. Derakhshani and Prof. N. Silvestris. The study of the analysis of the role of circulating EVs as predictors of response to immunotherapy with immune checkpoint inhibitors, for the selection of patients to start treatment and for monitoring the response to anti-PD1 has been completed and the data published.
In the experimental study to validate the diagnostic/prognostic role of the 7 lncRNAs in patients with prostate ca, characterization of these lncRNAs in EVs from urine is underway in order to validate them as diagnostic/prognostic biomarkers in liquid biopsy.
Collection of blood samples for the study of circulating circRNAs carried by EVs in plasma of patients with NSCLC and isolation of EVs has begun (AIRC PI project: Prof. Storlazzi - UNIBA).
The collection of blood samples for the identification of a panel of genes for the diagnosis/diagnosis of ovarian cancer and isolation of EVs has begun (UNIBA PI project: Prof. Scillimati - UNIBA)

In 2022, we demonstrated that circulating extracellular vesicles (EVs) are predictive biomarkers of response to anti-PD1 in metastatic melanoma patients:

- **three subpopulations of PD1+ EVs and PD-L1+ Evs, in plasma, were identified as independent biomarkers .**
- **a POC diagnostic device for their detection is currently being developed.**

In 2023, we demonstrated that circulating EVs aree biomarkers for monitoring the response to anti-PD1

- **only circulating PD1+ EVs, originating from tumor cells, decreased with the positive response to therapy and increased with the onset of resistance to treatment.**

Publications

- Circulating extracellular vesicles expressing PD1 and PD-L1 predict response and mediate resistance to checkpoint inhibitors immunotherapy in metastatic melanoma.
- Serratì S, Guida M, Di Fonte R, De Summa S, Strippoli S, Iacobazzi RM, Quarta A, De Risi I, Guida G, Paradiso A, Porcelli L, Azzariti A. Mol Cancer. 2022 Jan 18;21(1):20. doi: 10.1186/s12943-021-01490-9.
- Circulating extracellular vesicles are monitoring biomarkers of anti-PD1 response and enhancer of tumor progression and immunosuppression in metastatic melanoma.
- Serratì S, Di Fonte R, Porcelli L, De Summa S, De Risi I, Fucci L, Ruggieri E, Marvulli TM, Strippoli S, Fasano R, Rafaschieri T, Guida G, Guida M, Azzariti A. J Exp Clin Cancer Res. 2023 Sep 28;42(1):251. doi: 10.1186/s13046-023-02808-9.

Development of 3D cellular models of solid tumor diseases (patient-derived organoids-PDOs, short term-culture) and their validation for the study of drug response prediction and for screening of new active ingredients or drug combination

P.I. Amalia Azzariti
Start date: 2022
End date: 2024

Background

Models generated from disrupted cell samples, or "tumorids," can be used as preclinical tumor models in pharmacology studies to identify therapies in Precision Medicine. 3D cell models, short term-cultures, and patient-derived organoids (PDOs) accurately reproduce the tumor microenvironment, mimic the regulatory mechanisms between tumor and stroma, and exhibit a gene expression profile that reflects a differentiative phenotype. Their use has proven to be an efficient system to optimize and overcome the limitations associated with conventional systems in vitro and in animal models in drug screening studies. Short term-cultures allow rapid drug screening, in contrast PDOs can be generated and propagated with great efficiency and can be cryopreserved in liquid nitrogen for later reuse. By being able to develop them from biopsy or surgical fragments of both healthy and diseased tissue, PDOs enable important comparative analyses of cancer patient tissues. In addition, PDOs maintain the original population of myeloid and lymphocytic cells and allow the study of response to inhibitors of immunologic checkpoints under experimental conditions very similar to those of patients. PDOs allow detailed molecular and phenotypic characterization of the tumor (e.g., mutational, transcriptomic and proteomic profiling, cytokine secretion, clonal heterogeneity, etc.) and thus represent the ideal tool for ex vixo study of tumor characteristics and potential drug response.

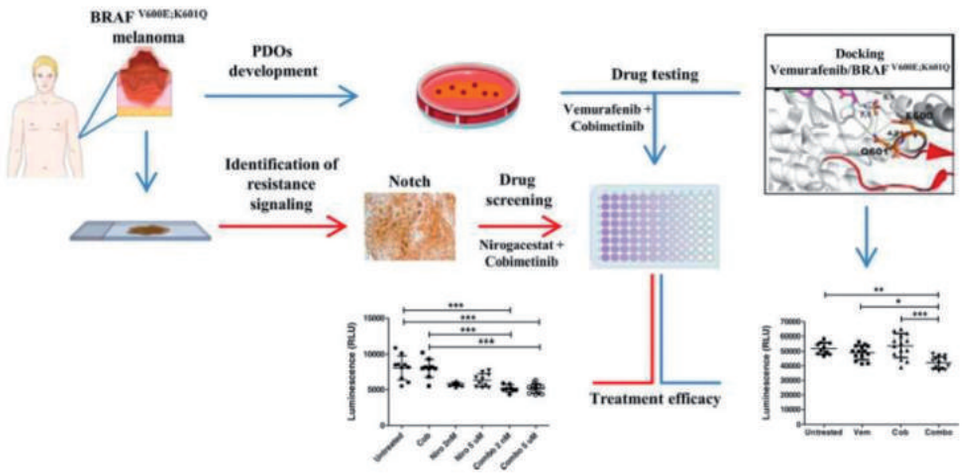
Aims

1. Setup of experimental protocols for preparation of PDOs from solid tumors, such as melanoma, CRC, HCC, pancreatic cancer, ovarian, cervix, breast, etc.
2. Validation of PDOs as 3D cellular models that mimic miniature organs or tumors by tumor microenvironement (TME) and tumor immune microenvironement (TIME) analysis.
3. Drug screening in PDOs and short term-cultures and study of mechanisms responsible for drug response/resistance.

Results

Metastatic melanoma: validation of PDOs as models for drug screening by analysis of response to combination to target-therapy (BRAFi/MEKi) or immunotherapy (anti-PD1) and comparison with responses obtained in patients treated with the same drugs.
CRC: validation of PDOs as models for drug screening of new drug combinations (e.g., nivolumab combined with sunitinib-angiogenic drug used as an immunomodulatory agent), for analysis of mechanisms responsible for drug response, and for identification of biomarkers predictive of response to combined treatment with antiangiogenic drug and immunotherapy.

Cervical cancer: drug screening in PDOs with Trabectedin as monotherapy or associated with propranolol (ß-blocker) to evaluate efficacy in this pathology (project in collaboration with PharmaMar and Prof. G. Cormio - UNIBA). HCC: development of experimental protocol for the generation of PDOs from HCC (multicenter project Prot. 806/CE). Pancreatic Ca: a system for the formation of PDOs in the presence of pH sensors was optimized. In 2023, drug screening analysis was completed in PDOs with Trabectedin as monotherapy or combined with propranolol (ß-blocker) to evaluate efficacy in cervical cancer, and the results were compiled in a published manuscript. In pancreatic ca, the influence of alcohol in determining a TGF-b related phenotype was investigated, and the results have been the subject of a published manuscript.



doi: 10.1016/j.phrs.2022.106323

Publications

- BRAFV600E;K601Q metastatic melanoma patient-derived organoids and docking analysis to predict the response to targeted therapy. Porcelli L, Di Fonte R, Pierri CL, Fucci L, Saponaro C, Armenio A, Serratì S, Strippoli S, Fasano R, Volpicella M, Daprile R, GUARINI S, Ressa CM, Guida M, Azzariti A. Pharmacol Res. 2022 Aug;182:106323. doi: 10.1016/j.phrs.2022.106323. Epub 2022 Jun 22.
- Probing Single-Cell Fermentation Fluxes and Exchange Networks via pH-Sensing Hybrid Nanofibers. Onesto V, Forciniti S, Alemanno F, Narayanankutty K, Chandra A, Prasad S, Azzariti A, Gigli G, Barra A, De Martino A, De Martino D, Del Mercato LL. ACS Nano. 2023 Feb 28;17(4):3313-3323. doi: 10.1021/acsnano.2c06114. Epub 2022 Dec 27
- Gene Expression Comparison between Alcohol-Exposed versus Not Exposed Pancreatic Ductal Adenocarcinoma Patients Reveals a Peculiar TGFß-Related Phenotype: An Exploratory Analysis. Doronzo A, Porcelli L, Marziliano D, Inglese G, Argentiero A, Azzariti A, Solimando AG. Medicina (Kaunas). 2023 Apr 30;59(5):872. doi: 10.3390/medicina59050872.
- Cervical cancer benefits from trabectedin combination with the ß-blocker propranolol: in vitro and ex vivo evaluations in patient-derived organoids. Di Fonte R, Strippoli S, Garofoli M, Cormio G, SerratÏ S, Loizzi V, Fasano R, Arezzo F, Volpicella M, Derakhshani A, Guida M, Porcelli L, Azzariti A. Front Cell Dev Biol. 2023 Jun 13;11:1178316. doi: 10.3389/fcell.2023.1178316. eCollection 2023.

Optimization of drug treatments by creating nanodelivery systems for selective drug delivery to tumor sites and analysis of cellular metabolites (metabolomics) and drugs and their metabolites in biological fluids

P.I. Amalia Azzariti
Start date: 2022
End date: 2024

Background

This project, in collaboration with the Department of Pharmacy Pharmaceutical Sciences (UNIBA) involves the design and preparation of biomimetic drug delivery systems, mostly of a nanoparticle nature, formed by fusing or coating nanoparticles of various natures (lipidic, polymeric or inorganic) with membranes extracted from EVs or from different types of cancer or immune system cells. Such biomimetic drug delivery systems are capable of selectively delivering to a given target site the drugs and/or diagnostic agents they carry. This type of study involves the characterization of such systems in terms of both intracellular internalization capacity and antitumor efficacy in 2D and 3D tumor models. These results compared with those obtained by testing the same drugs and/or imaging agents in free form, i.e., not included in the carrier, will allow validating the advantage of using drug delivery systems over free drug delivery. In addition, metabolomics and dosing studies of drugs and their metabolites are included in this project.

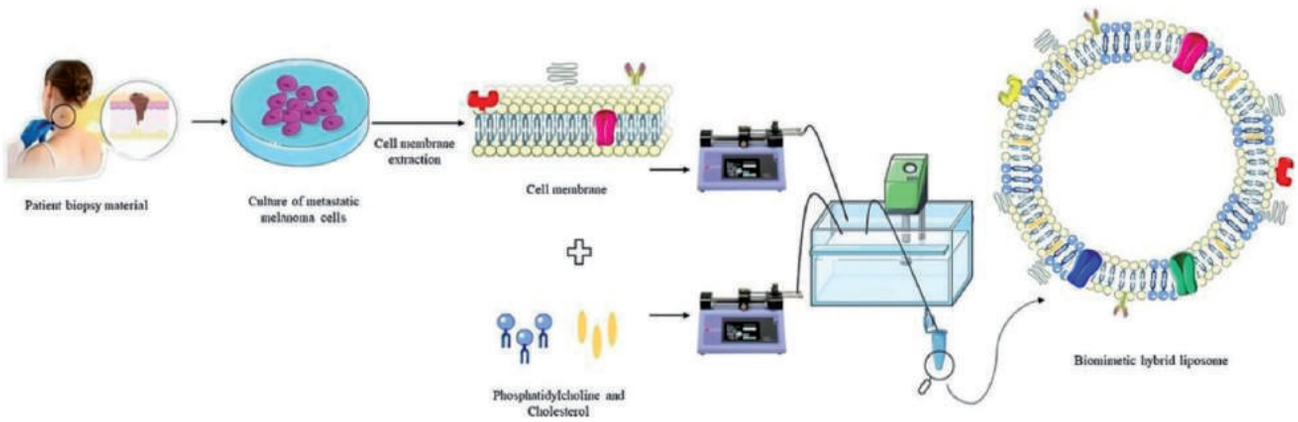
Aims

Design and implementation of innovative drug nano-delivery systems using hybrid liposomes, obtained by fusion with biological membranes, or appropriately functionalized nanoparticles. Validation of their efficacy in selectively transporting the selected drug to the target tumor site.
Metabolomics study using various biological fluids (plasma, serum, urine, saline, pleural or peritoneal effusions, etc.) obtained from patients with cancer diseases.
Analysis of plasma levels of drugs and their metabolites as predictors of response/toxicity to various anticancer strategies.

Results

Design, fabrication and characterization of hybrid nanovectors obtained by fusing liposomes with BRAF wt melanoma cell membranes (to optimize drug delivery directly to tumor cells). After characterization of the activity of Cobimetinib and Lenvatinib transported by the hybrid nanovector versus free drugs in a 3D model and finalized agreements to patent in delivery system, the drafting of the manuscript will be finalized.
Design, implementation and characterization of a nanoparticle system selectively directed to prostate cancer cells expressing at high density the PSMA receptor. Such a system, being also capable of selectively delivering a photosensitizing molecule that generates ROS upon irradiation with 808-nanometer lasers to the mitochondrial level, could be effectively used for photodynamic therapy as well as for diagnostic purposes. The next phase of this study will be carried out in vivo in collaboration with a research group of Prof. Lee (Seoul National University Bundang Hospital, Republic of Korea). Beginning the development of the protocol for the analysis of metabolites in GC-MS present in the urine of patients with prostate cancer.
On the design of the nanoparticle system selectively directed to prostate cancer cells, the in vivo study in the prostate Ca model in Korea has begun, upon completion of which the drafting of the manuscript will be completed.

Development of protocol in uHPLC-MS for analysis of plasma levels of drugs and their metabolites as predictors of response/toxicity to various anticancer strategies.



doi: 10.1016/j.ijpharm.2023.123697

Publications

- Microfluidic development and biological evaluation of targeted therapy-loaded biomimetic nano system to improve the metastatic melanoma treatment. Arduino I, Di Fonte R, Tiboni M, Porcelli L, Serratì S, Fondaj D, Rafaschieri T, Cutrignelli A, Guida G, Casettari L, Azzariti A, Lopedota AA, Denora N, Iacobazzi RM. Int J Pharm. 2024 Jan 25;650:123697. doi: 10.1016/j.ijpharm.2023.123697. Epub 2023 Dec 9.
- Magnetic implants in vivo guiding sorafenib liver delivery by superparamagnetic solid lipid nanoparticles. Iacobazzi RM, Vischio F, Arduino I, Canepa F, Laquintana V, Notarnicola M, Scavo MP, Bianco G, Fanizza E, Lopedota AA, Cutrignelli A, Lopalco A, Azzariti A, Curri ML, Franco M, Giannelli G, Lee BC, Depalo N, Denora N. J Colloid Interface Sci. 2022 Feb 15;608(Pt 1):239-254. doi: 10.1016/j.jcis.2021.09.174. Epub 2021 Sep 29.

Study of clinical, pathological and bio-immunological characteristics of patients with cutaneous squamous cell carcinomaand search for predictive factors of response to anti-PD1 Cemiplimab

P.I. Letizia Porcelli
Start date: 2022
End date: 2024

Background

Epidemiological data suggest a strong link between CSCC and the immune system. It has been widely demonstrated that immunosuppression is one of the most important risk factors in the development of CSCC. Currently, the approved immunologic therapy for CSCC is the use of Cemiplimab. In CSCC, the high presence of dysregulation of ncRNAs is known. Several studies have shown that some miRNAs are particularly dysregulated such as miR-125a and miR-125b that appear to promote tumorogenesis by negatively affecting the development and function of immunocompetent cells. In contrast to miRNAs, the role of lncRNAs and circRNAs in CSCC tumorigenesis is not yet well understood. The miRNAs and lncRNAs, which will be the subject of this study, were selected in silico by Dr. S. De Summa who evaluated among the lncRNAs, related to PD1/PD-L1 signaling and anti-PD1 response genes, which ones were differentially expressed in tumor tissues from patients with CSCC compared with those obtained from healthy donors.

Aims

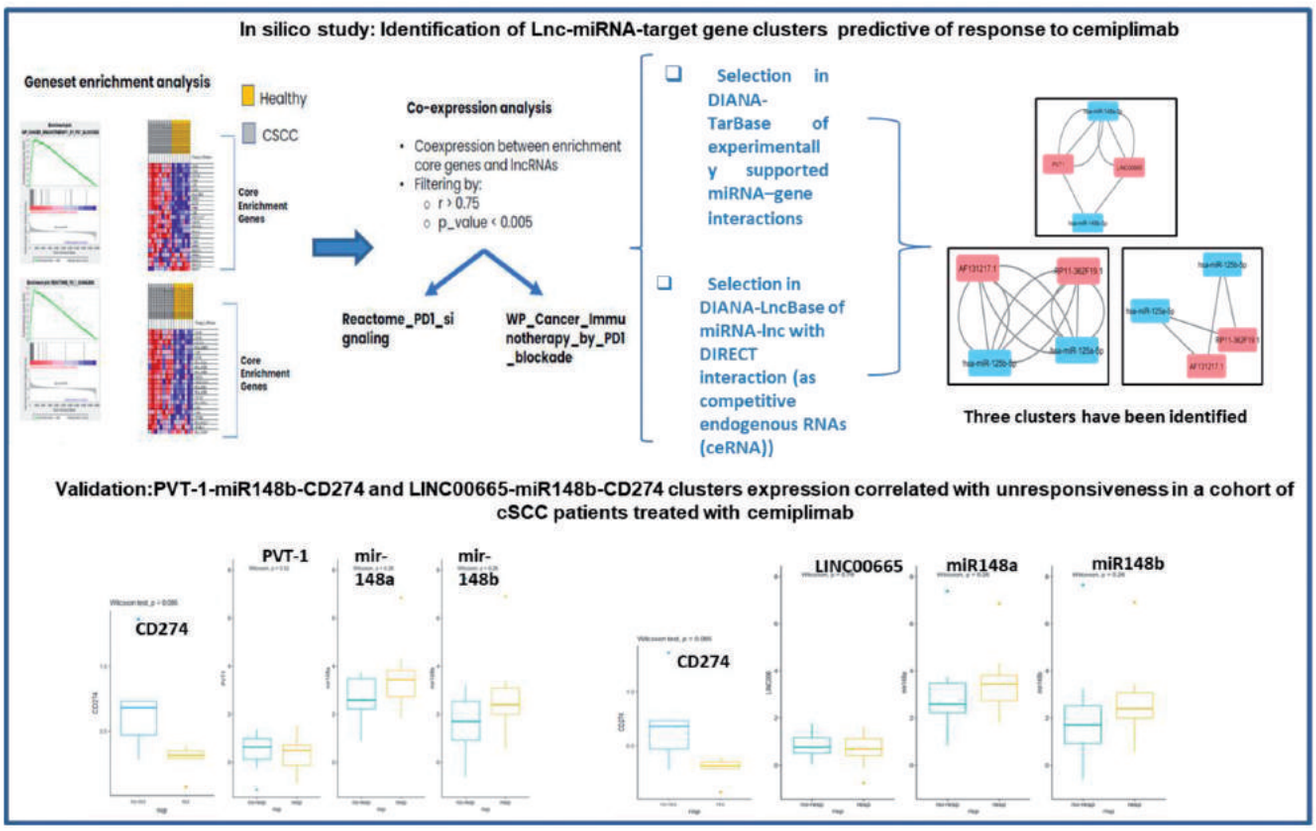
1. Clinical and chemico-clinical characterization of patients enrolled in the study.
2. Biomolecular and immunologic characterization to determine biomarkers for predicting response to cemiplimab and for monitoring its efficacy as a function of time of administration by profiling genes involved in immune response and inflammation, studying the expression of selected ncRNAs (long non-coding RNA, miRNA, and circular RNA) and correlating with changes in both circulating and tumor-infiltrating cell populations of immunity.
3. Obtaining patient-derivedorganoids (PDOs) from tumor tissue of patients with CSCC for analysis of signaling pathways involved in the efficacy of cemiplimab.

Results

In 2022, samples were collected from 33 patients with CSCC (17 new patients, 15 reevaluations) Analysis of the predictive role of response to Cemiplimab of circulating 4miRNAs and circulating 4lncRNAs found in the plasma of patients with CSCC taken before the start of immunotherapy. Analysis on the selected 4 miRNAs by Digital PCR was completed on 33 patients. Longitudinal study to evaluate whether the 4 miRNAs and 4 plasma lncRNAs can be biomarkers for monitoring response to cemiplimab. Analyses on the selected 4 miRNAs were completed on 5 patients with complete response, 22 with partial response/stable disease, and 6 who progressed.
Biomolecular characterization (profiling of genes involved in immune response and inflammation, study of circular RNA expression and evaluation of mutational load in relation to response to immunotherapy and clinical outcomes. The activity, of the collaborating Molecular Diagnostics and Pharmacogenetics group, is ongoing.
In 2023, samples were collected from 9 patients with CSCC (2 new patients, 7 reevaluations) Analysis of the predictive role of response to Cemiplimab of circulating 4miRNAs and circulating 4lncRNAs found in plasma of patients with CSCC taken before the start of immunotherapy. Analysis on the 4lncRNAs by Digital PCR was completed on 33 patients.

Longitudinal study to evaluate whether 4miRNAs and 4 plasma lncRNAs can be biomarkers for monitoring response to cemiplimab. Analyses on the selected 4 lncRNAs were completed on 5 patients with complete response, 22 with partial response/stable disease, and 6 who progressed.

Biomolecular characterization (profiling of genes involved in immune response and inflammation, study of circular RNA expression, and evaluation of mutational load in relation to response to immunotherapy and clinical outcomes. The activity, of the collaborating Molecular Diagnostics and Pharmacogenetics group, is ongoing.



Unravelling the molecular roadmap to CEBPA-mutant driven leukemogenesis

P.I. Attilio Guarini, Giacomo Volpe
Start date: 2022
End date: 2024

Background

Fifteen percent of patients with acute myeloid leukemia have biallelic mutations in the CEBPA gene, a transcription factor essential for hematopoietic stem cell self-renewal and granulopoiesis. To date, how sequential acquisition of CEBPA mutations reconfigures the epigenome to instruct myeloid transformation and drive the establishment of clonal disease is still not fully elucidated. A major obstacle in this effort is the lack of clinically relevant disease models to study disease establishment and progression. Our goal is to generate a series of isogenic cellular models using hiPSCs characterized by different combinations of mutations to study their effect on malignant transformation.

Aims

We aim to generate a panel of isogenic human pluripotent stem cell (hiPSC) lines with CEBPA mutations to study their molecular and phenotypic consequences in vitro and in vivo. Our objectives are:

1. Determine the mechanisms by which the acquisition of CEBPA mutations affects the kinetics of myeloid differentiation and instructs a leukemic phenotype in vitro;
2. Follow the dynamics of disease establishment and propagation in vivo;
3. Identify critical genetic dependencies and targetable molecular switches in leukemic cells with CEBPA mutations.

Results

- Generation of mutagenesis vectors by cloning guide RNAs (against C- or N-terminal mutations) into retroviral backbone containing Cas9 under antibiotic resistance.
- Infections of wild-type hiPSCs with the above guide RNAs to achieve mutagenesis.
- Screening of hiPSC lines for the presence of mutations by Sanger sequencing.
- Isolation, amplification and storage of new mutant hiPSC lines.
- Somatic characterization of the generated hiPSC lines.
- Implementation of assays of proliferation, pluripotency, and embryonic maturation.
- Validation of the ability of healthy and mutated hiPSCs to mature into hematopoietic progenitors and mature myeloid cells.

Characterization of the role of nuclear receptor "Liver X receptor alpha (LXRα)" in macrophages infiltrating diffuse large cell lymphoma (DLBCL) and study of its modulation as a possible therapeutic approach

P.I. Attilio Guarini, Sabino Ciavarella
Start date: 2022
End date: 2024

Background

The project is based on the hypothesis that significant inter-patient diversity may exist in DLBCL at the time of diagnosis in terms of enrichment of tumor-infiltrating immune cells, particularly Mo. These immune subpopulations may share similar phenotypic characteristics but differ in transcriptional programs and function, ultimately affecting patient survival independent of genetic heterogeneity of tumor cells. The latter aspect may gain intriguing prognostic - and even predictive - value not only toward standard therapy, but also toward new strategies incorporating immunomodulatory drugs such as Ibrutinib, Lenalidomide, and Bortezomib with large off-target effects on TME and limited clinical efficacy due to lack of robust molecular predictors.

Scopo

- Identification of LXRα role in DLBCL-associated macrophages.
- Demonstration of the prognostic value of LXRα using several independent case series of DLBCL).

Risultati

A mechanistic validation phase of the biological role of LXR receptors in in vitro models of DLBCL through organoid development is currently underway. This project phase has produced preliminary data on the development of three-dimensional co-culture systems of tumor and microenvironmental cells (stromal and immune

Publications

- Vegliante MC, et al. Hematol Oncol. 2022;
- Gian Maria Zaccaria, et al. Hemasphere 2023;
- Gian Maria Zaccaria, et al. Computer Methods and Programs in Biomedicine, 2023.

Role of NDRG1 in invasive breast cancer and the triple-negative subgroup. Evaluation of its clinical impact and therapeutic implications

P.I. Alfredo Zito
Start date: 2022
End date: 2024

Background

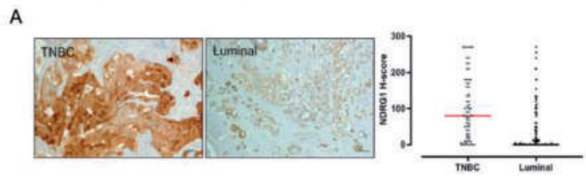
N-Myc downstream regulated gene 1 (NDRG1) protein is a stress protein involved in hypoxia, cell growth, lipid metabolism, and drug-resistance phenomena. It is known as an oncosuppressor, but recent studies have shown, instead, its oncogenic activity in aggressive BC phenotypes, highlighting how NDRG1 expression is associated with advanced stages of disease, with high grade, the onset of brain metastases and is linked to a worse clinical outcome. These studies suggest the possibility of using NDRG1 both as a therapeutic target and as a prognostic biomarker in aggressive BC phenotypes.

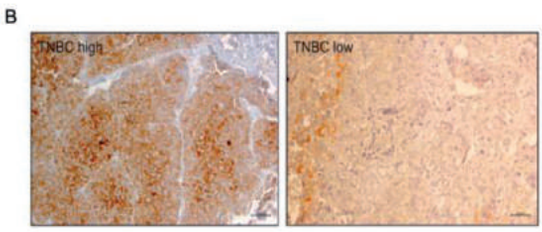
Aims

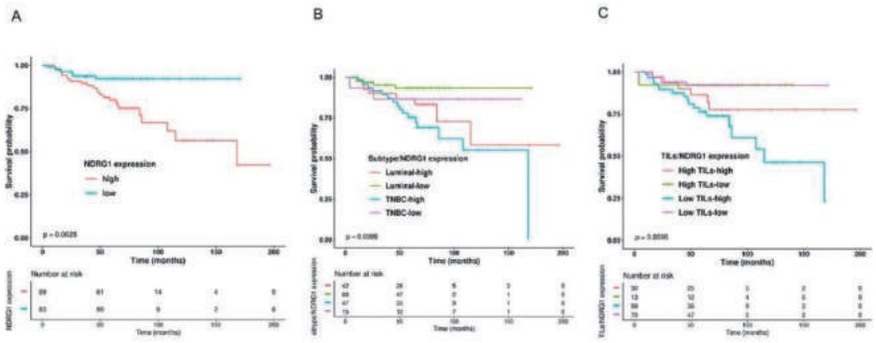
- To evaluate the expression of NDRG1 on a larger case series of BCs and TNBCs and analyze the association between its expression and the clinical course of patients.
- To study the gene structure of TNBCsNDRG1+ versus TNBCsNDRG1-, to understand which pathways are activated in the presence of high expression of this protein;
- To clarify the role of NDRG1 through "in vitro" functional studies (KO models) on different BC cell lines.

Results

Protein and gene expression of NDRG1 was higher in TNBCs than in luminal samples in 12 paraffin-embedded tissue sections. This finding was confirmed in IHC on 212 primary breast carcinomas. Furthermore, NDRG1 expression was found to be inversely proportional to ER receptors, PgR and Her2, and directly to Ki67 proliferation index. Kaplan- Meier curves showed that patients with higher NDRG1 expression had worse disease-free survival (DFS). We used a CRISPR/Cas9-based gene editing approach to inhibit NDRG1 expression. We observed that NDRG1 knockout cells showed significantly increased NDRG1 mRNA levels compared with ctr-CRISPR. Silencing of NDRG1 significantly reduced the migration of MDA-MD-231 cells after 5 days. In addition, we observed significant upregulation of NDRG1 in MDA-MB-231 cells under stress conditions.







Study of the interaction between human papilloma viruses and NHERF1 protein in pre-malignant lesions and cervical carcinomas

P.I. Alfredo Zito
Start date: 2022
End date: 2024

Background

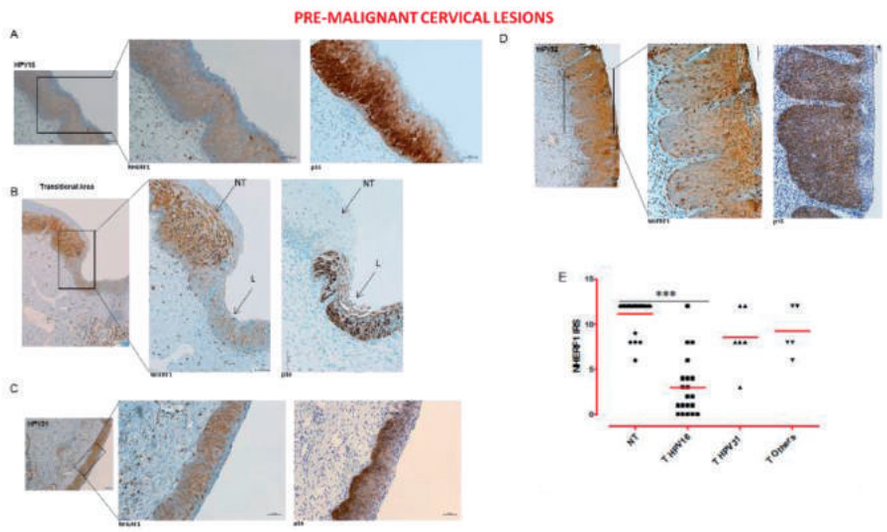
One of the major risk factors for cervical cancer is infection with human papilloma viruses, particularly those with high oncogenic risk (HR-HPV). The transition from HPV infection to HPV-associated cervical cancer is associated with persistence of HR-HPV infection and increased expression of the viral oncoproteins E6 and E7, which promote the virus' carcinogenic activity. The E6 protein is capable of interacting with proteins containing a PDZ domain, such as the adaptor protein NHERF-1. It has been shown that in high-grade cervical lesions, the E6 protein of HPV16 is able to induce degradation of the NHERF-1 protein more efficiently than in HPV18.

Aims

The aim of the present study is to evaluate possible variations in NHERF-1 protein expression in a series of female genital lesions caused by different types of LR-HPVs and HR-HPVs, trying to clarify whether different HPV genotypes have the same degradative efficiency of HPV16, toward NHERF-1 protein.

Results

A decrease in the expression level of NHERF-1 was observed in genital warts positive for HPV LR types compared with healthy epithelium. NHERF-1 protein levels decreased mainly in HPV16-positive pre-malignant and malignant lesions, while the other HPV HR types seemed to have a marginal effect. In HPV16-positive lesionsNHERF-1 protein levels correlated with cervical lesion severity, being less expressed in low-grade pre-malignant lesions than in high-grade lesions.



Publications

Alteration of Na/H exchange regulatory factor-1 protein levels in anogenital lesions positive for mucosal high-risk human papillomavirus type 16. Saponaro C, Galati L, Gheit T, Pappagallo SA, Zambetti M, Zito FA, Cardone RA, Reshkin SJ, Tommasino M. Virology. 2022 Nov;576:69-73

Role of Human Papillomavirus (HPV) and Epstein Barr virus (EBV) in the development of head and neck cancers

P.I. Alfredo Zito
Start date: 2022
End date: 2024

Background

Head-neck cancers (HNCs) comprise a heterogeneous group of neoplasms of the oral cavity of the larynx and oropharynx/hypopharynx. About 90% of these tumors are histologically classified as squamous cell carcinomas (HNSCC). Among the various etiologic agents, papilloma virus (HPV) is assuming an important role. It is now well established that HR-HPVs are responsible for a subset of oropharyngeal cancers as well as a low percentage of oral and laryngeal cancers. Biological studies have shown in in vitro models of oral keratinocytes a role of viral cooperation between HPV and Epstein-Barr virus (EBV). Some epidemiological studies have confirmed this hypothesis, reporting the presence of both viruses in cases of HNC, while others report no association with EBV.

Aims

- Identification of a retrospective case history of HNC the presence of EBV and/or HPV DNA/RNA on fixed and included tissue.
- Assess immunohistochemical expression of p16 as a surrogate marker of HR-HPV infection.
- Carry out by retrospective analysis the evaluation of the impact of HPV and EBV on disease progression compared with the corresponding HPV/EBV negative tumors.
- Prospectively characterize viral biomarkers in HNC.
- Correlate the positivity of viral biomarkers with histologic features of the tumor.

Results

Case study identification.

Signatures of noncoding RNAs in urinary extracellular vesicles as a noninvasive diagnostic biomarker for prostate cancer

P.I. Alfredo Zito, Giuseppe De Palma
Start date: 2022
End date: 2024

Background

The diagnosis of prostate cancer requires an invasive procedure that is not without complications. Extracellular vesicles, derived from the urinary tract and prostate, are also released in urine and contain pure nucleic acids also of tumor origin. We conducted a pilot study of NGS transcriptomics analysis on EVs isolated from urine samples patients with PCa and patients with BPH that showed us an association with a signature of deregulated ncRNAs.

Aims

To verify the results of the pilot study, namely, the ability of ncRNA profiling of urinary EVs to allow differential diagnostics between PCa and BPH thus increasing the diagnostic rate of prostate biopsy by including the analysis of extracellular vesicles present in patients' urine.

Results

Development of a specific ddPCR assay on EV-RNA for quantification of miR-375. Quantification of miR-375 that effectively confirms a case stratification trend based on an up-regulation of miR-375 detectable in urinary vesicles of patients with higher Gleason scores.

Publications

G. De Palma, E. Torchia, M. Notarangelo, V.F. Di Lorenzo, A. Tufaro, A. Mastrorosa, V.G. DíAgostino. Prognostic potential of urinary extracellular vesicle-micrornas for prostate cancer patients (Poster al 3º Symposium della Società Italiana per le Vescicole Extracellulari, Urbino 13-15 Settembre 2023) Extracell Vesicles Circ Nucleic Acids 4:641-642, 2023. doi: 10.20517/evcna.2023.57

Study Density-02: Multi-parametric radio-metabolic interrelationship analysis for defining personalized cancer risk for breast malignancies

P.I. Daniele Laforgia
Start date: 2022
End date: 2024

Background

Mammographic density is an important risk factor for the development of breast cancer: hence the need has emerged for a more objective estimation to be implemented by agreement between observers or by using dedicated automatic density calculation software such as VOLPARA. To date there is still an uncertain picture of the real impact of density associated with constitutional biotype on cancer risk, in particular the need emerges for tools that integrate information derived from BMI and patient body composition using vector bioimpedance analysis (BIVA).

Aims

The objective is to evaluate the role of the association between body composition, biotype, metabolic parameters, density, and mammographic structure in the risk of breast cancer occurrence in premenopausal women. Specifically, the study aims to investigate the association between breast density and genetic-constitutional factors (gynoid, intermediate android biotype) as a risk factor in the occurrence of breast cancer with the ultimate goal of defining a risk score based on mammographic characteristics and metabolic parameters.

Results

The study is currently in the enrollment phase, and a total of 44 women including 36 healthy and 8 with breast cancer were recruited. All participants were nutritionally assessed by anthropometric and bioimpedance examination with administration of a questionnaire on lifestyle and eating habits and subjected to venous blood sampling useful for the determination of metabolic parameters.

LINE 2 | Clinical Trials In The Age Of Precision Oncology

Overview

Clinical oncology has seen profound changes in recent years mainly due to the acquisition of new molecular biological knowledge that can be used for various purposes in the patient. Specific gene or protein alterations found in the individual tumor have become "targets" for individualized therapies with small molecules and/or moabs involving newly designed pharmacokinetics/dynamics studies and conceptually innovative clinical trials (CDx, adaptive studies, unbrella/basket trials, etc) (Janiaud P et Al, CTR, 2019). On the other hand, we are seeing the application of a range of new medical-surgical technologies that allow experimentation with "Remote" and "Assisted Surgery" approaches that are increasingly less invasive and/or robotic (Bhardari M, Curr Op Oncol, 2020); also increasingly sophisticated diagnostic techniques allow experimentation with new local integrated physicochemical approaches (Schoenberg S, Oncologist,2018). Finally, cell therapies, based on the genetic engineering of T lymphocytes (CAR-T cells) have successfully entered onco-hematology (Filley A, Front Oncol, 2020) opening important immunotherapeutic perspectives for solid tumors as well. However, the applicability of these new diagnostic-therapeutic possibilities must be based on a holistic approach to the patient, his or her reintegration into social life, and a focus on new ethical-legal implications.

Aims

These ambitious goals require fine-tuning of novel clinical trial models and strongly "technology-assisted" approaches to the patient. With this in mind, in a first area we will develop clinical trials in oncohematology using biomolecular information concerning the tumor and the host, an approach that will require optimization of biobanking of biological material from patients for pharmacokinetic/dynamic studies and conceptually innovative clinical trials (CDx, adaptive studies, unbrella/basket trials) especially for diseases in which mutational oncology and immunotherapy (breast, lung, colorectal, prostate, pancreas, lymphoma, leukemia) already play a key role. Surgery will also be required to have highly innovative scientific programming with the application of new technologies including robotic ones that allow "Remote" and "Assisted Surgery" to be increasingly less invasive and to apply new training and interventional possibilities even remotely. New diagnostic techniques will be the focus of new physical and chemical approaches also integrated locally. Finally, the whole area of clinical trials will make use of the knowledge gained in onco-hematology with cell therapies based on genetic engineering of T lymphocytes (CAR-T cells). Further development of the topic will require activation of ns GMP Facility and transfer of the CART-cell model to selected solid tumors as well. The applicability of these new diagnostic-therapeutic possibilities must, however, be based on a holistic approach to the patient, his or her reintegration into social life, and a focus on new ethical-legal implications.

This Line of Research will direct the Institute's nonprofit clinical trials toward what are the most promising/innovative areas of oncology research. The goal will be pursued by specifically promoting biospecimens biobanking activities, development of early clinical trials based on companion diagnostic tests, and use of innovative diagnostic/therapeutic technologies. Strong interaction is expected with Line 1 activities, which will transfer analytically validated biomarkers, especially of biomolecular and immunological interest, to the clinical validation phase. All in a context of a new holistic patient and ethical-legal approach.

Development of a molecular signature for the diagnostic-therapeutic characterization of mediastinal gray zone lymphomas (Bio-mGZL)

P.I. Attilio Guarini, Sabino Ciavarella
Start date: 2022
End date: 2024

Background

Mediastinal gray zone lymphomas (mGZLs) represent a rare entity of aggressive lymphomas with morphophenotypic features intermediate between Hodgkin's lymphoma (HL) and primary mediastinal lymphoma (PMBL). These aspects make the pathologic diagnosis of mGZLs very complex and critically affect the choice of the best therapeutic approach and the outcome of these patients, which appears inferior compared with their cancer counterparts. This project aims to apply innovative bioinformatics tools to HL- and PMBL-derived gene expression data to identify a useful transcriptomic signature for diagnostic support of mGZLs, applicable to clinical practice.

Aims

- Identification of a molecular signature that can characterize mGZLs by assigning them to the biological category of HL or primary mediastinal lymphoma (PMBCL).
- Validation of the signature on an independent real-life cohort of HL, PMBL and GZL by Nanostring technology.

Results

Using computational approaches and collaboration with the Department of Mathematics at the University of Bari, a signature of 168 genes characteristic of the microenvironment and tumor component of HL and PMBCL lymphomas was identified. This signature was derived from public Gene Expression Profiling data and validated on an independent real-life case series of HL, PMBCL and GZL made available by the collaborating centers included in the Italian Lymphoma Foundation network. Now, we will complete both the validation process and the collection of clinical data associated with molecular data.

Evaluation of the Impact of Chronic Myeloproliferative Neoplasms on Work Activity

P.I. Attilio Guarini, Paolo Ditonno
Start date: 2022
End date: 2024

Background

The project aims to screen a large population of patients with chronic myeloproliferative neoplasms and derive the effects that treatments, hospitalizations, and inherent characteristics of the disease impact on quality of life, with particular reference to work activity.

Aims

- Development of an ad hoc CRF on Redcap system for data collection;
- Data collection either through guided (physician/nurse/psychologist) or autonomous (tablet given to patient after brief explanation of operation) administration.

Results

During the year, the working group conducted retrospective data collection to begin to assess the significance of the "work activity" issue within a group of patients with chronically progressive myiloproliferative neoplasms. The working group thought it appropriate to implement data collection using a larger panel of Questionnaires. The aim is to allow for more complex inductions on the topic at hand while still maintaining the methodology adopted so far, which consists of the administration of the questionnaires by specialized personnel (a discriminating element in the reliability of the data collected).

Publications

https://ashpublications.org/blood/article/140/Supplement%201/13301/487653/Risk-of Unemployment-Among-Chronic

Improvement of the oncohematology patient pathway enrolled in clinical trials and technological implementation of processes

P.I. Attilio Guarini, Carla Minoia
Start date: 2022
End date: 2024

Background

Strengthening internal processes for enrollment and monitoring of hematology patients within profit and nonprofit institutional clinical trials.

Aims

- Establishment of working group of data managers and study coordinators and clinicians
- Mapping of the state of the art of active and activating clinical trials
- Interventions for early identification of critical issues and optimization of resources

Results

In the year 2022, the preliminary working group was formed, composed of study-coordinators Dr. Fabio Pavone, Felice Clemente (until July 2022), Alessandro Passiatore (collaborator), physician Dr. Carla Minoia, research coordinator nurse Dr. Antonio Leuci.

As of 12/31/2022, 31 clinical trials were active, of which 20 were actively recruited. Seven of these clinical trials were activated in the year 2022. In relation to the phase of the trial, no. 9 studies are phase II, no. 15 are phase III, and the remaining are observational.

Enrollment data for the year 2023 are being processed. It should be noted that new studies have been activated concerning diseases not previously involved in trials and a phase II basket trial has been opened.

Publications

- Argnani L, Broccoli A, Pellegrini C, Fabbri A, Puccini B, Bruna R, Tisi MC, Masia F, Flenghi L, Nizzoli ME, Musso M, Salerno M, Scalzulli PR, Dessì D, Ferrarini I, Pennese E, Lucchini E, Rossi FG, Minoia C, Gherlinzoni F, Musto P, Patti C, Stefoni V, Zinzani PL. Real-world Outcomes of Relapsed/Refractory Diffuse Large B-cell Lymphoma Treated With Polatuzumab Vedotin-based Therapy. Hemasphere. 2022 Nov 11;6(12):e798. doi: 10.1097/HS9.0000000000000798. PMID: 36398133; PMCID: PMC9663137.
- Maggialetti N, Ferrari C, Nappi AG, Rubini D, Pisani AR, Minoia C, Granata V, Moschetta M, Stabile Ianora Amato A, Rubini G. Prevalence and clinical impact of incidental findings on the unenhanced CT images of PET/CT scan in patients with multiple myeloma: the value of radiological reporting in the multimodal hybrid imaging. Eur Rev Med Pharmacol Sci. 2022 Aug;26(16):5902-5910. doi: 10.26355/eurrev_202208_29529. PMID: 36066165.
- Puzzovivo A, Fioretti AM, Minoia C, Villoni R, Carbonara S, Graziano G, Pavone F, Guarini A, Oliva S. Echocardiography monitoring during anthracycline administration in Hodgkin's and non-Hodgkin's lymphoma: the Tei-index evaluation. J Pers Med. 2022 Feb 16;12(2):290. doi: 10.3390/jpm12020290

Validation of biomarkers of long-term survivorship to lymphoma and application of Survivorship Care Plan as a tertiary prevention tool

P.I. Attilio Guarini, Carla Minoia
Start date: 2022
End date: 2024

Background & Aims

The project aims to improve knowledge in terms of survivorship in collaboration with leading scientific societies conducting clinical research on lymphoma and survivorship topics and to enhance care and clinical research on the same topic in the Institute by strengthening the working team already working in the current research project coordinated in the 2018-2021 triennium.

Results

In the year 2022, the 2018/2021 Current Research Project "Fertility Prevention and Assessment of Risky Lifestyles in Patients Diagnosed with Lymphoma" (Resolution No. 68/2019) was concluded, with the submission of the request for certification as a PMA center for the freezing of ovarian tissue for the purpose of fertility prevention in young women to be started on chemotherapy with curative intent, signed by the Director General (prot. 22624, 10/10/2022).

Publications

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Study of response and resistance mechanisms to immunotherapy and target therapy in Melanoma

P.I. Michele Guida
Start date: 2022
End date: 2024

Background

In recent years, therapy for metastatic melanoma (MM) has undergone a radical change due to the advent of new drugs both of the biologic type (anti-BRAF and anti-MEK), indicated for patients with BRAF mutation (approximately 50%), and of the immuno-modulator type consisting of monoclonal antibodies. Anti-BRAF + anti-MEK target drug therapy is characterized by a progression free survival of only 12-14 months due to the establishment of resistance mechanisms during treatment. Anti-PD-1 immunological drugs, indicated for both patients with BRAF mutation and those without mutation, give objective responses around 40% in monotherapy. However, half of the patients show primary resistance and about 10-15% develop resistance during therapy. Therefore, there is a need to identify biomarkers that can distinguish responder from non-responder patients to avoid unnecessary, costly, and not side-effect-free therapies to patients who do not benefit. In parallel, it is critical to devise new pharmacological approaches to overcome them.

Aims

Our Project aims to develop the following objectives: study of extracellular vesicles (EVs) and their significance in the mechanisms of response and resistance to checkpoint inhibitor immunotherapy; immunological monitoring during immunotherapy treatment in order to identify new markers and mechanisms of response and resistance; study of the predictive role of allele frequency (AF) of BRAF V600E and NRAS mutations in stage Ill (adjuvant setting) and stage IV (metastatic setting) melanoma patients treated with target therapy and checkpoint inhibitors; metabolomic profile study on peripheral blood of metastatic melanoma patients treated with immune checkpoint inhibitors.

Results

Regarding Aim 1, we measured PD-L1 and PD-1 levels and demonstrated that high levels of PD-1+ EVs are associated with reduced response to anti-PD-1 immunotherapy. We also performed functional studies showing that circulating EVs reduce trafficking and cytotoxic potential of lymphocytes in melanoma organoids. Regarding Aim 2, multivariate analyses have enabled the identification of the set of immunologic factors that correlate with a response or nonresponse to administered immunotherapy. Regarding Aim 3, a multicenter working group consisting of 22 Italian melanoma referral centers, and we collected FA data from 273 patients. BRAF gene FA was correlated with melanoma and clinical characteristics of patients and clinical outcomes of treatment. Regarding Aim4, we analyzed the serum metabolomic profile of 71 metastatic melanoma patients treated with anti-checkpoint inhibitors (43 first-line) from 2017 to 2021. Preliminary analyses revealed changes in metabolomic profiles (metabolites and lipoproteins) during immunotherapy. A prognostic risk model has been developed and shown to significantly stratify high- and low-risk patients for both OS and PFS.

Publications

Serratì S, Di Fonte R, Porcelli L, De Summa S, De Risi I, Fucci L, Ruggieri E, Marvulli TM, Strippoli S, Fasano R, Rafaschieri T, Guida G, Guida M, Azzariti A. Circulating extracellular vesicles are monitoring biomarkers of anti-PD1 response and enhancer of tumor progression and immunosuppression in metastatic melanoma. J Exp Clin Cancer Res. 2023 Sep 28;42(1):251

The social STIGMA of the lung cancer patient and the Smoker: a pilot study for the detection of the phenomenon and the Experimentation of an intervention protocol based ON EMDR

P.I. Domenico Galetta, Annamaria Catino
Start date: 2022
End date: 2024

Background

The "health stigma", of the lung cancer patient can lead to self-evaluation predicting negative social judgment. The smoking patient, perceiving their own improper lifestyle, tends to conceal symptoms of a disease for which he believes himself to be responsible. EMDR (Eye Movement Desensitization and Reprocessing, or. Desensitization through eye movements) allows the patient, through desensitization and cognitive restructuring, to change perspective and adopt more adaptive behaviors by reprocessing emotionally stressful moments related to the stages of the disease and personal history.

Aims

The project plans to start a tobacco cessation pathway for smokers afferent to the center anti-smoking through the EMDR technique. Such support will be provided both to smokers with oncological pathology and to outside smokers. The project therefore, in addition to the detection of the stigma phenomenon, intends to use and test the effectiveness of the EMDR technique in reducing of distress symptoms in cancer patients and in tobacco cessation for smokers oncology and non-oncology patients.

Results

Literature searches were conducted in order to structure the intervention protocol and define the state of the art with respect to the information already known in the literature on the topic of the project. Recruitment of dedicated project fellows (1 data manager; n.1 biologist; n.1 psychologist). Submission and approval of ethics committee (prot.528/23). Training activities: Insights in psycho-oncology and clinical practice 2023; Compassion focus therapy; EMDR course; participation in National Congress of Tabaccology and World Conferens of Lung Cancer. Renewal of fellows with no.1 administrative attached and hiring of 1 data manager. No.4 cancer patients and no.10 smokers were involved in the enrollment.

Biomarkers predictive of response to immunotherapy In pulmonary microcytoma

P.I. Domenico Galetta
Start date: 2022
End date: 2024

Background

Lung microcytoma is the most aggressive form with the greatest tendency to metastasize lung cancer. Immunotherapy added to chemotherapy standard platinum derivatives and etoposide increases median survival in a statistically significant manner, but nevertheless by a limited amount. Therefore, the identification of predictive factors of response, appears to be an issue of considerable interest in these patients. In contrast to NSCLC, no relationship between PD-L1 expression and outcome to immunotherapy has been found in lung microcytoma. This is probably also related to the qualitative and quantitative lack of biopsy material in these patients. Useful could be therefore, the use of tissue PD-L1 surrogates. Given the type of microcytoma biopsy material, it would be desirable to be able to test the expression of the PD1/PD-L1 axis by either assessing soluble PD1 and PD-L1 or in the extracellular vesicles of patients with microcytomas undergoing immunotherapy treatment.

Aims

The aim of the study is to identify predictive factors of response to immunotherapy in microcytoma, motivated by the current absence of biomarkers with such function, in this particular lung cancer histotype. In particular, the primary objective of the study is to evaluate the correlation between immune checkpoints and EVs with overall response rate (ORR). Secondary objectives are related to identification of possible correlations between immune checkpoints and EVs with survival parameters (overall survival and progression free survival), normalizing for clinical features such as metastasis sites, age, sex, and performance status.

Results

Project passed validation by the ethics committee of the Bari Polyclinic because it was identified as an observational study with drug (because of the purpose related to to the identification of predictive factors of response to immunotherapy), currently submitted and awaiting evaluation.

Pubblicazioni

- Longo V, Rizzo A, Catino A, Montrone M, Galetta D. Safety evaluation of immune checkpoint inhibitors combined with chemotherapy for the treatment of small cell lung cancer: A metaanalysis of randomized controlled trials. Thorac Cancer. 2023 Apr;14(11):1029-1035. doi:10.1111/1759-7714.14842. Epub 2023 Mar 3. PMID: 36869579; PMCID: PMC10101844.
- Longo V, Pizzutilo P, Catino A, Montrone M, Pesola F, Marerch I, Galetta D. Prognostic factors for survival in extensive-stage small cell lung cancer: An Italian real-world retrospective analysis of 244 patients treated over the last decade. Thorac Cancer. 2022 Dec;13(24):3486-3495. doi: 10.1111/1759-7714.14712. Epub 2022 Nov 5. PMID: 36333988; PMCID: PMC9750807.

DATA-LUNG (Creation of a database provided with adequate protection of sensitive data through updated software, which can be used for real-time monitoring of data epidemiology, outcomes of different therapeutic lines, study of therapeutic sequences and close monitoring of toxicities in lung malignancies)

P.I. Domenico Galetta, Pamela Pizzutilo
Start date: 2022
End date: 2024

Background

Observational drug studies are of particular importance for the safety profile under normal conditions of use and on large numbers of subjects, for insights into efficacy in clinical practice, for verification of prescriptive appropriateness, and for pharmaco economic. Because of their characteristics, observational studies do not pose additional risks to the subjects, who are offered the best conditions of clinical care. Already since 2008, the National Register of Observational Studies (AIFA determination 31.3.2008 GUn 76) to ensure descriptive analyses and prepare periodic reports. The in-house establishment of a database aimed at the secure storage of clinical, epidemiological, pathological, molecular, therapeutic and drug-related toxicities would allow to be always up to date on the outcomes of individual standardized systemic therapies, the outcome of therapeutic sequences, and safety in the real world especially in light of specific therapeutic developments in recent years. Of no less importance is the possibility of using the same database to monitor with periodic audits the adequacy of diagnostic-therapeutic timelines to improve the objectives internal.

Aims

- Real-time monitoring of the incidence at our OU of various lung cancers according to clinical, pathological, biomolecular, and therapeutic characteristics.
- Monitoring as defined on the outcome and safety of the respective therapies.
- Having up-to-date data available to participate in international observational studies and to propose in-house observational studies.
- Ability to periodically assess the adequacy of the timing of internal diagnostic-therapeutic pathways (e.g., hospitalization times, time to diagnosis and start of treatment) and be able to quickly adjust according to precise indicators.
- Significantly improve the evidence regarding lung cancer treatment with a thorough understanding of the advantages and limitations of the database used. Through collaboration don experts in advanced statistical techniques. In addition, integrating with other large-scale multi-institutional databases can determine and strengthen a process of better understanding of the impact of a given treatment in a given population and, in many situations, can also improve evidence on prognosis, effectiveness of interventions, and even disparities in treatment.

Results

Thanks to this data base, it was possible to collaborate on the inclusion of approximately 120 patients within the national ATLAS observational project and in the Rational observational protocol. By collaborating at national level to abstracts for AIOM and ESMO.

Forest therapy integrated with immunotherapy treatment of patients with Pulmonary neoplasia

P.I. Domenico Galetta, Vito Longo, Niccolò Varesano, Vito Lamorgese
Start date: 2022
End date: 2024

Background

Forest therapy is able to improve many aspects of an individual's mental health, such as stress, anxiety and depression. However, the benefits associated with forest therapy affect the immune system as well, with increase in NK cells and their activity, increase in granulysin, perforin and A/B granzymes, a reduction in Treg cells, an increase in cytotoxic C8 lymphocytes, and an activation of other immune system effectors designed to counteract the development and proliferation of neoplastic cells, also change in serum levels of IL-6, IL-8 and TNF-α

Aims

- Evaluation of the impact of forest therapy on different psychological aspects of the patients, such as stress, depression and anxiety.
- Analysis of changes related to lymphocyte population on blood peripheral.
- Analysis of changes related to pro-inflammatory cytokine expression.
- Impact on fatigue and algie control.
- Number of progressions following integrated therapeutic intervention.

Results

Experiment conducted on a pilot group of 10 patients (6 males; mean age 59.6 yrs,d.s.12) performed no.6 weekly exposures of 2h each in forest (Apulian Murgia). Performed determinations related to inflammatory cytokine status, lymphocytogram and screening pre and post intervention emotional.

Predictive values of cardiotoxicity in colorectal cancer patients treated for the first time with fluoropyrimidines, both in adjuvant and metastatic patients

P.I. Stefano Oliva, Agata Puzzovivo
Start date: 2022
End date: 2024

Background

Fluoropyrimidines are among the most widely used drugs in the treatment of colorectal cancer. Risk factors for developing cardiotoxicity from fluoropyrimidines are: age > 55 years, preexisting renal disease (creatinine clearance < 30 ml/min), hypertension, dyslipidemia, smoking, history of ischemic heart disease. To prevent adverse reactions, AIOM guidelines recommend DPYD pharmacogenetic analysis of known polymorphisms. However, other polymorphisms have been identified for which an analysis tool should be developed.

Aims

The main objective of the study is to identify gene profiling to be used in conjunction with the instrumental and laboratory diagnostic tools adopted in common clinical practice to identify patients at high risk of cardiotoxicity.

Results

Enrollment of 30 patients. Two patients lost to follow-up. 7% of those enrolled have a polymorphism associated with pathogenetic alteration of the DPYD gene, for which 85% reduction of fluoropyrimidines is recommended. Seven percent had a polymorphism of the UGT gene associated with pathogenetic alteration, with 70% reduction of irinotecan recommended. At one-month follow-up, 43% of patients show comparable intrarenal resistance index (RI) values.

Comfortable Sounds: Infusion of Hope with Sterile Room Patients

P.I. Pietro Milella
Start date: 2022
End date: 2024

Background

Prolonged isolation in a clean room is an experience that exposes the hematology patient to psychological fragility. One of the aspects that contributes to maintaining a high quality of life is hope. To promote psychological well-being, the specialized method of Guided Imagery and Music (GIM) is recognized among "receptive" music therapy interventions as a functional modality of specific classical music to elicit transformative experiences in which imagery is evoked during musical listening. Achieved a state of deep relaxation, spontaneous imagery and potential epiphanic moments of relational depth, positive and transcendent emotions are elicited in the listener, so as to consolidate a sense of security and consolation.

Aims

To evaluate the multifactorial impact of receptive music therapy in patients with hematologic malignancy during hospitalization for autologous stem cell transplantation on the following indicators:

- Heart rate and blood pressure, Salivary cortisol;
- Hope, Quality of Life (symptoms: pain, insomnia, nausea, asthenia), Psychological Distress, Anxiety and Depression.
- Reduce psychological distress during prolonged isolation.
- To improve the quality of hospitalization by offering patients a "measurable" humanizing experience.
- Understand the relationship between hope and psychological distress.

Results

Following a literature study, questionnaires to be administered to patients were identified, and the study was presented to the Ethics Committee

Screening and Psychological Evaluation in the project, "Musical interventions with breast cancer patients: psychological and cardiological effects."

P.I. Pietro Milella
Start date: 2022
End date: 2024

Background

The project stems from the need to carry out appropriate psychological Screening and Assessment of patients enrolled in the Study "Music Interventions with Breast Cancer Patients: psychological and cardiological effects"; to focus a careful methodological strategy of conducting the study, differentiating the investigator (music therapist) from the clinical psychologist. This figure is in charge of investigating the following components: Stress, Anxiety, Depression, Anger, Help Seeking; Post Traumatic Growth; Fatigue; Physical Health and Mental Health. "Guided Imagery with Music" (Helen Bonny - G.I.M.), which is known in the literature as a receptive music therapy approach with a humanistic and transpersonal psychological orientation, is nowadays one of the most accredited approaches worldwide. Music therapy assessment tools are to be standardized through a series of psychometric tests.

Aims

- Conduct screening of psychological variables in Breast Unit patients and eligible for music therapy study. Administer at T0 psychological tests and collect data.
- Carry out, during subsequent music therapy sessions, the interaction of psychological variables related to cardiological parameters in Breast Unit outpatients (on neoadjuvant or adjuvant chemotherapy or first/second line chemotherapy as detailed in the existing study).
- Create and update the database with the inclusion of the scoring that emerged from the psychological assessment.

Results

- Enrollment with psychological assessment
- Monitoring the presence of psychological variables related to cardiological parameters in conjunction with the music therapy intervention at Times T (T1/T7) indicated by the research protocol.
- Operationalization: raw scores obtained were standardized.

Translation and Validation of the Italian Version of the Checklist Concerns and Health Identifier for Medical Patients (CHIMP_Cancer)

P.I. Pietro Milella
Start date: 2022
End date: 2024

Background

Emotional distress is defined as an unpleasant emotional experience that is multifactorial and psychological (i.e., cognitive, behavioral, and emotional), social, and/or spiritual in nature, which may interfere with the ability to cope effectively with cancer, its symptom picture, and the intended treatment course (NCCN, 2012). Detection, monitoring, and early detection of emotional distress allow appropriate therapeutic intervention to be developed in advance.

Aims

- Translate the Concerns and Health Identifier for Medical Patients (CHIMP_Cancer) checklist into Italian.
- Validate the Italian version of the Concerns and Health Identifier for Medical Patients (CHIMP_Cancer) checklist.
- To detect perceived emotional distress, related to areas of subjective concerns of the cancer patient, in order to identify stressors and problems, intervene preventively, respond to specific needs, and promote a quality course of treatment.

Results

Development of a data collection database, into which the raw data collected for No. 340 patients were entered and operationalized.

LINE 3 | Computational Science and Technology of Artificial Intelligence: Drivers for a Digital Oncology

Overview

The term Big Data was originally coined by NASA scientists in 1997 as a result of the difficulty of visualizing and storing too large a dataset.

In recent years, the world's digital information has more than doubled in size, and the phenomenon is continuing to expand. In particular, medicine is a major player in this growth. Health-related Big Data is growing faster than that of other sectors, thanks to four important phenomena:

- Development of digital reporting techniques (electronic patient records and files);
- Digital development of imaging (radiological and pathological);
- Development of omics sciences (genomics, transcriptomics, proteomics, metabolomics) in both bulk and single-cell;
- Development of the "Internet of Things" (IoT), which is the development of sensors that can detect information from the human body in real-time (e.g., smartwatches).

Machine Learning (ML) algorithms and the development of AI-based computing systems are developing in tandem with the growth of Big Data; for example, systems to support diagnostics are being developed in the field of radiomics or pathomics. In addition, computational sciences for omics are developing to expand the capacity for data integration, such as spatial transcriptomics.

Aims

The availability of Big Data, both structured and unstructured, can enable the development of ML algorithms for the purpose of training AI systems. It is precisely through AI that the available data can be analyzed and interpreted to formulate hypotheses and obtain useful answers for better prevention, early diagnosis and treatment, tailored to the peculiarities of the individual patient. Specifically, the development of the new "omics" sciences (genomics, transcriptomics, metabolomics, etc.) and high throughput instrumentation has produced, in a scientific area originally related mainly to laboratory and imaging activities, a strong demand for support from the field of advanced computing and high-performance computing. It is therefore necessary and possible to pursue the goals of effectiveness, efficiency, and appropriateness typical of current medicine, through the use of technologies capable of refining and innovating the information obtained by classical epidemiological methodologies.

In this perspective, the areas of specific interest in Oncology for the application of said technologies are:

- Development of innovative algorithms for improving patient care (phenotyping, monitoring, personalized therapy);
- Development of more accurate computer-aided diagnostics applicable specifically in automated imaging;
- Management (automation, cost optimization);
- Research and development in omics sciences (genomics, transcriptomics, radiomics, pathomics, pharmacogenomics, metabolomics, etc.).

Implementation of an Artificial Intelligence algorithm on histological preparations of patients with Luminal B HER2-negative breast cancer as a surrogate to the Endopredict genomic test

P.I. Alfredo Zito
Start date: 2022
End date: 2024

Background

"Digital Pathology (DP)" and Artificial Intelligence (AI) systems, through the analysis of digitized quantitative images, can recognize and quantify complex patterns and relate various tissue constituents to each other, allowing the extraction of important biological information. In recent years, the use of genomic tests predictive of the risk of distant metastasis in patients with early-stage breast cancer of the Luminal B HER2-negative type has been increasingly implemented in clinical oncology practice to safely identify patients for whom adjuvant chemotherapy in addition to hormone therapy alone is indicated. Unfortunately, the costs of such tests are particularly high and they are not always available at all diagnostic centers.

Aims

Our study aims to evaluate whether through the application of AI algorithms on digitized images of histological preparations of breast cancer, it is possible to identify a set of digital biomarkers that can be a valid surrogate for such biomolecular tests.

Results

Case study identification.

Identification of an Artificial Intelligence algorithm to improve the diagnostic accuracy of early-stage myeloproliferative neoplasms on osteomidullary biopsies

P.I. Alfredo Zito
Start date: 2022
End date: 2024

Background

The diagnosis of myeloproliferative neoplasms (MPNs) requires the integration of clinical, morphological, and genetic data. Despite advances in the findings of the genetic and molecular basis of NPM, morphologic evaluation of osteomidullary biopsy (BM) remains the gold standard in differentiating the subtypes of NPM and the reactive forms that can mimic them. However, morphologic assessment is severely constrained by the use of subjective and qualitative criteria that are difficult to reproduce. NPMs are a group of disorders in which genetic driver mutations (JAK2, CALR, MPL) of the MPL-JAK-STAT pathway in the hematopoietic stem cell promote excessive proliferation of one or more hematopoietic lines. Polycythemia vera (PV) (with JAK2V617F mutation in >95%), essential thrombocythemia (TE), and primary myelofibrosis (MF) are the most common forms and may have clinical-laboratory and morphologic overlapping aspects that can make diagnosis difficult particularly in early stages of the disease and in triple-negative (TN) cases molecularly (5-10% of TE and MF cases).

Aims

To study a case series of reactive/non-neoplastic BM and BM with early stage NPM with Digital Pathology systems for:

- the quantification of specific cell populations in the hematopoiesis;
- the systematic description of tissue architecture and distinct hematopoietic populations;
- the identification, quantitative analysis and representation of aspects of megakaryocytes, such as those of cytology, topographical distribution, cell size variation, related to nuclear atypia and segmentation, complexity and cell aggregation;
- the degree of fibrosis 0/1.

Results

Identification of a case series of 120 patients, for whom hematosilin-eosin staining of the biopsy was done. Selection of significant areas for analysis and training of an artificial intelligence model.

Implementation of a computerized platform of "real-life" patients and design and development of prognostic tools in oncohematology using "machine learning" techniques

P.I. Attilio Guarini, Sabino Ciavarella
Start date: 2022
End date: 2024

Background

The collection of information related to histology, molecular and treatment outcome data of patients with lymphoma is significantly slowed by the use of highly fragmented and unstructured paper material. The project is in continuity with the results derived from the activity of developing an informatics tool, called ARGO (automatic record generator for onco-hematology), capable of semi-automatically collecting epidemiological, molecular and pathological information direttmaente from paper histopathology reports related to biopsies of lymphoma cases and executing systematic records in ReDCAP platform.

Aims

Extension of ARGO validation to reports collected on international centers. Design of a 'Beta' version of an app that would allow the paper report to be photographed during outpatient activity and create the patient record in REDCap automatically. Support to Clinical Trials for automated management in the selection of patients eligible for clinical trial enrollment.

Results

English-language reports have been cataloged and ready to be analyzed.

Publications

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Prognostic stratification in locally advanced non-small cell lung cancer unresectable and assessment of response to chemo-radiotherapy treatment: applications of artificial intelligence technologies

P.I. Domenico Galetta, Michele Montrone
Start date: 2022
End date: 2024

Background

Patients with stage III non-small cell lung cancer (NSCLC) represent about one-third of all NSCLC patients and are a somewhat heterogeneous, including potential candidates for radical surgery, patients candidated neoadjuvant therapy prior to surgery, and locally advanced forms of NSCLC (LA) not amenable to surgery but candidates for curative chemo-radiotherapy (CRT). The gold standard of treatment for unresectable LA-NSCLC is CRT concomitant in patients with good performance status, superior to the sequential in terms of overall survival (OS) and progression free survival (PFS)1. The addition of consolidation immunotherapy (IT) with durvalumab after CRT in subjects with disease stable or responding disease further improved patient outcomes2-6 and is clinical practice standard in subjects with PD-L1 TPS ≥1%7. The benefit from IT, although undisputed in all patients, is greatest when initiated early after CRT. One of the major limitations in clinical practice is the timing of radiological reassessment after CRT, a requirement essential to initiate PD-L1-positive patients who have not progressed to IT. The delay of reassessment and initiation of IT could reduce the benefit of IT itself. Morphological features of the disease extracted from computed tomography (CT) and digital slides of tumor biopsies, using artificial intelligence (AI) algorithms, have the potential to be used as predictive markers of response in patients with unresectable NSCLC resectable undergoing definitive CRT8.

Aims

The objective of the research is to determine whether in LA-NSCLC the features of baseline CT and possibly from digitized slides of tumor biopsy, can improve risk stratification.
The research, which is retrospective in nature, involves evaluating the ability of methods of deep learning to predict response to CRT alone in a population not selected for PD-L1, based on baseline CT. This would enable future accelerated access to IT of consolidation by improving outcome and would provide the basis for characterizing predictive factors of response to CRT and IT with important clinical and biological implications.

Results

Screening and enrollment of 30 patients. Identification of pre-treatment chemo-radiotherapy CT scans and definition of target lesions. Definition of radiological response obtained post-treatment chemo-radiotherapy for each patient based on the target lesions from the pre-treatment and post-treatment CT scans.

Development of predictive models of response to first-line therapy in patients with unresectable pleural mesothelioma using artificial intelligence techniques

P.I. Domenico Galetta, Annamaria Catino
Start date: 2022
End date: 2024

Background

Malignant pleural mesothelioma is a rare neoplasm generally diagnosed at an advanced, whose first-line therapy is systemic treatments. The design of the study, retrospective observational in nature, involves the analysis of clinical, histopathological, and radiological in order to predict therapeutic outcome. The radiomic analysis of the radiology and digitized biopsies will be interpreted using models of artificial intelligence artificial intelligence, with the aim of complementing the clinician's decision-making algorithm and realizing a precision oncology.

Aims

AIMS
The main objective of the project is to develop an automated and personalized system of therapeutic decision support for predicting the response to therapy of patients with advanced pleural mesothelioma. Automated models will be developed for planning and monitoring of therapeutic efficacy based on radiomic analysis of radiological and histopathological images, as well as on clinical-anamnestic data and risk factors such as previous exposure to asbestos.

Results

A predictive artificial intelligence model was trained, and the results were the subject of oral presentations at conference.

Prediction of pneumopathy in patients with stage III chemo-radiation-treated non-small cell lung cancer (NSCLC) using artificial intelligence techniques on clinical and imaging data

P.I. Raffaella Massafra
Start date: 2022
End date: 2024

Background

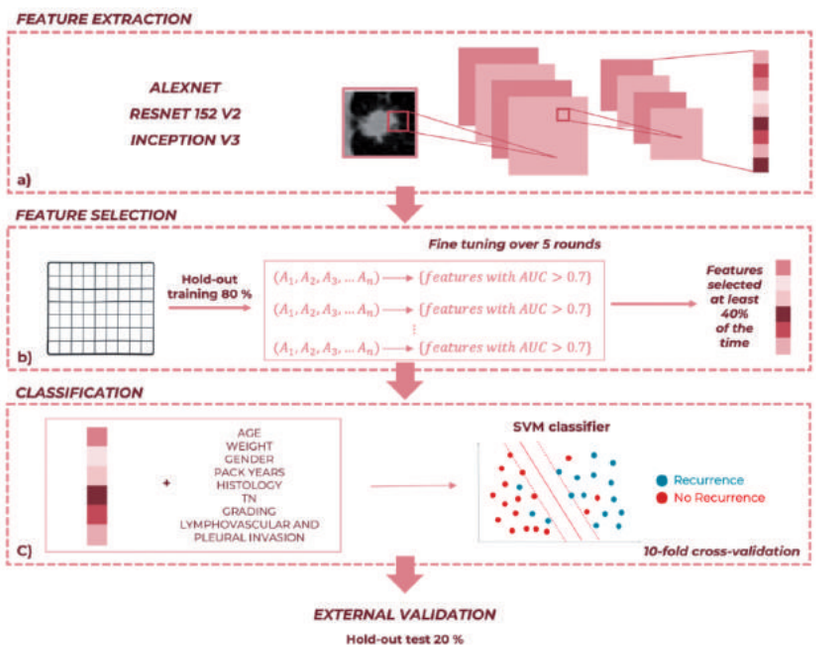
For patients with stage III non-small cell lung cancer (NSCLC) treated with chemo-radiotherapy (CRT) followed or not by immunotherapy, the occurrence of secondary treatment-related diseases such as PR (radiation pneumonitis) could be observed. Although reducing the dose of radiation therapy could decrease the risk of pneumonitis, this could at the same time also alter tumor control. In addition, it should be taken into account that some patients undergo treatment involving CRT in combination with immunotherapy, and this may result in the occurrence of pneumopathy also arising from the cumulative effect of the two treatments. Thus, the application of radiomic analysis of radiological images has opened the horizon for new approaches to identify biomarkers predictive of toxicity and/or response to a therapy in different biomedical fields.

Aims

The primary objective of this study is to develop an artificial intelligence model that can predict early occurrence of PR, in patients with stage III non-small cell lung cancer (NSCLC) treated with chemo-radiotherapy (CRT), by analysis of CT images acquired by the radiotherapist before the start of chemo-radiotherapy treatment. In addition, for patients who are also undergoing immunotherapy, a further aim of the study is to assess by means of a second artificial intelligence model whether the thickenings that the patient possibly presents with after an initial period of treatment are indicative of pneumopathy or disease progression.

Results

Pending enrollment of an adequate number of patients to develop the above model, a public database containing CT scans of NSCLC patients was analyzed with the aim of predicting disease recurrence.



Publications

Bove S, Fanizzi A, Fadda F, Comes MC, Catino A, ... & Massafra R. (2023) A CT-based transfer learning approach to predict NSCLC recurrence: The added-value of peritumoral region. PLoS ONE 18(5): e0285188. https://doi.org/10.1371/journal.pone.0285188

Artificial intelligence models for prediction of lymph node status and disease recurrence in T2-4 melanoma patients based on digital pathology

P.I. Raffaella Massafra
Start date: 2022
End date: 2024

Background

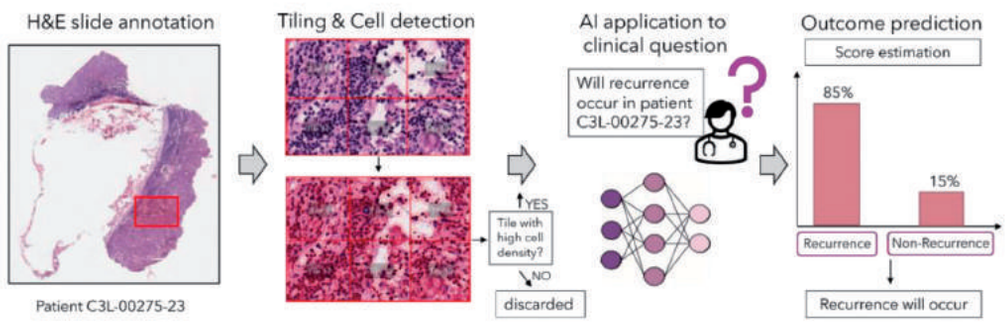
Sentinel lymph node (LSN) status is a crucial prognostic factor for survival of melanoma patients. It would be desirable to determine the likelihood of LSN+ by less invasive but accurate procedures. It is also crucial to predict the likelihood of recurrence in T2-4 patients with unimpaired lymph nodes, because although effective adjuvant therapies are available to prevent recurrence, they have significant toxicity and are very expensive. It is therefore necessary to spare patients from potentially toxic and/or ineffective treatments. Artificial intelligence and digital pathology can serve these purposes.

Aims

1.Development of a support system for early prediction of LSN status (before BLSN) of T2-4 melanoma patients based on the analysis of histological sections of the primary tumor (digital pathology), as well as clinical data of the patient prior to treatment.
2.Development of a support system for the early prediction of recurrence within 2 years after diagnosis of T2-4 and LSN- melanoma patients based on the analysis of histological sections of the primary tumor (digital pathology), mitotic index, as well as clinical data of the patient prior to treatment.

Results

We set up a deep learning model with the aim of identifying prognostic biomarkers from the digitized slides of primary melanoma stained in hematoxylin-eosin to predict disease recurrence in patients with cutaneous melanoma. The slides refer to a cohort of 43 stage I-III patients from the Clinical Proteomic Tumor Analysis Consortium Cutaneous Melanoma (CPTAC-CM) public database and were first annotated by our pathologists and then given as input to our model. The model was further validated on digitized slides related to an independent test, i.e., a validation cohort of 11 melanoma patients, whose data were collected at our Institute. The algorithm was optimized and validated on a cohort of 94 patients with stage IB-IIC melanoma.



Publications

Comes, M. C., Fucci, L., Mele, F., Bove, S., Cristofaro, C., De Risi, I., ... & Massafra, R. (2022). A deep learning model based on whole slide images to predict disease-free survival in cutaneous melanoma patients.†Scientific Reports,†12(1), 20366.

Prediction of HPV status in patients with locally advanced head-neck cancer

P.I. Raffaella Massafra
Start date: 2022
End date: 2024

Background

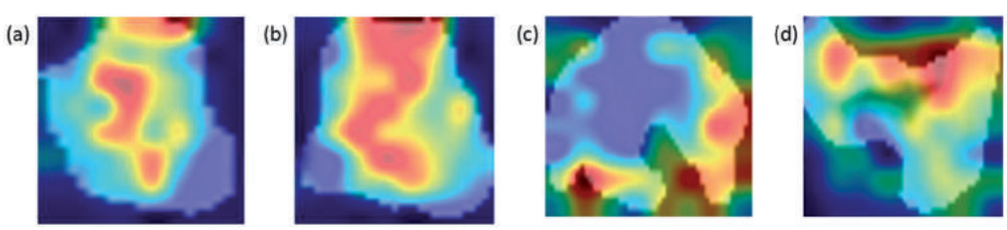
In the setting of oropharyngeal cancers (OPC), prognosis is often linked to human papilloma virus (HPV). However, HPV status is detected by laboratory tests, which usually require the collection of biological specimens from patients, thus being costly and invasive. Within this emerging scenario, it would be necessary to be able to define noninvasive yet accurate methods to assess HPV status that can accurately replace laboratory tests. Non invasive predictive models that give early, i.e., before therapy, prediction of HPV status (+/-) could be developed by exploiting advanced artificial intelligence methodologies.

Aims

Development of a therapeutic decision support system based on prediction of HPV status (+/-) in OPC patients with respect to quantitative features extracted from digitized images of the biopsy specimen and clinical features, so as to replace invasive and expensive laboratory tests for assessment of HPV status.

Results

We proposed the preliminary results related to an explainable HPV status prediction model. We used 499 patients (356 HPV+ and 143 HPV-) extracted from OPC-Radiomics public dataset to train end-to-end Inception-V3 convolutional neural network (CNN). Gross Tumor Volume (GTV) was extracted from pre-treatment CT images and used to train a CNN. we applied Gradient-weighted Class Activation Mapping (Grad-CAM) interpretability technique. The performed XAI algorithm, i.e. GRADcam, shown that the most involved areas in the decision-making process of the classifier, are those within the image and those on the edges. With reference to correctly classified HPV+ patients, the most informative areas are those more internal to the tumor, whereas for correctly classified HPV- patients, the areas most involved seem to be concentrated on the edges. The classification model provided the end user an additional information with respect to the accuracy of the classification, given by the visualization of the areas of greatest interest for predictive purposes for each case examined. Such a support tool could help to increase confidence in using the AI model, less understood as a black-box.



Examples of activation maps referring to correctly classified patients generated by the gradMAP algorithm. The first two images refer to two HPV+ cases, while the last two images refer to two HPV- cases. The red areas are the regions that have most influenced the process of assigning the positive or negative class.

Use of artificial intelligence models by machine learning to identify features of clinical outcomes such as progression-free survival and overall survival in HR+/HER2- metastatic locally advanced metastatic breast cancer patients treated with the combination of clinical kinase 4/6 inhibitors and hormone therapy

P.I. Francesco Giotta
Start date: 2022
End date: 2024

Background

International and national guidelines now agree that endocrinotherapy is the therapy of choice for the majority of patients with endocrine-responsive advanced breast cancer, i.e., hormone receptor-positive and HER2-negative. The latest generation of cyclin-dependent kinase (CDK4/6) inhibitors such as ribociclib, palbociclib, and abemaciclib have shown remarkable clinical efficacy and low toxicity profiles in combination with hormone therapy in the treatment of ER+/HER2- metastatic breast cancer. CDK4/6 kinases are activated upon binding to their regulatory protein, cyclin D, and regulate G1 to S phases of the cell cycle through phosphorylation of the Rb protein. These drugs all show high selectivity for CDK4/6, but different inhibition profiles on other kinases that could translate into different biological action and toxic effects on noncancer cells.

Aims

The aim of the project is to develop an AI-based support system by considering the following characteristics in order to identify features predictive of clinical outcomes such as progression-free survival and overall survival in patients with locally advanced metastatic HR+/HER2- breast cancer treated with the combination of cyclin kinase 4/6 inhibitors and hormone therapy.

- Menopausal status: pre- vs postmenopausal
- Hormonosensitivity
- First-line therapy vs second-line therapy
- Hormonal therapy: aromatase inhibitors vs fulvestrant
- Therapy carried out at progression

Results

Recruitment of a sufficiently adequate number of patients for analysis.

Development of a support system for the prediction of lymph node status in breast cancer patients based on the analysis of ultrasound images using artificial intelligence techniques

P.I. Francesco Giotta
Start date: 2022
End date: 2024

Background

After an initial diagnosis of breast cancer, patients undergo further diagnostic tests aimed at assessing the metastatic status of axillary lymph nodes. For patients whose lymph node status is negative on both clinical and instrumental examination, sentinel lymph node biopsy (SLNB) is mandatory. Although SLNB is a high-performance procedure, it is an expensive and time-consuming examination that may cause several side effects.

Aims

This study aims to develop an artificial intelligence model capable of early prediction of metastatic status of the sentinel lymph node in patients with breast cancer by exclusively analyzing ultrasound images of the primary tumor acquired by the radiologist at diagnosis. In fact, ultrasound is the most frequently performed diagnostic test in clinical practice for both breast cancer diagnosis and lymph node status assessment and is the least expansive and invasive technique compared with other diagnostic tools.

Results

Preliminary studies have been conducted on clinical data of enrollees, developing machine learning models for prediction of sentinel lymph node metastatic status of these patients. The collection of ultrasound images related to patients found to be enrollable in the earlier phase of the study has begun.

Publications

Lombardi, A.; Amoroso, N.; Bellantuono, L.; Bove, S.; Comes, M.C.; Fanizzi, A. ... & Massafra R. Accurate Evaluation of Feature Contributions for Sentinel Lymph Node Status Classification in Breast Cancer. Appl. Sci. 2022, 12, 7227. https://doi.org/10.3390/ app12147227

Employing artificial intelligence models to evaluate by radiomic features the efficacy of neoadjuvant single- or double-block anti HER-2 therapy in combination with chemotherapy in patients with HER-2-positive breast cancer

P.I. Agnese Latorre
Start date: 2022
End date: 2024

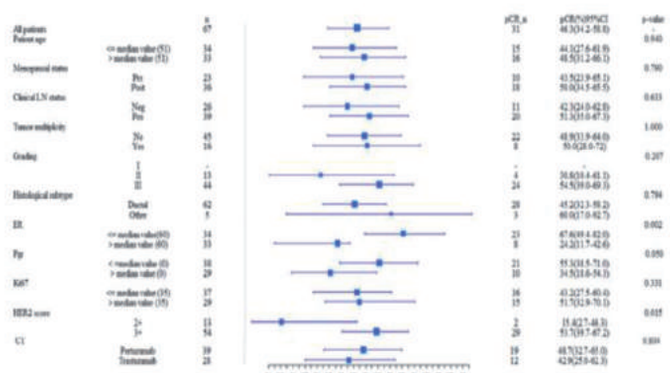
Background

Approximately 15-20% of breast cancers are classified as HER2-positive (HER2+), characterized by a more aggressive clinical phenotype and worse prognosis. In that subgroup chemotherapy neoadjuvant (NAC) has become a standard clinical practice. The addition of trastuzumab to NAC approximately doubles the percentage of patients with HER2+ breast cancer who achieve a pathologic complete response (pCR). Patients with pCR demonstrated better prognosis than those with residual disease after neoadjuvant therapy. The double block HER2 with pertuzumab and pertuzumab can increase further the rateCR rate.

Aims

The study aims to retrospectively/prospectively examine the efficacy of NAC in combination with either trastuzumab or trastuzumab and pertuzumab double blockade, in a population of patients with early-stage HER2+ breast cancer, referred to our Institute. The aim of the study is to evaluate the response to treatment in terms of pCR in the two study populations and to correlate this result with the patients' clinical characteristics, clinical-radiological response, assessed by Mammography or breast MRI, in order to explore whether radiological response can be a prognostic indicator of pCR.

Results



We defined a machine learning algorithm based on clinical features to predict pCR attainment at NAC in HER2-positive patients. We first assessed the significance of the association of clinical features with outcome (pCR) on retrospectively collected data referred to 67 patients referred to the IRCCS Cancer Institute “Giovanni Paolo II”. Next, we performed a feature selection procedure to identify a subset of features to be used for training the machine learning algorithm. We found that outcome was significantly associated with ER status, Pgr status, and HER2.

Publications

Fanizzi, A., Latorre, A., Bavaro, D. A., Bove, S., Comes, M. C., Di Benedetto, E. F., ... & Massafra, R. (2023). Prognostic power assessment of clinical parameters to predict neoadjuvant response therapy in HER2–f1 positive breast cancer patients: A machine learning approach. Cancer Medicine, 12(22), 20663-20669.

Development of a radiomic-based treatment choice support tool for planning and monitoring the efficacy of PD-(L)1 immunotherapy in patients with advanced NonSmallCellLung Cancer (NSCLC)

P.I. Annarita Fanizzi
Start date: 2022
End date: 2024

Background

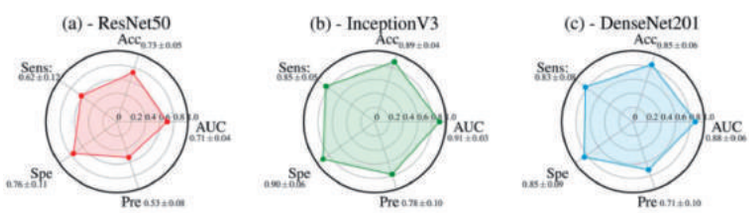
Recent studies have shown that immune checkpoint blockade significantly improved clinical outcomes of patients with lung cancer. However, currently only PDL1 expression represents the approved biomarker for immunotherapy treatment upon which the therapeutic choice in patients with advanced or stage IV NSCLC is based, although the ability to predict resistance or benefit from immunotherapy with clinically meaningful accuracy constitutes one of the most important "unmet needs" in the current therapeutic scenario of these cancers. Many factors, including tumor heterogeneity and dynamic changes in PDL1 expression during therapy can influence the therapeutic response in these patients. Therefore, this type of patients also exists the need to define personalized medicine tools capable of early prediction of response or resistance to immunotherapy in patients with advanced NSCLC, both to better select patients best responsive to immunotherapy, given the costs and possible toxicity associated with treatment with these drugs.

Aims

a. Development of a treatment planning support model that predicts IT response based on pre-treatment CT images and baseline clinical information;
b. Gender or gender-specific medicine assessments, as defined by the World Health Organization (WHO), with respect to response to therapy.

Results

Data and images of patients with stage IV NSCLC undergoing immunotherapy were retrospectively collected. Moreover, the radiomic analysis of CT images has already shown great potential in solving this task; specifically, Convolutional Neural Networks (CNNs) have already been proposed providing good performances. Recently, Vision Transformers (ViTs) have been introduced, reaching comparable and even better performances than traditional CNNs in image classification. The aim of the proposed paper was to compare the performances of different state-of-the-art deep learning algorithms to predict cancer recurrence in NSCLC patients. In this work, using a public database of 144 patients, we implemented a transfer learning approach to predict the recurrence of NSCLC patients from CT images, comparing their performances with state-of-the-art CNNs.



Publications

Fanizzi, A., Fadda, F., Comes, M.C. et al. Comparison between vision transformers and convolutional neural networks to predict non-small lung cancer recurrence. Sci Rep 13, 20605 (2023). https://doi.org/10.1038/s41598-023-48004-9

Single-cell transcriptomics and pathomics in colon cancer

P.I. Simona De Summa, Oronzo Brunetti
Start date: 2022
End date: 2024

Background

Colon cancer (CC) is one of the highest incidence neoplasms in the world. The evolution of scientific knowledge, with the emergence of the so-called "omics" sciences and the synthesis of biological and immunological therapies, has made it possible to introduce the principle of precision medicine in oncology as well, disrupting therapeutic approaches for many cancers. First-line immunotherapy has demonstrated efficacy in the albeit small proportion of colon neoplasms with microsatellite instability. Although several guidelines have tried to give sometimes even different indications on clinical, laboratory, and pathological parameters that stratify a risk of recurrence and justify the use of adjuvant chemotherapy, the mechanisms of biological stratification on the risk of recurrence are unclear. The advent of single-cell omics has made it possible to explore tumor heterogeneity. The use of these methods will allow us to learn about unexplored biological aspects and to identify genomic-tissue markers that can estimate the risk of recurrence. These markers could be identified noninvasively in liquid biopsy through periodic patient monitoring, synchronous with standard clinical follow-up.

Aims

A retrospective/prospective observational study is proposed with the following objectives:

- identify genomic-structural patterns capable of identifying risk factors for recurrence and validation in an independent cohort;
- confirm the importance of liquid biopsy in monitoring and predicting disease risk, using biomarkers identified in the retrospective phase; and
- comparison between standard sequencing and fourth-generation Nanopore sequencing.

Results

Cases from the retrospective cohort that underwent single-cell sequencing were enrolled. In addition, a working group including pathologists, biologists, and laboratory technicians was organized to finalize the spatial transcriptomics protocol. Moreover, the first cases from the prospective study were enrolled in liquid biopsy.

Implementation of the "datawareomics" project: omics data import activities within the "data-lake" and "machine-learning" algorithm developments

P.I. Vito Angiulli
Start date: 2022
End date: 2024

Background

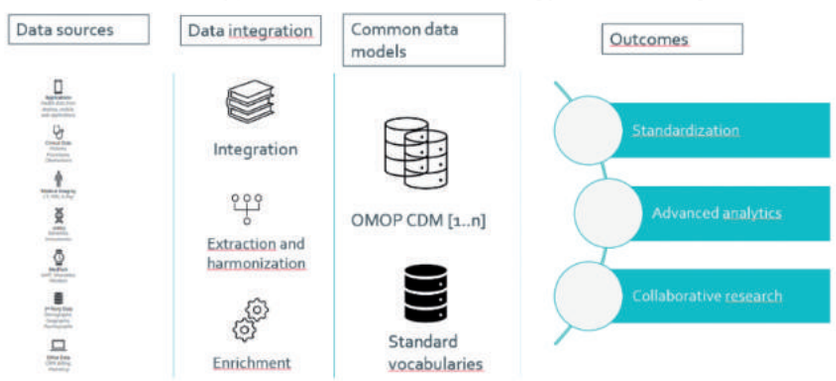
Oncologic diseases, classified by origin, tissue, differentiation and spread, reveal their peculiarities from "unstructured" data from "multi-omics" (genomes, epigenomes, metabolomes, etc.), "radiomics" (diagnostic images from both imaging and pathologic anatomy specialties), "clinical" (referrals) and "real life" (PROMs) and "structured" data found in clinical care information management databases. The collection of all such information in a so-called "data-lake" of research that we have termed "datawareomics" can enable a holistic understanding of biology, bridging the genotype-phenotype gap and achieving, through the typical mechanisms of Artificial Intelligence and rule-driven engines, improvements in prognosis, phenotypic prediction, and oncological treatment.

Aims

The objectives of the project are the systematic collection and import of all data into the "research data-lake" and the subsequent cataloging and implementation of AI algorithms. The experimental approach includes importing and organizing data from the databases of the Operating Units (OUs) with standardization of terminology according to the "Observational Health Data Science and Informatics" (OHDSI) initiative, organizing them into an "OMOP-compliant" model, pseudonymizing them and applying "block-chain" methodologies for data quality control, research feasibility study, and implementation of ML-DL models using supervised and unsupervised methodologies. Sub-objectives are to predict response to therapy and recurrence/death of cancer patients, with the process including data preparation and validation of model accuracy.

Results

After identifying the most suitable pseudonymization procedures (keyed hashing), data from the various sources were extracted using standard interoperability techniques (access databases, HL7/FHIR messages, etc.) including from unstructured sources, subjected to ETL filtering, standardized to OHDSI terminology using ATHENA and organized all data, structured or unstructured, in an OMOP-CMS model hypothesis. The methodology for building the catalog of observational data present for research purposes was initiated. Finally, the IAAS infrastructure was sized to host the "data-lake" on InnovaPuglia's Cloud and Oracle licenses were sized and applied for under the Region of Puglia's "Regional Unlimited Licence Agreement."



LINE 4 | New Organizational-Management Models in Oncology

Overview

Medical science, and oncology in particular, manifests some unequivocal 'trends' such as:

- The personalization of therapies on the basis of more accurate risk-diagnostic-predictive information of efficacy, leading, however, to increased relative costs;
- The clinical contextualization of therapies on patient specifics with the development of models of disease progression, comorbidities and relationship to outcomes (disease trajectories);
- The availability of more "digital or digitized" diagnostic and clinical data on structured and unstructured patients;
- The need to manage the complexity of patient oncology pathology in multiprofessional and multidisciplinary shared-information decision-making settings;
- The availability of connectivity and IoT technologies, safely enabling innovative and/or telemedicine approaches that can innovate the organization of diagnostic, therapeutic and care pathways in terms of efficiency and effectiveness;
- The need to begin systematically assessing causal and prognostic relationships of disease with environmental (ecobiological, structural, and socio-cultural) data for support to policy makers;
- The need to substantiate with cost-effectiveness analysis, appropriateness and cost-effectiveness (best outcome with limited resources) of health care choices for patients.

The proposed Line of Research concerns the development of "new organizational-management models in oncology" (cf. NRP-Par. 5.1.1., Art. 7) to produce scientific evidence aimed at improving organizational cost-effectiveness in equity, access to services and solidarity with available resources. Activities will cover: a) Local, national, international networks: data, catalogs, services; b) Systematization of HTA assessments; c) Telemedicine from testing to accreditation; d) PDTA modeling and accreditation; e) Sustainability of precision medicine; f) Governance of data; g) Governance of intellectual property (UTT).

Aims

The development of Precision Oncology has led to a clear improvement in clinical outcomes but also to other effects of strong social impact such as: the costliness of targeted therapies; the importance of the reliability of increasingly sophisticated and costly predictive-prognostic diagnostic assessments; the NEED for innovative, shared PDTA pathways tailored to new outcomes; the possibilities offered by telemedicine in revising the hospital/territorial/domiciliary care model; and the need to develop innovative multidisciplinary models for the management of the oncology patient capable of producing, integrating, and managing clinical, biomolecular, genetic, and pathological information. On this basis, research activities will aim to create stable, automated and "GDPR compliant" mechanisms of structured and de-structured data collection, in ordinary patient management processes, standardization of classifications, semantics and ontologies in catalogs available in research networks (e.g. Big Health Data) as well as processing resources and services available in networks; testing, evaluating and accrediting organizational models in laboratory diagnostics (MTB), imaging (telepathology), care (de-hospitalization of care), medical information by "MDT teams" (teleconsultation) in telemedicine; modeling organizational formulas of hospital, territorial and home care mixes of diagnostic-therapeutic pathways by collecting outcomes (efficiency and effectiveness) for systematic HTA evaluation of organizational models; verifying the economic and managerial impact arising from the use of drug companion tests; systematically enhancing knowledge and intellectual property as a unifying element.

Training and monitoring the skills of the Clinical Trials Nurse

P.I. Elsa Vitale
Start date: 2022
End date: 2024

Background

As of May 2021, IRCCS Istituto Tumori di Bari has hired research nurses to be employed in the care activities of patients enrolled in experimental studies. Recruitment of the research nurse is carried out by the human resources office, drawing from public competition rankings, through a one-year renewable fixed-term contract. Each nurse is assigned to a PI and is supervised by the clinical mentor who is the nursing coordinator of the OU to which he or she is assigned. The acquisition of skills acquired in the working field are monitored at one month and three months by nurses attached to the Scientific Directorate. The aforementioned research nurses are also engaged in the activities of Multidisciplinary Teams dealing with PDTA of oncology patients afferent to the Institute itself. Assignment to the OUs is made according to precise criteria established in advance by the IRCCS CTS. As of July 2023, IRCCS has also hired 3 nurse health researchers on a Research Pyramid contract.

Aims

- Define optimal timeframes and modalities for the acquisition and monitoring of advanced nursing skills aimed at ensuring best practice and safety in the nursing care to be delivered to the patient undergoing drug trials with antiblastic drugs (and therefore at high risk).
- Define job descriptions for the research nurse (JD), considering what has already been suggested by the Ministry of Health, AIFA, Italian and international scientific societies.
- Creation and Administration of a structured questionnaire for the detection and subsequent monitoring of the skills described in the JD. Preliminarily it will be used to verify the input ones to identify training needs.
- Drafting of an Annual Training Plan (for three years), approval by Strategic Management, organization of events, CME accreditation and subsequent implementation.

Results

A predictive artificial intelligence model was trained, and the results were the subject of oral presentations at conference.

Lean Approach

P.I. Vito Angiulli
Start date: 2022
End date: 2024

Background

Timeliness, therapeutic appropriateness, adherence and continuity of care are crucial to the success of patient care, influencing the sustainability of the Health Care System. Successful outcomes of proper caretaking depend on an organization conducive to placing the patient on an efficient pathway aimed at optimizing resources. Enhancing the quality of care is a priority for health systems, with more and more facilities adopting Lean practices to reorganize the system, reduce waste, and meet required quality standards.

Aims

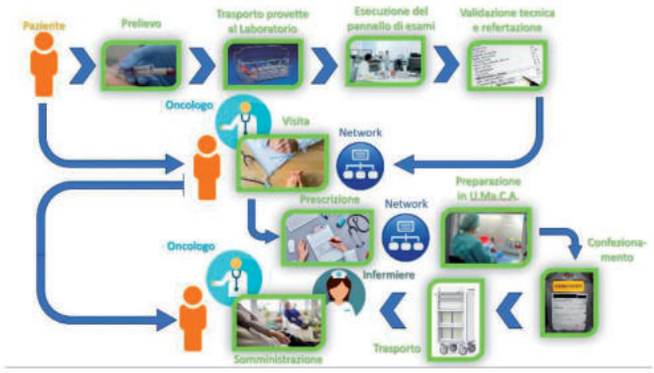
The goal of the project is to apply "Lean" methodology to key processes at IRCCS Giovanni Paolo II Cancer Institute:

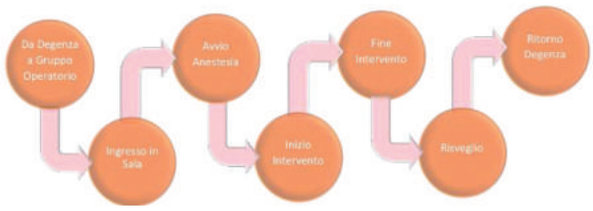
- Chemotherapy administration;
- Operation of the Operating Group;
- Activities of the C.Or.O..

Results

For chemotherapies, all activities were mapped: laboratory tests, visits, drug prescriptions, their preparation and distribution, and finally administration and time measurements were made for the procedures of:

- Withdrawal with detection of typical laboratory test panels and determination of "Turn Around Time."
- Performing examinations with determination for each outpatient "queue" of physicians (no. servants), arrival flows and service times and logic (FIFO);
- Preparation of therapies with determination of the number of active servants (hoods) of the preparation times of each active ingredient and preparation groupings.
- Therapy administration with determination of the number of chairs per facility (no. of servants) and duration according to protocols (drug quantity and flow).





For surgical activities in the Operating Room, all activities were mapped: transfers from inpatient wards to the operating block, entering the room, anesthesia, surgery, waking up, leaving the room, and returning to the inpatient ward. Activities, all sequential were measured, as were active rooms and staffing. Several interviews were conducted with all professionals and operating teams.

Soft tissue sarcomas: a model of a network approach

P.I. Michele Guida
Start date: 2022
End date: 2024

Background

With the European Directive 2011/24/EU, European Reference Networks, (ERNs) or virtual networks aimed at facilitating access to high-quality cross-border health care, involving highly specialized clinical and research centers, were born. Among these networks, EURACAN represents the European reference network for rare cancers. The value of such an organization is particularly relevant in cases of rare diseases and cancers, complex and low-prevalence diseases and as such involving patients dispersed over a wide geographic area. In the Puglia region, rare cancers cause a high rate of health care migration. To curb this issue, the Rare Tumors and Melanoma O.U. has therefore become a welcoming place for patients and relatives involved by soft tissue sarcomas, and collaborates with the Institute's experimental laboratories in order to study the genetic-molecular and microenvironmental characteristics of different sarcoma histotypes and define new molecular targets for innovative targeted therapies, literature reporting of clinical cases and case series through the involvement of national centers.

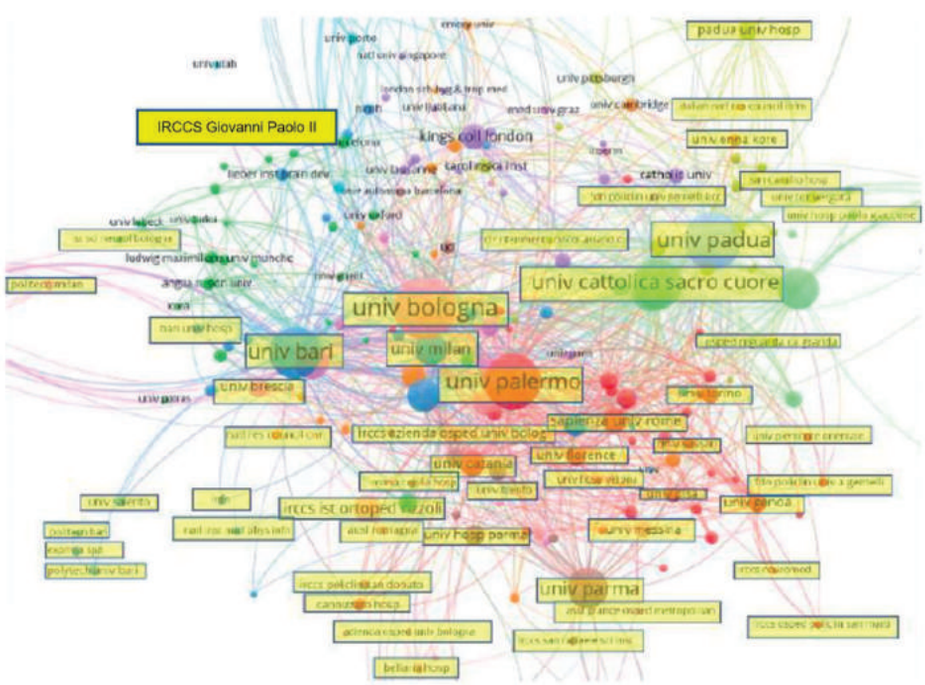
Aims

- Compilation of all regional case histories into a common database through the creation of a platform that is initially accessible to oncology physicians from the various oncology operating units in the region and can later be accessed by primary care physicians.
- Participation in the creation of European databases within the ERN/EURACAN network.
- Analysis of the peculiarities of psychological needs of patients with sarcomas.
- Definition of unified and shared diagnostic-therapeutic pathways for the Apulia Region on soft tissue sarcomas.
- Centralized collection of biological specimens (blood, tumor tissue, etc.) at the Institute's Biobank in order to obtain a series of cases to be able to validate in silico analyses of predictive biomarkers and therapeutic targets, and to set up cell cultures also in 3D.
- Validation in preclinical models of molecular targeted therapies.

Results

Centralized collection of biological samples (blood, plasma, serum, tumor tissue) that will be used to establish 3D organotypic culture models has begun. In addition, a working table was started with the regional agency for health and social welfare (AReSS Puglia) to develop a model of a Regional Network for Rare Tumors and its subsequent implementation.

ONGOING GRANTED PROJECTS & NETWORKS



PNC0000002 - "DARE - Digital Lifelong Prevention"

P.I. Prof. L. Chiari - Università di Bologna "Alma Mater Studiorum"
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Raffaella Massafra
P.I. Pilot Study WP3 - 3.2d Dr. R. Massafra
P.I. Pilot Study WP4.b Dr. A. Azzariti
Start date: 2022
End date: 2026

Background

The DARE (DigitAl lifelong pRevEntion) project is an initiative, financed with European funds, of broad scope aimed at creating and developing themes of disease prevention, including oncology, through the use of digital technologies. It envisages the participation of 48 Research Centers with multidisciplinary expertise (technical, ethical-legal and organizational) divided into 3 Spokes. Each center will propose pilot studies that, after a thorough internal evaluation process within the consortium and approval by the Ethics Committees of centers enrolling patients, will move to the development phase. Our Institute is Affiliated Center No. 7 of Spoke 3: DIGITALLY-ENABLED SECONDARY AND TERTIARY PREVENTION (Principal Investigator Prof. Massimo Federici - UniRoma2) and is involved in the projects related to WP3: Digital Tools for Screening and Early Diagnosis (responsible Prof. Massimo Federici - UniRoma2) and WP4: Digitally-enabled Biomarker Discovery (responsible Prof. Paola Pontrelli - University of Bari).

Aims

- The Laboratory of Experimental Pharmacology is involved in 2 pilot studies afferent to WP4, WP4.3a and WP4.3b WP4.3a Pilot Study: Potential Liquid-Biopsy/Cytology Biomarkers for early diagnosis and monitoring of HPV positive and negative Gynecological Cancers (PI: Prof. Luisa Torsi). Our institute will be involved in the enrollment of the 60 HPV positive and 60 HPV negative patients and the collection and storage of samples. These include cervical brushing cells and blood and urine samples that will be collected and used as materials for liquid biopsy testing of the presence of particular HPV strains. The SiMoT platform will use both tissue samples and fluids for the initial training phase of the test and for validation. The detection measures will be analyzed using machine learning techniques.WP4.3b Pilot Study: Potential Liquid-Biopsy/Cytology Biomarkers for Early Diagnosis and Monitoring of HPV Positive and Negative Gynecological Cancers (PI: Dr. Amalia Azzariti) - Purpose: To identify novel biomarkers in liquid biopsy/cytology for early diagnosis of gynecological cancers, HPV positive or negative.
- The Laboratory of Biostatistics and Bioinformatics is the promoter of a pilot study afferent to WP3: "Radiogenomic approaches predicting response to neoadjuvant therapy in breast cancer patients" (PI: Dr. Raffaella Massafra). This project aims to implement an artificial intelligence model based on the multimodal integration of advanced molecular diagnostics, radiological and histological imaging and clinical data in order to predict early complete pathological response in patients undergoing neoadjuvant therapy. Having such data available within our institution, we can define a retrospective observational study.

Results

WP4.3b: A preliminary in silico analysis was performed using the endometrial and ovarian cancer datasets from the CPTAC repository. Specifically, a tumor/normal comparison was performed using the python package cptac( ) to detect significantly deregulated phosphoproteins. The analysis selected 20 phosphoproteins that are differentially expressed in endometrial and ovarian cancers compared with healthy ones. Of these proteins, caveolin 1(Y14), HSPB6(S16), and LRP1(S4523) were identified with a strong scientific rationale as being a tumor suppressor gene in human ovarian epithelium, able to decrease in high-grade squamous intraepithelial lesions and cervical carcinoma cells, and involved in endometrial carcinoma formation, respectively. We have already set up the HPV DNA detection and genotyping system by Single-Step PCR and Reverse Line Blot (AMPLIQUALITY HPV-TYPE EXPRESS v3.0-AB Analytical) and analyzed 3 samples from patients with cervical cancer. We started PTM protein characterization by analyzing p-AKT and p-STAT3 by Western Blot in 4 patients with cervical cancer and 4 healthy patients and metabolomic analysis on 4 urine samples from 4 patients with cancer..

WP3 - 3.2d: From the beginning to today, we have evaluated the eligibility criteria of a set of 200 breast cancer patients, who underwent neoadjuvant chemotherapy at our Institute. During this period, the enrollment began (54 patients), and both the radiological images (pre-treatment MRI exams) and the histological samples were collected. The histological slides stained with hematoxylin and eosin were digitalized by a performing scanner (Aperio AT2, Leica Biosystems) to obtain digital slides.

PNC-E3-2022-23683266 PNC - HLS - DA - Diagnostica Avanzata -LHS-DA (INNOVA)

P.I. L. Blandini - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Amalia Azzariti
Start date: 2023
End date: 2026

Background

The project proposes the creation of a new advanced diagnostic platform (INNOVA) incorporating 43 public and private facilities entities operating within the national health system (NHS) and life sciences research across Italy. The platform will promote the development of an ecosystem that will absorb validated advanced diagnostic approaches, fostering their dissemination and commercial use in clinical settings. The main goal is to make available many phenotypic biomarkers of organ damage and develop an integrated and advanced molecular and imaging platform system, thus providing new tools for prevention, early diagnosis and drug monitoring in human diseases, according to the principles of personalized and precision medicine. It is planned to first implement molecular diagnostics by validating biomarkers and pathways involved in noncommunicable diseases (neurological, cardiovascular, degenerative diseases, vascular, inflammatory, metabolic, and cancers), with a focus on those with difficult diagnosis, poor therapeutic response, and prognosis problems. The network will examine ways to move from standard diagnostics to future multimodal strategies that can improve outcomes and personalized clinical decisions. The network will benefit from the critical mass of technological expertise provided by its members to develop shared procedures leading to new tools, methods, and guidelines in the field of new advanced diagnostics.

Aims

Our Institute is involved in this project in WP4 and WP5. The objectives of the 2 WPs are:
WP4: The goal is to develop a high-resolution national reference hub based on Liquid Biopsy for next-generation diagnostics by exploiting patients' body fluids. For this purpose, cutting-edge technologies based on NGS, digital PCR, proteomics and metabolomics will be used to provide service activities for public and commercial purposes.
WP5: The goal is to develop multimodal data collection and fusion tools for creating reliable predictive models, according to individual WPs. Integration of imaging, omics, clinical and demographic will enable advanced multi-level analyses for creating innovative diagnostic algorithms.

Results

WP4: After an initial survey to define the homogeneity of the technology base of the various centers participating in WP4, 2 Ring Studies, 4.1 and 4.2, were defined to test the reproducibility of analyses conducted in afferent centers performed on synthetic material using techniques such as NGS and Digital PCR. The former has already been carried out by all centers and results are awaited, the processing of which is the responsibility of the group at the Regina Elena Institute in Rome; the latter has been delayed at the central level for the delivery of materials and will be developed as soon as these are available. The next projects on which the consortium will focus were also defined. Our Institute has agreed to participate in 2 studies on the use of liquid biopsy in prostate cancer and NSCLC diseases and has proposed 2 of them, of which the synopsis is being written.
WP5: Definition of data harmonization processes.

PNRR-POC-2022-12376580: Analyses of HPV and host body fluid biomarkers as non-invasive strategy for detection of head and neck cancer relapse

P.I. Dr. Giovanni Blandino (IRE, Roma) - Università di Milano, Milano
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Raffaella Massafra
Start date: 2023
End date: 2025

Background

Locoregional recurrence occurring in nearly 50% of patients with HNSCC is the leading cause of cancer-related death, as the response to therapy of patients with recurrent HNSCC is very poor. To date, monitoring of HNSCC recurrence relies mainly on imaging platforms (MRI and PET) and direct histological sampling of the patient combined with specific genetic testing. Both approaches are invasive, expensive, and often ineffective. There is an urgent need to develop a reliable and noninvasive strategy to detect recurrence early and monitor its progression in patients with HNSCC.In this project, we propose the validation of an already patented miRNA signature coupled with HPV DNA in head and neck cancer tissues and body fluids as predictive and prognostic biomarkers of recurrent HNSCC patients. This goal will be pursued using retrospective and prospective cohorts of HNSCC patients synergistically enrolled by the proposing institutions.

Aims

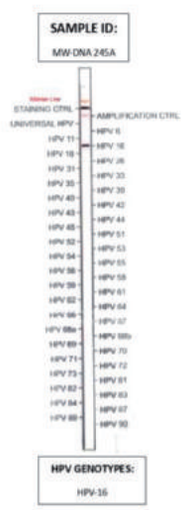
The aims of this project are:
WP1: Study methodology and patient enrollment.
WP2: Assessment of miRNA and ctDNA from tissues and liquid biopsies of HNSCC patients
WP3: Evaluation of HPV DNA from tissues and liquid biopsies of HNSCC patients
The Experimental Pharmacology laboratory, under the supervision of Dr. A.Azzariti, is involved in tasK WP2 for multiplex analysis of 4 miRNAs using Luminex technology and WP3 for determination of the presence of HPV infection, and subsequent genotyping in liquid biopsy samples from partners.

Results

During these first few months, procedures for detection and genotyping of HPV strains were developed. To date, the first tranche of samples arrived from the coordinating center has been analyzed. In addition, we are in the process of finalizing the procedure for multiplex analysis of the 4 miRNAs.

Genotipizzazione HPV

Numero	ID	Estratto	Risultati
1	241I	ctDNA	HPV-16
2	255A	ctDNA	Negativo
3	260A	ctDNA	HPV-16
4	261A	ctDNA	HPV-16
5	271D	ctDNA	Negativo
6	281A	ctDNA	HPV-16
7	366L	tDNA	HPV-16
8	366V	tDNA	HPV-16
9	375 Linf	tDNA	Negativo
10	377T	tDNA	HPV-16
11	381T	tDNA	HPV-16
12	241A	MW-DNA	Negativo
13	241C	MW-DNA	Negativo
14	241G	MW-DNA	Negativo
15	245A	MW-DNA	HPV-16
16	271H	MW-DNA	Negativo



PNRR-MAD-2022-12376508: Dissecting the role of tau in ovarian carcinoma pathogenesis and drug resistance

P.I. Perego Paola Maria Chiara (INT_Milano) - Istituto Besta, Milano
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Amalia Azzariti
Start date: 2023
End date: 2025

Background

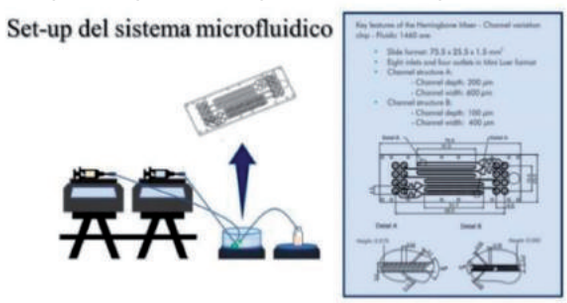
The microtubule-associated protein tau plays a role in the pathogenesis of neurodegenerative diseases called tauopathies. In addition, tau is recognized as a multitasking protein with a role in chromosomal stability, as evidenced by the presence of chromosomal aberrations and aneuploidies in peripheral cells and brain tissues of patients carrying a tau mutation and the involvement of tau in DNA and chromatin protection and transcription. On this basis, it has been shown that tau mutations increase cancer risk and may modulate cancer-relevant pathways, thus implying that tau function may contribute to cancer etiopathogenesis. The involvement of tau in drug resistance is still poorly understood. Because tau is physically associated with microtubules, it may impact the response to microtubule stabilizers such as taxanes, which are used in first-line therapy of ovarian cancer. In addition, evidence on the role of tau in genome stability suggests its involvement in resistance to DNA-damaging agents clinically available for the management of ovarian carcinoma, such as cisplatin and Poly-ADP ribose polymerase inhibitors. It is known that most ovarian cancers are aneuploid, but the causes and significance of this aneuploidy are only partially understood.

Aims

Based on this background, the overall goal of this project is to analyze the role of tau in ovarian carcinoma pathogenesis and drug resistance. It will investigate the role of tau in the onset of ovarian carcinoma by expressing wild-type and mutated tau in nontumorigenic cell models and assessing their tumorigenic potential by morphological and functional assays. In a large panel of ovarian cancer cell lines, tau expression will be correlated with drug response/resistance using gain- and loss-of-function approaches. Hybrid nanoparticles derived from the fusion of carcinoma cell membranes and liposomes, loaded with tau-directed nucleic acids (i.e., small interfering RNAs, siRNAs) developed in our Laboratory of Experimental Pharmacology, will be used. Finally, a translational study will be performed on patient-derived samples. Organids derived from ovarian cancer patients will be generated and exploited to validate the contribution of tau to drug resistance. In addition, analyses of tau levels in tumor samples and liquid biopsies from patients will be performed.

Results

During these first months of the project within the specific expertise of our Institute, patients were enrolled, and blood and tissue samples were collected, which were and will be used to generate organoids for subsequent analysis. In addition, ovarian cancer cell lines were cultured for the isolation of cell membranes that will be used to obtain the hybrid nanoparticles composed of liposomes and cancer cell membranes and that will be the device for selective siRNA transport to silence the Tau gene.



Schematizzazione del set-up automatizzato per la produzione di nanosistemi particellari in flusso. In dettaglio, le caratteristiche della geometria interna del dispositivo microfluidico.

PNRR-MAD-2022-12376059: A multiomics approach to identify signatures of response and resistance to immunoteraphy in R/R Diffuse Large B-Cell Lymphoma

P.I. Dr. Carmelo Carlo Stella (Istituto Clinico Humanitas - Humanitas Mirasole S.p.A.)
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Sabino Ciavarella
Start date: 2023
End date: 2025

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin Lymphoma (NHL) subtype, accounting for 35% to 40% of all NHL. On average, 50% of newly diagnosed DLBCL are cured by first-line chemoimmunotherapy, whereas 40% are refractory to or relapse no more than 12 months after first-line therapy and respond poorly to salvage therapy. Chimeric Antigen Receptor T-cells (CAR-T cells) have substantially improved the outcome of primary refractory or early relapsing (R/R) DLBCL. However, approximately 50% of patients treated with CAR-T cells do not achieve long-term disease control, raising the clinically relevant issue of appropriate identification of CAR-T-responsive patients. More recently, bi-specific Tcell engagers, such as Glofitamab, have emerged as critical agents capable of inducing prolonged disease control in a significant proportion of R/R DLBCL. In analogy to CAR-T cells, the biomarkers of response and the mechanisms of resistance to bispecific antibodies remain unknown. Understanding the molecular determinants of resistance to the different highly active immuno-activating therapy categories is crucial to defining their rational use. The lack of robust tools for predicting disease outcome, monitoring disease eradication, and analysis of resistance/sensitivity to immunotherapies represent a significant limitation for optimizing the therapeutic decision-making process and designing innovative therapeutic programs for R/R DLBCL.

Aims

- To investigate disease mutational heterogeneity and clonal evolution by ctdna sequencing in patients receiving car t-cell therapy or bispecfic antibodies;
- To analyze pbmcs and circulating t cells in patients receiving car t-cell therapy or bispecfic antibodies and in patients failing cd19 directed car-t cell therapy but responding to glofitamab;
- To investigate tumor microenvironment in r/r DLBCL undergoing immunotherapy;

Results

CD3+ lymphocytes will be isolated and transcriptomic analyses will be conducted. CAR T-cell expansion kinetics will also be monitored by flow cytometry. To identify TME features affecting immunotherapy efficacy, we will characterize patient biopsy specimens pre-and post-therapy using either the Digital Spatial Profiling or RNA sequencing data.

PNRR-MAD-2022-12376441: Leukemic cell and microenvironment interactions as the culprit of chronicity in CLL

P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Carla Minoia, Dr. Attilio Guarini
Start date: 2022
End date: 2025

Background

Chronic lymphocytic leukemia (CLL) is a paradigmatic example of a chronic neoplasia affecting the elderly population with a high socio-economic burden for patients, care-givers and the Italian National Health System. CLL is the most common leukemia among the adults in the Western countries and its incidence is rising due to the increasing life expectancy of the general population. In addition, CLL is characterized by a high prevalence due to a long median overall survival, in the order of decades, due to the long natural history of the disease but also to the therapeutic advancements with the use of novel chemo-free targeted therapies. In this project, we aim at investigating the crucial pathways and molecules that are responsible for the chronic behavior of the disease and for its clinical progression occurring in a portion of patients.

Aims

- Dissecting the effect of the microenvironment on CLL cells.
- Unveiling the contribution of microenvironmental components in the progression of CLL.

PNRR-POC-2022-12375862: A multi-omic approach for gene fusion detection in hematological malignancies: towards improved diagnostic screening and therapeutic targeting - FUSION-TARGET

P.I. Prof. Giovanni Martinelli (IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST s.r.l)
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Giacomo Volpe
Start date: 2022
End date: 2025

Background

Gene fusions generated by chromosomal translocations or other mechanisms are involved in malignant transformation. Many of them have been implicated in leukemogenesis, including common and rare translocations with prognostic or therapeutic significance. However, the identification of fusion transcripts for diagnostic purposes is currently limited to a few translocations with well-known clinical relevance. In addition, RNA-sequencing (RNA-seq)-based approaches, which would allow more translocations to be identified, are not used in clinics because of the complexity of data analysis. The FUSION-TARGET aims to identify novel gene fusions and characterize their leukemic potential in order to develop new cellular and molecular models for the study of new therapeutic approaches for the treatment of leukemias.

Aims

- Collect a cohort of patients with acute myeloid leukemia (1000 patients over 2 years among the 4 centers involved)
- Generating WGS sequencing libraries for identification of novel gene fusions
- Generation of genetic manipulation vectors for insertions of such gene fusions into IPS cellular models for study of the same.
- Molecular characterization of the pathological changes produced by such gene fusions and definition of potential new therapeutic targets

Results

- Collection of cohort of samples (15 in our center) that were sent to the coordinating center "IRST Meldola" for generation of sequencing libraries.
- Generation and sequencing libraries WGS and RNA-seq in all collected patients
- Analysis of omics data (currently in progress)
- Implementation and validation of genetic manipulation system using hIPSC platform and validation of CRISPR/Cas9 system for mutagenesis in our laboratory

PNRR - Development and validation of a biomedical device for the detection, characterization and removal of Circulating Tumor Cells from the peripheral blood of patients for the treatment and diagnosis of cancer - EVOLUTION -

P.I. Dr. Paola Ulivi (Istituto scientifico romagnolo per lo studio e la cura dei tumori)
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Brunella Pilato
Start date: 2023
End date: 2025

Background

The project aims to design, implement, and evaluate a device capable of counting, capturing, and subsequently characterizing circulating CTCs, aimed at personalized cancer treatments. This project uses innovative technological devices/approaches developed at IRST (CTC-sorting) and UniSannio (Raman-based detection and characterization unit).

Aims

Interest in CTCs in the field of oncology is growing as the wide variety of specific information that can be obtained through their counting and molecular characterization allows and would allow clinicians to exponentially improve patient management. Given the complexity of analysis, CTCs are mainly considered as a marker of prognosis.

PNRR - Systematic reclassification of Variants of Unknown Significance in cancer predisposing genes through machine learning applied to CRISPR based functional screens

P.I. IEO
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Stefania Tommasi
Start date: 2023
End date: 2025

Background

Algorithms to classify germline variants in cancer predisposing genes (CPGs) are still inefficient, as an increasing proportion of reported variants remain of unknown significance (VUS). A report of VUS does not allow clinicians to have adequate information regarding prophylaxis and treatment (e.g., PARP inhibitors) or familial screening. Biological information, based on the functional consequences of genetic variant on protein function, can be greatly improved using the high-throughput screens offered by CRISPR1 technology and recent advances in structural information offered by CryoEM3.
In addition, machine learning (ML) algorithms, such as the recently published lead agency (IEO) Renovo2, can predict pathogenicity with greater than 95% accuracy and can be used to inform the classification of VUS or unreported variants. The accuracy of ML algorithms can decrease significantly for rarely mutated genes, which are often associated with lower levels of genetic, functional, or clinical evidence; however, threshold adjustment of the RENOVO score for pathogenicity classification based on gene-specific evidence (e.g., dedicated functional assays) can significantly improve accuracy.
We propose to systematically evaluate genotype-phenotype associations in CPGs using high-throughput CRISPR screens; these data will be integrated with emerging structural data to train a new ML-based classification algorithm, with the goal of significantly reducing the VUS rate of CPGs.

Aims

Specific Aim 1: Systematically map functionally impacted VUS CPGs through CRISPR-based high throughput screens.
Specific Aim 2: Build a database to integrate structural and functional information of cancer predisposing genes (CPGs).
Specific Aim 3 Train ML-based algorithms to improve the interpretation of variant

PNRR - Cancer of unknown primary: shifting the paradigm from undefined heterogeneous malignancies to a new tumor type arising from cancer stem cells by specific pathogenetic mechanisms and targetable dysregulated pathways

P.I. Prof.ssa Carla Boccaccio (Candiolo Cancer Center)
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Alfredo Zito
Start date: 2023
End date: 2025

Background

Carcinomas of unknown primitivity (CUP) are difficult clinical and pathologic entities, describing patients with multiple metastases in the absence of an anatomically or histologically recognizable tumor. The definition of CUP currently applies to at least 2-5% of all malignancies and characterizes a median survival < 1 year, thus representing an unsolved clinical problem. So far, CUPs have been studied primarily with pragmatic goals: (i) to discover the molecular or epigenetic signature of a putative "tissue of origin," and treat them accordingly; (ii) to identify mutated tumor genes and apply personalized targeted therapies.

Aims

The objective of the study is to collect samples of biological material from CUP patients, including viable tumor tissue from biopsies or surgical procedures, archived and paraffin-fixed (FFPE) tumor tissue, and biological fluids, in order to define the molecular profile of CUPs, with a specific focus on oncogenes involved in invasive growth and stemness processes (MET, RON, AXL, MER, TYRO3) and correlate genetic status and response to drug targets in pre-clinical models, including xenopatient/spheroplastic CUPs.

PNRR-MAD-2022-12376570 - Identification of common pathogenic mechanisms driving squamous cell carcinomas of the anogenital tract and head&neck region to develop overarching therapeutic strategies

P.I. Tornesello Maria Lina (Istituto nazionale tumori Fondazione Giovanni Pascale)
P.I. IRCCS Istituto Tumori Giovanni Paolo II Dr. Oronzo Brunetti
Start date: 2023
End date: 2025

Background

Squamous cell carcinomas (SCC) originating from the mucosal epithelium of the anogenital tract and head and neck region (particularly oral and oropharyngeal tract) share common cancerous pathways that are primarily triggered by a panel of risk factors, e.g. aging, smoking, alcohol consumption, and, to a lesser extent, the human papillomavirus (HPV) infection. Currently, the standard treatments for these tumors involve radiotherapy, chemotherapy, or surgery, all with devastating effects on the targeted anatomical sites. Thus, alternative therapies with higher efficacy and fewer side effects are urgently needed to improve patient outcomes. The proposing group has recently observed that activating mutations in the telomerase reverse transcriptase promoter (TERTpm) are frequent in this setting and cause enhanced TERT expression in both oral (60%) and genital (20%-60%) SCC. High expression levels of endogenous TERT in cancer cells can trigger extra-telomeric oncogenic pathways and tumorigenesis, which demand new combined therapeutic approaches, including telomerase inhibitors. They have also recently shown that HPV-related SIRT1 upregulation in oropharyngeal SCC, characterized by dysregulated TERT expression and wild-type p53, causes p53 deacetylation and enhanced stabilization. Inhibition of SIRT1 with the small molecule EX527 determines p53 restoration in cervix and oropharynx SCC rendering tumor cells more sensitive to either genotoxic agents or ionizing radiation. In addition, a novel approach of gene editing, more effective than CRISPR/Cas9, has also been developed by the proposing group to target neoplastic cells bearing specific mutations. Thus, we propose to identify common molecular pathways underlying SCC development in the anogenital tract and head and neck region and to develop host-targeted therapeutic interventions against these cancers.

Aims

1. To characterize the molecular platforms underlying telomerase re-activation and SIRT1 overexpression in anogenital and head and neck SCC as well as in SCC-derived cell lines, along with their clinical significance.
2. To establish organoids from patients-derived SCC using both cancer-associated fibroblasts (CAFs) and squamous cancer cells to mirror tumor architecture and microenvironment useful for in vitro drug responsiveness screening assays.
3. To evaluate new therapeutic combinations, including a thermo-inducible double-strand DNA break g-RNA/dCas9 editing system, in NOD scid gamma (NSG) mice engrafted with organoids derived from oral, oropharyngeal, and anogenital cancers as clinical surrogate of human tumors.

Ricerca Finalizzata 2018 - Definition and testing of a new model of clinical governance based on the integration of tools such as Health Technology Assessment, Clinical Practice Guidelines, Clinical Pathways, and healthcare performance measurement for planning, implementation and management of healthcare interventions in different settings - INTEGRATE-HEALTH-GOV

Principal Investigator Proposing Entity: National Institute of Health,
Principal Investigator IRCCS Cancer Institute "Giovanni Paolo II": Francesco Giotta
Researcher collaborators: Massafra Raffaella, Zito Francesco Alfredo
Participating centers:
WP1 - Istituto Superiore di Sanità - National HTA Center
WP2 - Regione Lombardia - Direzione Generale Sanità Asst Grande Ospedale Metropolitano Niguarda
WP3 - Galeazzi Orthopaedic Institute Scientific direction
WP4 - National Institute of Rest and Care for the Elderly Department of Geriatric Medicine
WP5 - IRCCS Cancer Institute "Giovanni Paolo II" UOC Medical Oncology
WP6 - Toscana AOUC Azienda Ospedaliero-Universitaria Careggi
WP7 - Tuscany Scuola Superiore Sant'Anna di Pisa - SSSA
WP8 - Veneto Region - Zero Company
Start date: September 2020
End date: September 2025

Background

The multicenter project aims to define a governance model for the introduction of health policies and programs into the Italian National Health Service (NHS) based on the integration of tools such as Health Technology Assessment (HTA), Clinical Practice Guidelines (CPGs) and Clinical Pathways (CPs), stressing the creation of partnerships between the various stakeholders, particularly citizens/patients and professionals. Specifically, for our Institute the specific aim of study is the experimentation of the integrated use of the HTA methodology with machine learning techniques used for the construction of automated decision support systems to clinicians in the development of personalized treatment paths. Machine learning approach will be applied to the management of a complex multidisciplinary care path, and it will provide elements to support clinicians' decision.

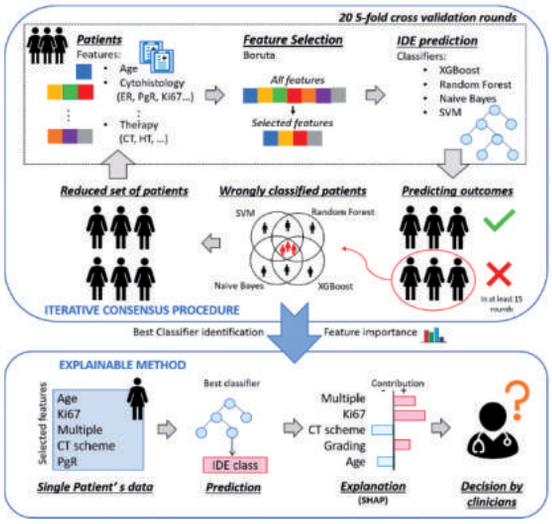
Aims

The objectives set for this project are:
1. drafting of the PDTA following some basic steps as indicated by the Italian Group Method for Evidence-Based Medicine,
2. development of an automated method to support therapeutic decisions
3. integration of breast unit care pathway assessment with the decision support system

Results

The research carried out in the last two years basically focuses on the development of diagnostic and therapeutic decision support systems for breast cancer patients using artificial intelligence techniques. Basically, they are developed in 3 research tasks: (i) prediction of lymph node status, (ii) prediction of response to neoadjuvant therapy, and (iii) prediction of disease recurrence in patients undergoing adjuvant therapy. These models thus fit at multiple points in the treatment pathway

of a breast cancer patient, i.e., at the stage of diagnosis for prediction of lymph node status, at the start of neoadjuvant therapy, and at the end of adjuvant therapy. Furthermore, with the aim of providing clinicians with a tool that can bridge the gap between clinical practice and the information provided by artificial intelligence, we have contextually developed predictive models through an explainable artificial intelligence approach. Such a downstream system with respect to prediction for the individual patient provides an even graphical representation of how the classifier came to a particular conclusion. In this way, the clinician has the opportunity to more consciously evaluate the suggestion provided by the automated system, which is basically the result of modeling retrospective data collected over time on similar patients.



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Ricerca Finalizzata 2021 - PEERAD - PrEdicting Endopredict score with RADiomics: a novel radiomics model based on artificial intelligence to drive adjuvant treatment in patients with early-stage, intermediate-risk, hormone-receptor positive HER2 negative breast cancer

Principal Investigator: Dr. Annarita Fanizzi - IRCCS Istituto Tumori "Giovanni Paolo II-Bari);
Collaboration Unit:
Breast-oriented radiodiagnostics, Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari;
Director of Oncology Molecular Biology Unit, Azienda Ospedaliero Universitaria - Ospedali Riuniti, Foggia - Collaborating Unit Referent;
Medical Director U.O. Level of Oncology, San Paolo Hospital (Asl), Bari - Collaborating Operational Unit Referent.

Background

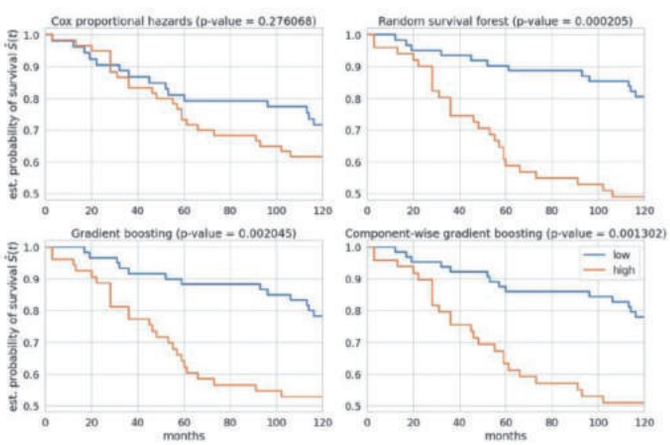
The decree of the Ministry of Health of May 2021 establishes the breast cancer patients susceptible to perform genomic tests for whom the benefit of adding chemotherapy to adjuvant endocrine therapy is controversial. Several genomic tests are available on the market. The EndoPredict (EP) is a molecular prognosis classifier based on the evaluation of 12 genes in BC cells. The reimbursement of these tests has been approved only in some Italian regions. Therefore, there is the urgent need to explore novel reliable and less expensive prognostic tools in this setting.

Aims

The objectives set for this project are: design and definition of a CDM for the systematic collection of data relating to the population under study; develop and validation of an automated system for predicting the Recurrence Score Risk generated by the EP genomic test; validation study of the result of the EP genomic test evaluated on retrospective data (patients with more than 10 years of follow-up for whom it was not possible to carry out the genomic test at the time of the first breast cancer); evaluation of the clinical and economic impact of the use of the PEERAD model on the clinical governance and quality of life (QoL) of patients.

Results

Retrospective clinical data were collected referring to a set of approximately 145 patients eligible for the Endopredict genomic test and for whom therapeutic follow-up was known at least 5 years after the end of hormonal therapy. Data from this set of patients was analyzed using machine learning techniques to predict disease-free survival 5 and 10 years after the end of treatment. machine learning survival models have accurately discriminated low- and high-risk patients, and so a large group which can be spared additional chemotherapy to hormone therapy. Machine learning survival models trained on clinical data have accurately discriminated low- and high-risk patients.



Publications

Fanizzi, Annarita, et al. "Machine learning survival models trained on clinical data to identify high risk patients with hormone responsive HER2 negative breast cancer." Scientific Reports 13.1 (2023): 8575.

Development of an immunosenescence-based risk predictor for elderly patients with Diffuse Large B-Cell Lymphoma

FOUNDING: FIL CLUB (Euro 341.000)
P.I. Sabino Ciavarella
Start date: 2023
End date: 2026

Background

The "Elderly Project", a prospective study by the Fondazione Italiana Linfomi (FIL), recently developed the Elderly Prognostic Index (EPI), a clinical prognosticator for older DLBCL pts. However, there is still an unmet need for older pts (especially the frail ones), who may benefit of new therapies, such as bispecific antibodies, immunomodulators and cell-therapies, whose efficacy may be affected by immunosenescence. This project represents a unique opportunity to investigate a huge subset of elderly pts enrolled in the "Elderly Project", using global and in situ transcriptomics to capture data from the entire tumor ecosystem (centralized biopsy tissue) in keeping with standardized clinical information. Such approach could unprecedently dissect TME in frail and non-frail settings, identifying frailty-related biomarkers/cell-types predictive of survival and/or toxicity.

Aims

1. To discover frailty-related biomarkers/cell types predictive of survival and/or toxicity easily and routinely detectable on FFPE tissues in the clinical practice.
2. To identify distinct immune cell populations within the TME using a transcriptomic-based approach to investigating their phenotype, functional state, spatial relationships and interactions among different age and fitness subgroups.
3. To investigate whether aging and fitness (sCGA) at the systemic level correlates with cellular aging in the TME.

Results

The entire study workflow will be carried out on 200 DLBCL samples (encompassing both EBV+ vs EBV- cases) with FFPE tissue suitable for RNA sequencing and single-cell in situ spatial transcriptomics using the CosMx™ SMI (150 samples from the Elderly Project, 150 samples from an additional cohort of real-life DLBCL patients < 65 years of age) and IHC/IF validation (50 samples from the Elderly Project). Transcriptomic data will be matched to the sGCA (fit, unfit and frail) and EPI (low, intermediate and high risk) categories of the corresponding patients.
- Starting task on RNA extraction from FFPE biopsy tissues and quality check before RNAseq profiling.

REALIZATION OF A REGIONAL INTEREST LABORATORY FOR THE PRODUCTION OF "ATPM" (Advanced Therapeutic Medicinal Products) in the context of the "Life Science Hub".

Founding: Piano operativo salute (FSC 2014-2020) - traiettoria 4 - codice locale progetto T4-AN-01
Principal Investigator: PI, Attilio Guarini IRCCS (Cancer Institute "Giovanni Paolo II");
Other centers involved:
REGIONE PUGLIA - Special Structure of "Health Marketplace Coordination";
IRCCS Children's Hospital Bambino Gesù;
University of Salento;
University of Bari Aldo Moro;
IRCCS "Casa Sollievo della Sofferenza" - Opera di San Pio da Pietralcina;
IRCCS "Saverio De Bellis";
IRCCS "Agostino Gemelli" University Polyclinic Foundation;
Italian Institute of Technology Foundation;

Background

Optimization of prospects for the implementation of CAR T production units at the Tumor Institute of Bari, related to the establishment of a CAR T Production Unit for the manufacture of academic products and the appropriate training of laboratory personnel. In this regard, procedures are underway to activate a Phase 1 Clinical Trial Unit and start experimental activities at the Laboratory of Cellular Therapies of the UOC of Hematology and Cell Therapy (Director: Attilio Guarini) of IRCCS "Giovanni Paolo II." This laboratory, equipped with 4 negative-pressure chambers for GMP production of immunocompetents and 1 "CliniMACS Prodigy", has been equipped with the necessary supply of medical gases (CO2) for the development of primary cell culture and expansion processes as a prerequisite for decentralized production of commercial products. The adaptation of the Laboratory to regulatory standards went hand in hand with the implementation of the capacity for biobanking and utilization of biological material with special reference to hematologic malignancies (diffuse large B-cell lymphomas and acute myeloid leukemias).

Aims

- Continuing specialty training activities through agreements with highly specialized national centers in the field of cell therapies;
- Handling of lymphocyte cells derived from peripheral and/or bone marrow blood (obtained according to normal clinical practice procedures and not requiring additional ad hoc collection) from subjects with diffuse large B-cell lymphoma, acute lymphoblastic and myeloid leukemia.

Results

Adaptation of the Laboratory to regulatory standards went hand in hand with the implementation of biobanking capacity and utilization of biological material with special reference to hematologic malignancies (diffuse large B-cell lymphomas and acute myeloid leukemias). Several tumor cell culture models were generated in two- and three-dimensional systems subjected to immunophenotypic characterization, cytotoxicity testing, characterization of sterility and stability of expansion and time maintenance.

Development of a platform for clinical implementation of precision oncology in south-central regions of Italy - COESIT

Founding: Piano operativo salute (FSC 2014-2020) - codice locale progetto T3-AN-06
Principal Investigator: PI, Stefania Tommasi IRCCS (Cancer Institute "Giovanni Paolo II");
Other centers involved:
REGIONE PUGLIA - Special Structure of "Health Marketplace Coordination";
IRCCS Children's Hospital Bambino Gesù;
University of Salento;
University of Bari Aldo Moro;
IRCCS "Casa Sollievo della Sofferenza" - Opera di San Pio da Pietralcina;
IRCCS "Saverio De Bellis";
IRCCS "Agostino Gemelli" University Polyclinic Foundation;
Italian Institute of Technology Foundation;

Background

Institutions participating in COESIT have the technical expertise to ensure implementation. All participating centers have genomics laboratories involved in oncology research projects, and more generally have documented experience in conducting research programs. Finally, the institutions participating in COESIT also have specific expertise in different areas of oncology research, such as the study of hereditary cancer syndromes, identification of prognostic and predictive biomarkers, conduct of phase I clinical trials, bioinformatics pipeline development, and artificial intelligence, which complement each other in the context of the cluster. The establishment of a laboratory network with standardized procedures and the availability of large collections of biological specimens and clinical-pathological data will facilitate the possibility of successful participation in other nationally and internationally competitive research calls. Most importantly, the research infrastructure created by this project application will be able to offer itself as a preferred partner of private companies operating in the pharmaceutical and biotechnology sectors. In particular, the availability of a mass of "real world" data on frequency and prognostic and predictive value of genomic alterations, with a focus on southern regions, will provide an important competitive advantage to the grouping of institutions participating in COESIT in establishing agreements with pharmaceutical and biotech companies. Finally, the discovery of prognostic or predictive biomarkers will open up the possibility of patenting new diagnostic modalities, possibly to be developed in collaboration with private partners as well.

Aims

The project aims to establish a network of reference laboratories in the regions of central and southern Italy for the genomic characterization of malignancies, aimed at the implementation of precision and personalized oncology in clinical practice. It involves strengthening the genomics laboratories of the participating institutions, sharing analytical and bioinformatics procedures, and creating a common database of genomic and clinical-pathological data on which studies aimed at: (i) assess the impact of tumor heterogeneity on the efficacy of molecular-targeted therapies and immunotherapy; (ii) define the frequency of pathogenic germline mutations in cancer patients in the regions of central and southern Italy and search for new cancer predisposition genes; and (iii) study the correlation between genetic profile, presence of specific mutational signatures and exposure to carcinogens linked to environmental factors and/or lifestyle.

Taken together, these studies will increase the specific knowledge about the genomic characteristics of neoplasms of patients in central and southern Italy and foster the clinical implementation of precision and personalized medicine based on genomic analysis.

Results

The first project phase involved the sharing and standardization of sequencing procedures by ensuring that the results of sequencing performed in different centers can be pooled in a single database. The referral role for the diagnosis and treatment of malignancies of the participating institutions in their respective regional areas, the high volumes of care, and the presence of organized institutional biobanks will also ensure the availability of an adequate number of cases and biological material for the implementation of the project.

Progetto Tecnopolo per la Medicina di Precisione-CUP B84I 18000540002
D2.2 Development of new hydrogels and microfluidic system for the generation of patient's derived 3D models from tumor tissues (T2.2.2. Optimization of the establishment of hematological cancer PDOs and drug screening).
D4.1 Production of clinical-grade CAR T cells exploiting nonviral approaches for T cell transduction

Principal Investigator: Dr. Attilio Guarini, Dr. Sabino Ciavarella
Start date: 2022

Background

D2.2 - Precision medicine in oncohematology has increasing needs for preclinical models to study the biology of disease development and treatment resistance. Emerging findings suggest the importance of implementing three-dimensional "patient-derived" cell culture systems for the development of high-performance personalized medicine processes for prognostic prediction and "drug repurposing."
D4.1 - Numerous studies are currently underway to refine techniques for cell engineering of immune effector cells for therapeutic purposes. Among them, the use of nanoparticles (NPs) to transduce PBMCs (Peripheral blood mononuclear cells) and CD8+ T lymphocytes, as well as CAR, represent the study rationale of this project task. Thus, all lymphocytes and PBMCs transduced with NPs are, at the same time, easily visible by GFP through cytofluorimetry and fluorescence microscopy.

Aims

D2.2 - Optimization of a spheroid formation protocol derived from diffuse large cell lymphoma cell lines (DLBCLs) purchased in past years directly from the American Type Culture Collection (ATCC). Approximately ten DLBCL lines will be used for co-culture studies with microenvironment components such as stromal cyto-types and macrophages (cell lines), in 3D structures using different animal free polymer compositions (such as chitosan and gelatin).
D4.1 - Optimization of TCD4 lymphocyte transduction by nanoparticles.

Results

D2.2 - To reduce the time for spheroid formation for potential use with primary lines, another combination of hydrogels (chitosan/gelatin 1:1) was developed to optimize the protocol by reducing the time for spheroid formation to four days. Flow cytofluorimetry and immunohistochemistry techniques were used to assess viability and morphology. Despite the achievement of preliminary results, it was not possible to schedule more experiments preparatory to the writing of the manuscript due to a significant slowdown in the procurement of reagents useful for carrying out laboratory activities;
D4.1 - PBMCs were isolated by centrifugation on Ficoll-Histopaque density gradient from buffy coat, and then CD8+ T lymphocytes were isolated using a magnetic bead system. After isolating the PBMCs and extracting CD8+ T lymphocytes, the two cell lines were transduced with the NPs and then the transduction efficiency was evaluated by fluorescence microscopy and cytofluorimetry.
At this first stage of analysis, no GFP-positive cells were observed, and therefore transduced, with the NPs at any of the time points analyzed and at any of the different concentrations of NPs tested. However, by cytofluorimetry assays it was observed that a high concentration of NPs causes high cell death especially at the later time points (day 10 and 14), accentuated more in CD8+ T lymphocytes than in PBMCs.

Progetto Tecnopolo per la Medicina di Precisione-CUP B84I 18000540002

Principal Investigator: Dr. Amalia Azzariti
Start date: 2022

Background

The activities of the Laboratory of Experimental Pharmacology under the Technopole for Precision Medicine project will focus on:

- On the development of three-dimensional organotypic cultures generated from ex-vivo tumor material, such as patient-derived organoids (PDOs), and stable cultures from hiPS cells, in order to create collections of three-dimensional organotypic cultures that will be stored at the Institute's Institutional Biobank. These three-dimensional organotypic cultures will be collected and stored so that they can be expanded and reused later, enabling screening for new therapeutic opportunities in Personalized Donor Patient Medicine or research studies, after approvals from the relevant Scientific Technical Committee. Complex cell culture systems, based on the use of biocompatible 3-D matrices (hydrogels) and organ-on-chip microfluidic devices, are an innovative investigative tool for studying healthy and diseased patient tissues for the purpose of developing innovative and personalized treatments. These mimic in vitro the three-dimensional structure of human organs and tissues and have replaced in drug screening 2D cell cultures that did not allow replicating patient-like experimental conditions due to the absence of native microenvironment consisting of other cell populations (immune, collagen, fibroblasts, etc.). These complex cell culture systems, characterized by the maintenance of the cross-talk that is established between the pathological cells and their surrounding microenvironment, allow the identification of biomarkers of disease progression and drug response/resistance and of novel therapeutic targets for target-oriented therapies by detailed molecular and phenotypic characterization (e.g., mutational, transcriptomic and proteomic profiling, cytokine secretion, clonal heterogeneity, etc.), as well as being a valuable tool for preclinical validation of the efficacy of new drugs or specific therapeutic combinations.However, even the best 3D culture models fail to mimic the cellular properties of an organ in many respects, including tissue-tissue interfaces (e.g., epithelium and vascular endothelium) of fundamental importance in the study of therapies such as immunotherapy, which has as its main players the cells of immunity that are transported by the bloodstream. The application of microfluidics in organ-on-chips enables efficient transport and delivery of solutes and cells of immunity to three-dimensional organotypic cultures.
- A growing interest in liquid biopsy, i.e., analysis of biological fluids by noninvasive methods, concerns the study and analysis of ncRNA a Extracellular Vesicles (EVs) as novel biomarkers of diagnosis, prognosis, or prediction of response to therapies. EVs, physiologically released and internalized by all cell types, are responsible not only for cell-to-cell communication but are also considered crucial in the regulation of metastatic and drug resistance processes in oncology, in the progression of neurodegenerative diseases, and as therapeutic targets or potential drug and/or gene therapy delivery systems. Standard techniques greatly limit the investigation of these biomarkers and intercepting the vesicles carrying the "pathological" information among all those released physiologically in the circulatory stream is one of the most difficult challenges for analysis in the clinical field. This activity aims to use a microfluidic device in combination with optical methods (fluorescence microscopy analysis) coupled with molecular characterization, using membrane markers of EVs, identified on device sequentially.

The aim is to obtain evidence of the simultaneous presence of more than one marker (subsequently aiming at their quantification). Methods of either reversible trapping (using TiO2 particles, modulating the pH of the solution) or irreversible trapping using plastic microfluidic channel functionalization chemistry will be evaluated. Next, interaction with labeled antibodies by fluorescence microscopy will be evaluated. This device is intended to represent a cross-cutting technology with respect to different applications in both oncology and neurology. The information arising from the characterization of the composition, in terms of biomarkers, of the membrane of EVs is considered very important for understanding ongoing pathological processes involving the cells from which the EVs originated.

- Nanotechnological approaches in delivery systems can improve the delivery of specific therapeutic agents, such as growth factors, proteins, peptides, DNA, RNAi, and drugs that are vital for various applications ranging from cancer therapy to gene therapy. In general, controlled-release systems are able to deliver biologically active molecules in the optimal dosage over long periods, thereby increasing their therapeutic efficacy while maximizing patient compliance. Using nanoparticles will improve the ability to use toxic, poorly soluble, or relatively unstable drugs

Aims

- lncRNA from prostate cancer tissues: A) RNA extraction from prostate cancer tissues and lncRNA analysis by RT-PCR or Digital PCR in order to set up the best protocol for lncRNA analysis. B) Isolation of EV from urine of prostate cancer patients, extraction of RNA from EV and analysis of lncRNAs by RT-PCR or Digital PCR in order to set up the best protocol for lncRNA analysis. C) Correlation studies with clinical parameters of prostate cancer patients. D) Development of high electron mobility transistors (HEMTs) based on gallium nitride (GaN) and aluminum gallium nitride (AlGaN) substrates. A single sensor will be validated for the lncRNA assay. Depending on the selected analyte to be detected, the performance of the sensor will be compared with that of the chiral sensors and validated.
- Characterization of miRNAs in CSCC patient plasma samples: A) miRNAs and lncRNAs identified in CSCC patient plasma samples as predictors of Cemiplimab will be evaluated in PBMCs as modulators of PD1/PD-L1 expression. B) miRNA and lncRNA identified in plasma samples from patients with CSCC as predictors of Cemiplimab will be evaluated in EVs isolated from plasma as modulators of PD1/PD-L1 expression. C) Development of high electron mobility transistors (HEMTs) based on gallium nitride (GaN) and aluminum gallium nitride (AlGaN) substrates. A single sensor will be validated for miRNA and lncRNA assay. Depending on the selected analyte to be detected, the performance of the sensor will be compared with that of chiral sensors and validated.
- New hydrogel for the generation of anti-cancer PDOs A) In solid tumors such as melanoma, colorectal cancer, gynecological cancers, and head-neck cancers, PDOs will be generated from tissues of cancer patients under standard conditions and in alginate matrix. PDOs will be evaluated for their growth rate and morphological and functional characteristics. Hydrogel plus sensors for pH, O2 and lactate biosensing and drug screening in microfluidic devices. Tuning of alginate matrix in the presence and absence of sensors for pH, O2 and lactate biosensing, physicochemical characterization and drug screening. B) Pharmacological screening of PDOs from cancer patients using the microfluidic system in order to evaluate the efficacy of immunotherapy in the presence of PBMCs or the release of cytokines and soluble factors after the addition of target therapy. C) Correlation studies between drug screening in PDOs and clinical parameters of patients.
- Biomimetic drug delivery system: A) Isolation of membranes from cells and construction of hybrid nanocarriers

obtained by fusing liposomes with cancer cell membranes (to optimize drug delivery directly to cancer cells). Physicochemical characterization of biomimetic drug delivery systems by AFM, TEM, NTA, etc. and loading of selected drug(s). B) Characterization of antitumor activity of biomimetic drug delivery systems in 2D and 3D tumor models.

Results

- Analysis of previous data showed that in our case series consisting of prostate cancer tissues, 3 of the 7 selected lncRNAs were found to be expressed at a higher level than those of prostatic hyperplasia. In order to consider these lncRNAs as biomarkers of early diagnosis, it was decided to start with the determination of their concentration in urine and then, if necessary, in EVs. The determinations will be carried out by extraction of ncRNAs from urine, amplification of them and analysis in RT-PCR or Digital-PCR. For the lncRNAs that show the most promise, sensor development for their detection will be carried out in collaboration with Nanotec.
- The expression study of miRNAs and lncRNAs in the plasma of patients with CSCC has been completed, and statistical analysis of correlation with clinical data to determine their predictivity of response to Cemiplimab is underway. The next step will be to identify among the 8 biomarkers under analysis the most promising ones as predictors of response to anti-PD1 and to develop with colleagues at Nanotec the innovative system for their detection. Identification of patients with CSCC whose PBMCs are available for correlation studies between selected populations of these and response to Cemiplimab is also being carried out
- Cytofluorimetry analyses of extracellular vesicles isolated from the postoperative lavage fluid of 35 patients with colon cancer have been completed, and statistical analyses of the acquired cytofluorimetric data are underway.
- After appropriate modifications in the protocol standardized by Nanotec colleagues for the growth of spheroids in alginate, the validity of using this matrix for the growth of oncology patient organoids (PDOs) has been confirmed through exchange of researchers between the two partners involved. Currently, the protocol for growth of PDOs in the presence of pH and O2 sensors is being developed. This type of experiments will allow the analysis of these parameters during drug screening. The chosen study model is colon cancer.
- Physical-chemical characterization of NPs was completed using methodologies such as dynamic light scattering (DLS), nanoparticle tracking analysis (NTA) and resonance energy transfer (FRET). These analyses confirmed the hybrid nature of these novel nanosystems for drug delivery. Their ability to be incorporated into cancer cells was evaluated by selecting a panel of cells from different oncological diseases. These experiments will allow evaluation of selectivity toward melanoma cells. Drug screening is underway to evaluate the increased activity of certain drugs when encapsulated in these newly synthesized hybrid systems.

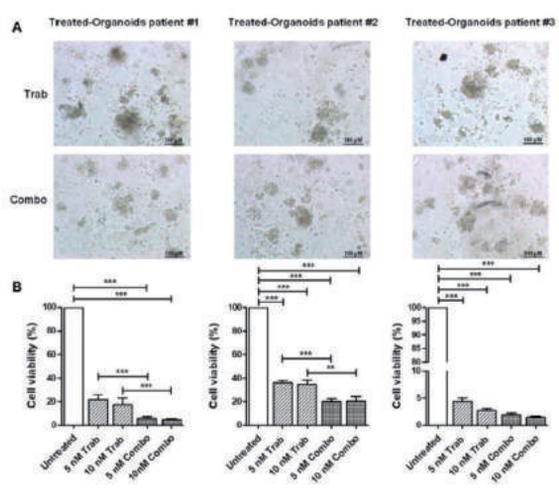


FIGURE 4
Viability assay in CC.ex vivo model corroborates the efficacy of combination treatment. (A) Representative images of pz-1-, pz-2-, and pz-3-PDOs treated with 10 nM of trabectedin alone or combined with propranolol for 48 h; scale bar 100 µm. (B) Histogram plots of cell viability (%) reported as the mean ± SD of three independent experiments; $^{**}p < 0.01$; $^{***}p < 0.001$.

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Progetto Tecnopolo per la Medicina di Precisione - Biomarkers predictive of response to immune checkpoint inhibitors

Principal Investigator: Dr. Stefania Tommasi
Start date: 2019

Background

Colon cancer is one of the diseases that has the highest incidence and mortality rate within oncological diseases. Thanks to the advent of high-throughput sequencing technologies, it has been possible to classify tumors not only according to oncological but also molecular characteristics. Colon cancer has also been molecularly classified into four so-called Consensus Molecular Subtypes (CMSs). However, as with many other diseases, molecular classification has not entered clinical practice because it is a classification that requires analysis of the entire transcriptome. Therefore, we aim to identify a methodology applicable in clinical practice. In addition, the integration of histological features by digital pathology, could make the tool to be built even more powerful.

Aims

1. Identification of a panel applicable in clinical practice for molecular subtyping of colon cancer
2. Construction of a local multi-omics dataset including DNA alteration, microsatellite status, transcriptomics and whole slide images (WSIs) in hematoxylin-eosin.

Results

In silico study for panel identification and its construction. Selection of the local cohort, which includes 100 patients, and sample collection, scanning of slides in hematoxylin-eosin. Completion of RNA-Seq sequencing and validation analysis.

Publications

- Altini N, Marvulli TM, Zito FA, Caputo M, Tommasi S, Azzariti A, Brunetti A, Prencipe B, Mattioli E, De Summa S, Bevilacqua V. The role of unpaired image to image translation for stain color normalization in colorectal cancer histology classification. Comput Methods Programs Biomed. 2023 Jun; 234:107511. doi: 10.1016/j.cmpb.2023.107511. Epub 2023 Mar 26. PMID: 37011426.
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Progetto Tecnopolo per la Medicina di Precisione - 3D in vitro models

Principal Investigator: Dr. Michele Guida
Start date: 2022

Background

The work of this project is based on the development of 3D organotypic cultures of tissues directly isolated from patients. The mechanisms of tumor progression and response/resistance to currently available therapies arise not only from alterations in tumor cells, but also from the bidirectional interactions that the tumor establishes with the surrounding microenvironment and distant organs normally the site of metastasis. Currently available cell culture platforms are very varied and are based on both monoculture and co-culture models, both 2D and 3D. However, such models are reductive as they are based on altered cell composition (decided by the investigator), loss of spatial relationships between different cell types present in vivo, and different concentration/composition of extracellular matrix. For this reason, the use of more complex organotypic cultures based on the use of tissue directly isolated from the patient can help in the study of tumor-specific perturbations that occur in vivo in a more physiological and patient-specific manner. This approach makes it possible to reproduce in vitro the three-dimensional structure of human organs and tissues and to reproduce experimental conditions similar to the patient due to the presence of a native microenvironment consisting of immune cells, fibroblasts, tumor subpopulations, and extracellular matrix. In this way, it is possible to preserve the cross-talk that is established between pathological cells and their surrounding microenvironment, allow the identification of biomarkers of disease progression and drug response/resistance and new therapeutic targets for target-oriented therapies by detailed molecular and phenotypic characterization (e.g., mutational, transcriptomic and proteomic profiling, cytokine secretion, clonal heterogeneity, etc.). Such platforms also provide a tool for preclinical validation of the efficacy of new drugs or specific therapeutic combinations. Tumors produce alterations not only locally, but also systemically, such as with other organs that are often sites of metastasis. For this reason, it is important to understand the complex system of interactions that the tumor establishes with other tissues. The creation of a multi-organ-on-chip platform, in which two or more tissues are linked together through a microfluidics system, will allow us to recapitulate the alterations induced by the primary tumor at the tissue-specific level. In particular, we will focus on the crosstalk between tumor and lymph node. Indeed, lymph nodes represent one of the earliest sites of metastasis and are critical both for the establishment of anti-tumor immunity and for the response to currently available immunotherapies.

Aims

The main objective of this Project is to build single and multi organ-on-chip (tumor and lymph node) platforms for melanoma and lung cancer in order to model and study tumor evolution and monitor therapeutic responses. The project is divided into two Aims:

- Development of static single-organ-on-chip systems. Identification of 3D matrices that mimic organ-specific physical properties for long-term cultures of tumor and lymph node tissues from melanoma and lung cancer patients In detail, tissues derived from patients undergoing surgery will be processed in order to obtain core biopsies of 2mm diameter that will be included in different 3D matrices and cultured. At different time points,

the composition, spatial organization and cell viability of the different organotypic cultures will be evaluated to identify which of the matrices used allows their organ-specific physiological characteristics (tumor vs. lymph node) to remain intact.

- Development of dynamic multi-organ-on-chip systems. Using the platforms developed in the previous Aim (single organ-on-chip organotypic cultures) we will develop multi-organ-on-chip systems using tumor tissues (melanoma and lung cancer) and tumor-draining lymph nodes (TDLN). The individual tissues included in the respective 3D arrays will be linked together using a microfluidics-on-chip system that will help mimic the complex systemic interactions established between tumor and TDLN during cancer progression and drug treatment. The developed platforms will be validated through assays of viability, cell function, and spatial organization. Ultimately, the multi-organ-on-chip approach will allow the study of tumor-lymph node interactions in order to identify markers predictive of progression and/or response to currently available therapies, test novel drug combinations, and identify new therapeutic targets.

Results

An experimental protocol was drafted for submission to the ethics committee for the use of tumor and lymph node samples from melanoma patients. After approval by the ethics committee, sample collection was started. In 2023, 1 melanoma metastasis sample and 10 tumor-draining lymph nodes (positive and negative) were collected from 5 different patients. Peripheral blood samples were also stored from all patients. Two lymph node samples were used to test 3 different 3D matrices under static conditions: GelMa (gelatin-based), Chitosan, and Matrigel. The results showed GelMa is the 3D matrix that can preserve cell viability more after 3 and 5 days of culture (79% and 80% live cells, respectively) than Chitosan (3 days: 75%, 5 days: 25%) and Matrigel (3 days: 66%, 5 days: 44%).

Progetto Tecnopolo per la Medicina di Precisione - Implementation of a NanoMedicine Technology Platform

Principal Investigator: Dr. Alfredo Zito

Start date: 2019

Background

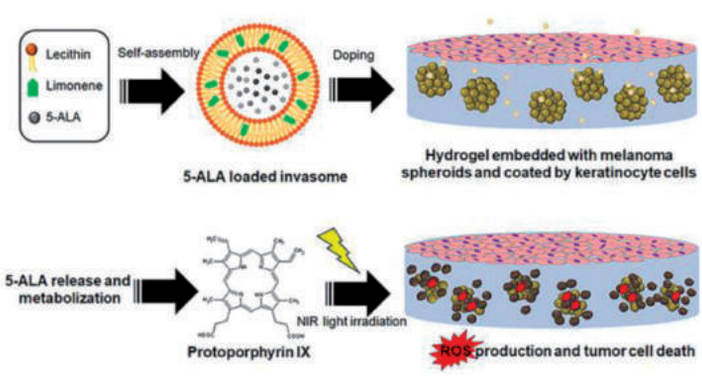
Photodynamic therapy represents a widely used therapeutic strategy that has demonstrated efficacy in the treatment of cutaneous precancerous lesions (actinic keratoses) and superficial basal cell carcinomas (nonmelanoma skin cancer). It consists of topical application at the skin neoplasm, of a photo-sensitizing substance and followed by skin irradiation with a lamp using a light source with a wavelength of 635 nm. The greater selectivity (selective localization at the level of the neoplastic tissue and photoactivation), makes PDT a more favorable treatment modality than chemotherapy and radiotherapy, which are burdened with greater systemic side effects. The limitation of the method is the poor penetration of the photo-sensitizer. For this reason, a collaboration is under way with researchers at CNR Nanotec in Lecce to develop lipid nanovectors for the purpose of enhancing the penetration of photosensitizing anticancer drugs at the skin level.

Aims

• To study the role of HPVs in the neoplastic progression of skin cancers, so the modality is based on searching for the presence of viral genome belonging to known and newly identified viruses in healthy tissues and in tissues taken from precancerous lesions (actinic keratoses) and malignant neoplasms of the skin, such as basal cell carcinoma and spinocellular carcinoma.
• Development of nanovectors for the purpose of enhancing the penetration of the photosensitizing drug (5 aminolevulinate) into the skin and reaching cancer cells.

Results

Samples of biological material belonging to the 16 patients included in group A were analyzed. For each of these 16 patients, determinations were made from 5 different sites (axilla, glabella, saliva, photo-exposed skin and non-photo-exposed skin). In the 16 patients examined, we found the presence of different subtypes of HPV at five anatomical sites. Analysis and evaluation the samples from 150 patients enrolled (divided between cases and controls) at the IARC Institute in Lyon. In vitro nanovector studies conducted at CNR-Nanotec in Lecce, Italy.



Publications

Enhanced Delivery of 5-Aminolevulinic Acid by Lecithin Invasomes in 3D Melanoma Cancer Model. Gaballo A, Ragusa A, Nobile C, Gallo N, Salvatore L, Piccirillo C, Nito A, Caputo A, Guida G, Zito A, Filotico R, Quarta A. Mol Pharm. 2023 Nov 6;20(11):5593-5606. doi: 10.1021/acs.molpharmaceut.3c00494.

Progetto Tecnopolo per la Medicina di Precisione - Implementation of Multimodal Imaging Platform Combined with Artificial Intelligence in Precision Medicine

Principal Investigator: Dr. Raffaella Massafra

Start date: 2022

Background

Tecnomed Puglia operates in the field of Precision Medicine through innovative approaches based on nanotechnology and translation of results in the prevention and treatment of cancer and neurodegenerative diseases. In this context, the research group in the specific research task will work on implementing artificial intelligence models based on biomedical image analysis for three particular settings of oncology patients, such as patients with advanced melanoma, patients with lung cancer diseases undergoing radiotherapy, and patients with colon cancer. The radiomic-based models to be developed in collaboration with research centers participating in the TecnoMed program aim to provide a decision-support tool in the management of the oncology patient.

Aims

The project is developed along two main lines of research. The first involves the development of new analysis methods to be applied to digital pathology images. In particular, the different imaging data will be used for the development of deep learning and artificial intelligence models that will allow in the oncology field to predict molecular subtypes and actionable changes in colon carcinoma and response to therapy in patients with stage IV melanoma. The second line of research targets the analysis and modeling of radio-induced toxicity in cancer patients treated with radiation therapy (RT). Specifically, by exploiting voxel-based analysis techniques of 3D RT dose distributions and radiomics on treatment planning CT scans, predictive factors of toxicity to healthy tissues will be sought. These will be exploited to train an integrated toxicity model that, using recently developed Machine Learning techniques (PACE model), incorporates clinical, dosimetric, and structural risk factors in the evaluation of radiotherapy outcome. Analyses will be conducted retrospectively on cohorts of patients extracted from public databases and validated on a set of patients referred to the 'Giovanni Paolo II' Cancer Institute in Bari.

Results

With reference to the first research task, the multimodal colon cancer dataset has been completed regarding transcriptomics and pathological imaging data. Collection of radiological images and completion of the database with clinical information, including follow-up data, is in progress. Collaborations have been initiated with CNR references aimed at developing a modality for the prediction of radio-induced toxicity in lung cancer patients using voxel-based analysis techniques of 3D radiotherapy dose distributions integrated with radiomic analysis of pretreatment CTs.

ACC - The ACC preclinical research platform for precision oncology

Principal Investigator IRCCS Cancer Institute 'Giovanni Paolo II': Dr. Amalia Azzariti

Background

The program from which the current proposal stems has focused in recent years on a global activity that the ACC has funded with the goal of creating networking activities among various participants within specific cancer types, or cross-cutting activities (genomics, pathology, immunotherapy, radiomics). Several IRCCSs have developed patient-derived preclinical cancer models under the program, including patient-derived xenografts (PDX), organoids (PDO), and cell lines (PDCL). Notably, specific WPs from previous ACC projects (e.g., WP4, WP8, and WP13 of the 2021 project) involved the derivation, molecular profiling, and drug testing of PDCMs from different tumor types, such as melanoma and a wide range of sarcomas and soft tissue tumors. In addition, many ACC Partner Institutes have been deeply involved in European or national projects in the field of preclinical PDCM. Overall, ACC has generated molecular profiles for hundreds of patients and thousands are expected soon, resulting in the generation of therapeutic hypotheses based on precision oncology. It is therefore now mandatory for the ACC to further strengthen the network's capacity for generation, molecular characterization, drug testing, and sharing of PDCMs. This will enable preclinical validation of therapeutic hypotheses emerging from the molecular profiles of cancer patients managed by ACC partners.

Aims

It is expected that this project will greatly increase ACC network research capacity on patient-derived cancer models (PDCMs) by providing:

1. Improved generation and sharing of PDCMs, particularly advanced ex vivo models that summarize the complexity of the neoplastic microenvironment.
2. Generation of an online "ACC PDCM catalog" by posting the PDCM metadata in the public "PDCM-finder" repository (www.cancermodels.org).
3. Systematic DNA and RNA profiles of more than 200 established in vitro and in vivo PDCMs, corresponding to the tumors of patients profiled in the network.
4. Implementation of a "cBioPortal ACC PDCM" that includes DNA and RNA profiles generated in the project as well as pre-existing profiles.
5. Increase drug screening capacity and validation of proof of concept therapeutic hypotheses generated from cancer molecular profiling in the ACC network.
6. Leveraging antidrug testing in a pan-cancer context of many preclinical models.

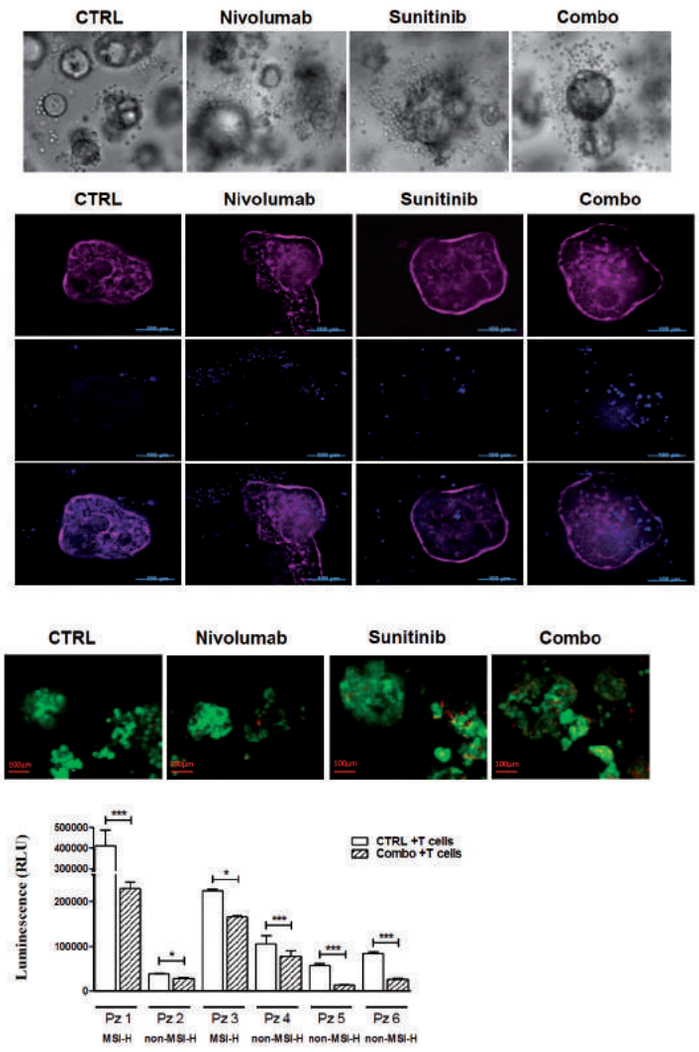
In the long term, these activities will bridge a long-standing gap in in-depth molecular characterization of high-risk malignancies coupled with standardized preclinical testing procedures in ex vivo models. The use of the models already generated, along with the development of more innovative ones, will be useful in expanding knowledge of tumor biology and drug sensitivity to identify precise and effective drugs in specific patient settings.

Results

A series of online meetings were organized and followed to define the procedures for annotating the data, appropriately anonymized, of the patients from whom The various tumor models (primary cell lines and organoids) were obtained and the characteristics of the models themselves. It should be noted that the tumor models were generated from tissues explanted from cancer patients recruited in previous studies that had been approved, for this activity, by the Institutional Ethics Committee. The compilation of the exel sheet that will be sent to the responsible Dr. G. Russo of the Fondazione Luigi Maria Monti IDI - IRCCS in Rome for evaluation and upload to the CancerModel.org portal has begun.

Under this WP2, 20 models (paraffin-embedded tissues, organoids and cell lines) were expanded to obtain sufficient material for DNA and RNA extraction that will later be sent to partners for sequencing. Subsequently, DNA and RNA were extracted and sent to the Negedia Company for sequencing.

The WP3 coordination decided, due to issues related to project timelines, to proceed with preliminary screening, with drug libraries, only of tumor models from the largest case series. Not being among the groups involved, the study of combining immunotherapy with anti-angiogenic drugs in colon Ca organoids is proceeding. The study of combination of immunotherapy with anti-angiogenic drugs in organoids of colon ca has been completed, and the manuscript is proceeding.



Publications

Serratì S, Di Fonte R, Porcelli L, De Summa S, De Risi I, Fucci L, Ruggieri E, Marvulli TM, Strippoli S, Fasano R, Rafaschieri T, Guida G, Guida M, Azzariti A. Circulating extracellular vesicles are monitoring biomarkers of anti-PD1 response and enhancer of tumor progression and immunosuppression in metastatic melanoma. J Exp Clin Cancer Res. 2023 Sep 28;42(1):251. doi: 10.1186/s13046-023-02808-9. PMID: 37759291

ACC - Feasibility study for the diagnosis joint genomic diagnosis of genetic risk and sensitivity to new drugs in breast, ovarian and colon malignancies - Gersom

Principal Investigator IRCCS Cancer Institute 'Giovanni Paolo II': Dr. Stefania Tommasi

Background

Our understanding of hereditary susceptibility to cancer has grown considerably over the past 30 years with the progressive identification of dozens of genes (established or putative) predisposing to cancer (Cancer Predisposing Genes; CPGs).

The identification of inherited (germline) mutations at CPGs in patients with cancer has made it possible to study their presence in their family members, and to plan diagnostic surveillance (e.g., diagnostic imaging in breast or colon cancer) or risk reduction (e.g., aspirin in colon cancer) plans in individuals with inherited CPGs mutations. There is considerable overlap between CPGs and mutated genes in cancers. In addition, a fraction of CPGs (like somatically mutated genes) is informative for prognosis and therapeutic stratification (actionable genes, those genes i.e., on which drugs can already be acted upon). With the recognition that the presence of mutations in CPGs in tumors has important implications with respect to tumor treatment, tumor prognosis, and treatment of non-tumor-associated complications (e.g., renal dysfunction in patients with mutations in certain CPGs), the need for new technologies for mutational testing is introduced (e.g., the strong need to reduce testing time and increase sample "throughput" in order to ensure a timely treatment plan for all patients). Performing mutational tests, including actionable genes and CPGs, will enable the simultaneous acquisition and at diagnosis of information relevant to both therapeutic stratification and genetic risk definition.

Aims

This Research Project has as its overall goal to study the feasibility of a joint diagnostic pathway, at the time of tumor diagnosis, for the identification of actionable genes in the tumor (for prognostic purposes and for defining response to therapy) and CPGs in the germline (for purposes of mapping genetic risk of cancer).

Results

About 80 patients have been enrolled in our institute, of whom 62 have been sequenced at the germinal and somatic levels at present. Most of the patients have ovarian carcinoma. To date, 2618 patients are included in eCRF of the whole project. Upon completion of all data entry, bioinformatics analysis will be conducted.

Circulating Tumour DNA - Centres of Excellence Study

Principal Investigator: EMQN
Principal Investigator IRCCS Cancer Institute 'Giovanni Paolo II': Dr. Stefania Tommasi
Participating centers:
Institut Gustave Roussy, Francia
Hospital Universitario Puerta del hierro, Spagna

Background

In Italy, prostate cancer is currently the most frequent malignancy among men and accounts for more than 20% of all cancers diagnosed at age 50 years and older. The mechanism of repair by homologous recombination (HRR) plays a significant role in maintaining genomic stability and the process of repairing damaged DNA. These genes play a key role in supporting DNA replication and maintaining telomere structure. Gene defect mutations in the HRR system-particularly the BRCA 1 and 2 genes-increase the risk of incidence of several cancer types, including prostate cancer. Globally, about 12 percent of patients with metastatic prostate cancer carry germline mutations in at least one of 16 genes involved in DNA repair (ATM, BRCA1, BRCA2, CHECK2, PALB2, RAD51D, RAD51C, ATR, NBN, PMNS2, GEN1, MSH2, MSH6, MRE11A, BRIP1, FAM175A). The most frequently mutated gene in the prostate with mutation percentage greater than 13% (germline) is BRCA2. However, somatic alterations in this disease are more frequent than germline alterations. It is often not possible to detect somatic mutations on tissue because of problems issues related to pre-analytic of samples and sampling site (often these are bone biopsies). For this reason, plasma seems the most suitable matrix for the evaluation of genetic alterations in metastatic castration-resistant patients. Most of these mutations affect the BRCA2 and ATM genes. Overall, about 13% of castration-resistant metastatic prostate cancers (mCRPCs) have a germline or somatic mutation affecting the BRCA 1/2 genes. Prostate neoplasms in individuals carrying mutations at the BRCA1 and 2 genes develop earlier and tend to have more aggressive behavior that is a cause of reduced life expectancy. The study of BRCA1 and BRCA2 in plasma, where ctDNA is very often fragmented highlights technical problems that are being attempted to be overcome by the use of very sensitive methods and accurate protocols.

Aims

The objective of this study is to test the possibility of detecting mutations in the BRCA1 and BRCA2 genes at the plasma level with the different methodological approaches in use in the four laboratories participating in the study.

Results

Recruitment of cases (no. 16) is finished. All cases were sequenced with the new custom panel under validation.

Publications

BRCA1/2 ctDNA detected by an AmpliSeq™ custom panel in metastatic Castration Resistant Prostate Cancer (mCRPC) patients. Coppola C A, Pilato B, Matera G, Lacalamita R, Lasorella A, De Summa S, Traversa D, Di Lorenzo V, Caniglia A, Colonna F, Tommasi S. Abs in ESHG meeting 2024

Screening In Lung Cancer (Stp) : A Parallel Pathway Between Clinical Prevention And Support For Tobacco Cessation

P.I. IRCCS Istituto Tumori Giovanni Paolo II Domenico Galetta
Funding Source Funds from the Ministry of Health for the 5 x 1000, year 2020

Background

According to OMS, tobacco smoking is the most important cause of preventable death. The substances carcinogens contained in smoking are responsible for 90 percent of lung cancers and the majority of cancers of the oral cavity, larynx and bladder. However, there is a lack of adequate Anti-smoking and there are still many smokers in Italy who do not stop smoking and do not have adequate screening. Our Institute, in addition to activating the Anti-Smoking Center (DDG 520/18), has been identified as the only Pugliese center for the national program for cancer screening lung (RISP).

Aims

Promote early detection of lung cancer for those most at risk, such as heavy smokers or former heavy smokers, through screening and psychological support; - Define individual risk profile, based on the set of epidemiological, radiomic data obtained using low-dose radiation CT scans; - Promote tobacco cessation through psycho-motivational and pharmacological support pathways.

Results

In 2022, 117 users made eligible were involved; of these, 97 had CT of the chest at low doses (LDCT, Low Dose Computed Tomography). All smokers were offered the pathway at the smoke-free center; of these 21 participated in the anti-smoking center to quit smoking and 13 completed the pathway by ceasing addiction. In 2023, n.982 users made eligible were involved; of these, n.653 underwent CT of the chest at low dose computed tomography (LDCT). In addition, n. performed, as planned by the program, n. 41 follow-up CT scans after 12 months and n. 7 CT scans anticipated. All smokers were offered the pathway at the smoke-free center, of which these 77 attended the smoke-free center to quit smoking and 33 have completed the pathway by ceasing addiction.

Publications

- Cani M., Mercadante E., Cardellicchio S., Zuccatosta L., Pattacini P., Milanese G., Bafunno D., DeFilippis A., Del Giudice T., Trussardo S., Riglietta M., Franzese N.,Aloè T., Caffo O., Camerano F.,Cammarota A., DiPieri M., Papale M. Primary prevention strategies within the Italian Lung Cancer Screening Program (RISP): a first update. Tumori Journal 2023, Vol. 109(2S) p.64 (Accepted as POSTER at AIOM 2023).
- Ferrari G., Cani M., Garbo E., Passiglia F., Capelletto E., Bertaglia V., Bironzo P., Tinivella M., Pasqualini G., Mogavero A., Gasparro M., Bernardi G., Mangiapane F., Butticè S., Baldan S., Biffi D., Bafunno D., D'Alonzo G., Barbieri V., Novello S. Diet and lifestyle habits among participants to the lung cancer Italian screening program. Tumori Journal 2023, Vol. 109(2S) p.70 (Accepted as POSTER at AIOM 2023).
- Catino A., Catino A., Zamparella M., Buono C., Ambron A., Zinfollino M., Manzari S., Bafunno D., Calabrese N., Lamorgese V., Galetta D. Electronic cigarettes (E-cyg) and Heat not burn (HnB) products: the need of a correct information from General Practitioners (GP) Tumori Journal 2023, Vol. 109(2S) p.264 (Accepted as POSTER at AIOM 2023).

Detection of known and newly identification in healthy tissues and malignant solid neoplasms by developing laboratory methods and protocols

P.I. IRCCS Istituto Tumori Giovanni Paolo II Alfredo Zito
Funding Source Funds from the Ministry of Health for the 5x1000, year 2017

Background

The family Papillomaviridae includes a heterogeneous group of papillomaviruses (PVs) with circular bicatenary DNA (dsDNA) genome of about 6-8 Kb. Currently, more than 300 PV types have been fully, characterized, including more than 200 HPVs that are classified into five genera: alpha, beta, gamma, mu and nu. The beta and gamma HPV types were initially isolated on healthy skin so much so that they are referred to as cutaneous HPVs. However, many studies have shown that these viruses can also be present in oral and nasal mucosal epithelia, eyebrow hair, and male and female external genital epithelia. Although more than 200 HPV types have been isolated so far, some species include a very small number of HPV types.

Aims

- Identify new human viruses or viruses already known but at sites or in neoplasms where they had not been isolated so far.
- Provide information on the prevalence of specific genotypes of HPV, HPyV, HHV, and Adenovirus in normal and transformed epithelia present at different anatomical sites and human tumors
- Implement laboratory methods and protocols for genotyping

Results

- Obtained an extension of the project deadline to February 27, 2024
- Obtained a positive opinion from the EC
- Purchased the necessary instrumentation to genotype the samples
- Started the experiments to genotype the collected samples

Publications

Evaluation of human papillomavirus DNA in colorectal cancer and adjacent mucosal tissue samples. Galati L, Gupta P, Tufaro A, Marinaro M, Saponaro C, Escobar Marcillo DI, Loisi D, Sen R, Robitaille A, Brancaccio RN, Cuenin C, McKay-Chopin S, Paradiso AV, Liška V, Souček P, Zito FA, Hughes DJ, Tommasino M, Gheit T

Integration of Digital Pathology into the Workflow of Anatomic Pathology and biobank

P.I. IRCCS Istituto Tumori Giovanni Paolo II Alfredo Zito
Funding Source Funds from the Ministry of Health for the 5x1000, year 2018

Background

The technological revolution, which has affected different areas of daily life in recent years, has also affected pathological anatomy, where the advent of new digitization and telecommunication tools has made it possible to transform cytohistological slides traditionally observed under a microscope into "digital images." Digital images, obtained through a process of slide scanning, represent true faithful copies of the cytohistological slide with the possibility of using different magnifications for their visualization, as if one were working with a slide and a "conventional" microscope. This innovation has given birth to digital pathology, which ranges from telepathology, understood as the transmission of images at a distance, to the improvement of management and archiving systems of diagnostic material in laboratories (work-flow), up to "pathomics," i.e., the computerized analysis of preparations, in order to use the greatest number of data and identify even those alterations not visible to the human eye through artificial intelligence systems.

Aims

The aim of this project is to carry out a diagnostic reproducibility study on both digitized, high-resolution histological and cytological preparations that are resistant to damage or breakage over time, correlating them with preparations performed traditionally and observed under an optical microscope, thus realizing a step-by-step process that can progressively rely on monitor observation alone for diagnosis, removing dependence on physical space and specimens through the simple use of a computer connected to the Internet.

Results

All histological diagnoses since 2010 have been imported into a single database (Filemaker19). The acquisitions of the technological supports necessary for the implementation of the project (Scanner, Image Analysis Software, etc.) have been arranged.
Following the installation of the Digital Scanner in March 2023 and the Visiopharm Image Analysis Software, a Digital Pathology Work Station was set up for use by all research groups and for the various artificial intelligence application projects at the Institute.

Publications

- Tumor Cellularity Assessment of Breast Histopathological Slides via Instance Segmentation and Pathomic Features Explainability
- Altini N, Puro E, Taccogna MG, Marino F, De Summa S, Saponaro C, Mattioli E, Zito FA, Bevilacqua V. Bioengineering (Basel). 2023 Mar 23;10(4):396. doi: 10.3390/bioengineering10040396.
- NDG-CAM: Nuclei Detection in Histopathology Images with Semantic Segmentation Networks and Grad-CAM
- Altini N, Brunetti A, Puro E, Taccogna MG, Saponaro C, Zito FA, De Summa S, Bevilacqua V.

Pharmaco-economic analysis on the main therapy schemes based on antiblastic drugs, monoclonal antibodies and immunotherapeutics, broken down by anatomical district

P.I. IRCCS Istituto Tumori Giovanni Paolo II Patrizia Nardulli
Start Date: 2023
End Date: 2025
Funding Source Funds from the Ministry of Health for the 5x1000

Background

The containment and rationalization of health expenditure represents a need shared by all management realities of the NHS. The development of tables of pharmacoeconomic data on the expenditure incurred for the purchase of antiblastic drugs used in clinical practice can become an aid in contextualizing therapeutic needs in relation to available economic resources and the health budget allocated to individual hospitals. In recent years, oncology therapy has experienced the introduction of monoclonal antibodies, immunotherapeutics, and combotherapy that have greatly changed clinical outcomes compared to chemotherapy-only treatments, but also challenged the NHS because of their high cost. rationalization of pharmaceutical spending allows the recovery of budgets to be redeployed to other areas and trigger a virtuous circle by which an oncology IRCCS could succeed first in evaluating the place-in-therapy of new drugs. Dividing the pharmacoeconomic analysis by disease district makes the comparison of overlapping treatment options more immediate, and the printouts could become a tool for the oncologist/hematologist to evaluate and choose the most sustainable.

Multicenter retrospective evaluation of predictive factors for the development of heart disease in patients with Diffuse Large Cell Lymphoma (DLBCL) undergoing anthracycline chemotherapy

P.I. IRCCS Istituto Tumori Giovanni Paolo II Stefano Oliva
Funding Source Istituto Gentili srl
Participating centers: Aziende Ospedaliere Universitarie

Background

More than half of patients treated with anthracyclines experience overt heart failure (5% of cases) and arrhythmic phenomena (40% of cases). Given the individual variability in the onset and progression of cardiotoxic injury, it is important to recognize its onset in the preclinical phase in order to achieve complete functional recovery with discontinuation of chemotherapy and appropriate cardiologic therapy. There is still a search for the best monitoring system of the chemotherapy-treated patient.

Aims

The objective of the study is to identify and validate a risk score related to the occurrence of acute and late cardiac toxicity in a historical cohort of patients receiving CHOP-Rituximab treatment including conventional anthracycline following first diagnosis of diffuse large cell lymphoma (DLBCL). The score will be identified by the combination of a number of independent biological and volitional factors that are predictive of the development of cardiac toxicity.

Results

Activation of No. 7 centers of the 25 originally planned.
Expansion of the No. of centers to be involved nationwide.
Enrollment of No. 21 patients at the IRCCS "Giovanni Paolo II" Cancer Institute.

DESTINY- Breast05: A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF TRASTUZUMAB DERUXTECAN (T-DXd) VERSUS TRASTUZUMAB EMTANSINE (T-DM1) IN SUBJECTS WITH HIGH-RISK HER2-POSITIVE PRIMARY BREAST CANCER WHO HAVE RESIDUAL INVASIVE DISEASE IN BREAST OR AXILLARY LYMPH NODES FOLLOWING NEOADJUVANT THERAPY

Funding source - Start and end dates:

For-profit studio, sponsor Daichii Sankyo
STart 29/10/2021
Interventional, multicenter foreign

Principal Investigator - Proposing Institution - Other Institutions involved

Dr. Francesco Giotta
Daichii Sankyo
459 global centers, 18 Italian centers

Status of patient enrollment

Enrollment closed 12/20/2023
In our center 2 patients were screening failure, 2 patients were randomized of which 1 patient was in the TRASTUZUMAB EMTANSINE (T-DM1) arm and 1 patient was in the TRASTUZUMAB DERUXTECAN (T-DXd) investigational arm.

Aims

Subjects with human epidermal growth factor receptor type 2 (HER2)-positive breast cancer who have residual disease in the breast or axillary lymph nodes following neoadjuvant therapy and at high risk of developing recurrent disease. High-risk disease is defined as inoperable (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) or operable (clinical stages T1-3, N0-1, M0) at the occurrence of disease with positive pathologic nodal status (ypN1-3) after neoadjuvant therapy.
The primary objective of the study is to evaluate IDFS with T-DXd treatment compared with T-DM1. IDFS is defined as the time interval from randomization to local invasive, axillary or distant recurrence, contralateral invasive breast cancer or death from any cause. IDFS will be determined based on disease recurrence, which will be assessed by the Investigator based on all available clinical evaluations.

EPIK-B5: "A Phase III, randomized, double-blind, placebo-controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor."

Funding source - Start and end dates:
Profit study, Novartis Pharma S.P.A.
Start 12/15/2022 study end prediction 09/2027
Interventional, multicenter foreign

Principal investigator - proposing institution - other institutions involved
DR. Francesco Giotta
Novartis Pharma S.P.A.
95 foreign centers of which 20 national centers (Humanitas coordinating center - Milan)

Status of patient enrollment
As of 31/12/2023 globally 260 patients screened, 953 pre-screened, 157 randomized. Italy has 224 pre-screened, 78 screened, 48 randomized patients. Enrollment is still active. In our center 4 patients were found to be screen failure at pre-screening, 1 patient withdrew consent during pre-screening, 2 patients were randomized and are still on treatment.

Aims
The primary objective of this study is to confirm whether treatment with alpelisib in combination with fulvestrant prolongs progression-free survival (PFS) in comparison with placebo in combination with fulvestrant in postmenopausal men and women with advanced, HR-positive, HER2-negative, PIK3CA-mutated breast cancer that has manifested progression during or after aromatase inhibitor (AI) and CDK4/6 inhibitor.
The primary scientific question of interest is: what is the effect of PFS-based treatment for alpelisib in combination with fulvestrant compared with placebo in combination with fulvestrant in men and postmenopausal women with advanced, HR-positive, HER2-negative, PIK3CA-mutated breast cancer who manifested progression during or after treatment based on aromatase inhibitor (AI) plus CDK4/6 inhibitor, regardless of discontinuation of study treatment or initiation of new cancer therapy?

postMONARCH: Phase III, randomized, double-blind, placebo-controlled trial to compare the efficacy of Abemaciclib in combination with Fulvestrant versus Fulvestrant in combination with placebo in patients with locally advanced or metastatic, HR-positive, HER2-negative breast cancer after progression to CDK4/6 inhibitor and endocrine therapy

Funding source - Start and end dates:
Profit study, SPONSOR: ELI LILLY
Start 30/11/2022 end 06/2026
Interventional, multicenter foreign

Principal investigator - proposing institution - other institutions involved
Dr Davide Quaresmini
157 centers involved including 7 national centers (coordinating center in ITALY San Raffaele Hospital Milan)

Status of patient enrollment
Enrollment closed. One patient enrolled and still in treatment.

Aims
The incorporation of CDK4/6 inhibitors in combination with endocrine therapy (ET) in the first-line treatment of locally advanced or metastatic hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 (HER2-) negative breast cancer has significantly improved outcomes (Finn et al. 2016; Tripathy et al. 2018; Johnston et al. 2019). However, these therapies are not curative, and almost all patients with metastatic breast cancer (MBC) will show disease progression. More recently, abemaciclib showed significant improvement in invasive disease-free survival (IDFS) and distant recurrence-free survival (DRFS) in the adjuvant setting (Johnston et al. 2020). As the use of CDK4/6 inhibitors increases in early lines of therapy, answering the question of how best to treat patients after disease progression or relapse after CDK4/6-based therapy will become increasingly important to provide valuable information for future clinical practice. Following disease progression with a CDK4/6 inhibitor plus ET, several treatment options are available. However, most of these treatment options were tested before CDK4/6 inhibitors were available, with the exception of alpelisib in the BYLieve study (Rugo et al. 2021). Therefore, outcomes after treatment with therapy containing CDK4/6 inhibitors are not well understood, and there are no prospective phase III studies that provide guidance on therapy in this population. After CDK4/6 inhibitor-containing therapy, mechanisms of resistance are multifactorial and could include direct resistance to ET and/or CDK4/6 inhibitors included in the regimen (Alvarez-Fernandez and Malumbres 2020). Importantly, tumors that have developed class-specific ET resistance (e.g., ESR1 mutations in the context of aromatase inhibitors) could have an ongoing dependence on CDK4/6 lifespan inhibition. Given the safety and tolerability of CDK4/6 inhibitors in combination with ET, there is growing interest in observing data on the continuation of CDK4/6 inhibition beyond progression by changing baseline ET therapy. The benefit of continuation of therapy beyond progression has been established in other disease states, such as in HER2+ MBC, where HER2-directed therapy is continued while a new ET or cytotoxic chemotherapy regimen is initiated (von Minckwitz et al. 2011; Baselga et al. 2012b). I3Y-MC-JPEF(c). The ability to maintain disease control across multiple lines of endocrine-based therapies suggests a persistent dependence on endocrine signaling after disease progression (Weatherman et al. 1999; Baselga et al. 2012a). Switching to a partner ET with a different mechanism provides continued inhibition of endocrine signaling that may induce a response or control disease progression, thereby delaying the need for chemotherapy. Fulvestrant, a selective estrogen receptor degrader (SERD), is one such option and is approved for use in second-line therapy. postMONARCH aims to compare the efficacy of fulvestrant with or without abamaciclib.

Assessment of Ramucirumab plus paclitaxel as switch MANteInance versus continuation of firstline chemotherapy in patients with advanced HER-2 negative gastric or gastroesophageal junction cancers: the ARMANI phase III Trial

Funding source - Start and end dates:
Funding source: Eli Lilly Italia S.p.A.
Study start and end: february 28, 2018- september 2024
Study type: phase III, multicenter, randomized, open label study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Dott. Oronzo Brunetti
Proposing institution: Fondazione IRCCS Istituto Nazionale dei Tumori
Other institutions involved: FICOG centers

Status of patient enrollment
10 patients enrolled

Aims
To evaluate the efficacy in terms of progression-free survival (PFS) of a maintenance treatment with ramucirumab plus paclitaxel (arm A) compared with continuation of first line until disease progression/unacceptable toxicity/death (arm B), after first-line chemotherapy line-based regimens containing oxaliplatin and fluoropyrimidines in patients with carcinoma of the gastric or gastroesophageal junction advanced and HER 2 negative.

A Phase 3, Open-Label, Randomized, Active-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Gemcitabine Plus Cisplatin Chemotherapy in First-Line Treatment of Participants With Unresectable or Metastatic Cholangiocarcinoma With FGFR2 Rearrangement (FIGHT-302)

Funding source - Start and end dates:
Funding source: IQVIA RDS italy SRL
Study start and end: september 17, 2019- july 27, 2028
Study type: phase III, multicenter, randomized, open label study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Dott. Oronzo Brunetti
Proposing Institute: Incyte Corporation
Other institutions involved: 218 centers globally, 27 Italian centers

Status of patient enrollment
28 enrolled patients

Aims
To evaluate the efficacy of pemigatinib versus gemcitabine and cisplatin in first-line treatment in participants with cholangiocarcinoma and bearing FGFR2 rearrangement.

Intermittent or continuous treatment with first-line panitumumab + FOLFIRI in patients with RAS/BRAF wild-type metastatic colorectal cancer: randomized phase 2 trial

Funding source - Start and end dates:
Funding source: AMGEN
Study start and end: September 24, 2018-September 2024
Study type: phase II, multicenter, randomized, open label study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Dr. Oronzo Brunetti
Proposing Institute: National Cancer Institute, "G. Pascale" Foundation
Other institutions involved: 20 Italian centers in total

Status of patient enrollment
20 enrolled patients

Aims
To evaluate whether intermittent experimental treatment with Panitumumab + FOLFIRI (administered until progression during treatment or cumulative toxicity) reports a progression-free time during treatment (PFSOT) similar to that achieved with continuous treatment in standard mode (administered until progression or cumulative toxicity). PFSOT is defined as the time from randomization to the first objective documented disease progression in those patients undergoing treatment (excluding intervals of disease progression occurring during treatment breaks) or death due to any cause.

Validation of new markers of serous ovarian cancer: the Gene Expression and Oncometabolic Profile (PREGO) study

Funding source - Start and end dates:

Source of funding: funds from the "GENESI" project, funded by the Ministry of Economic Development, and from the Scientific Head, Prof. Antonio Scilimati of the Department of Pharmacy-Pharmaceutical Sciences, University of Bari Aldo Moro (as the sponsor of the study)
Study start and end date: May 22, 2023 - May 2024
Study type: nonprofit multicenter ex-vivo clinical diagnostic trial on human biological material

Principal investigator - proposing institution - other institutions involved

Principal Investigator: Prof. Gennaro Cormio
Proposing institute: Prof. Antonio Scilimati, Department of Pharmacy-Pharmaceutical Sciences, University of Bari Aldo Moro
Other institutions involved:
- Department of Pharmacy-Pharmaceutical Sciences (SFARM)
- Department of Biomedical Sciences and Human Oncology (DIMO/U.O. of Gynecology and Obstetrics)
- Department of Basic Medical Sciences/Neuroscience and Sense Organs (DSMBNOS) of the University of Bari
- IRCCS Cancer Institute "Giovanni Paolo II" of Bari
- Institute of Biomembranes, Bioenergetics and Molecular Biotechnology (Bari)
- Campus Biomedico University of Rome

Status of patient enrollment

66 enrolled patients

Aims

Lo scopo del progetto è di validare un pannello di 41 geni da impiegare come nuovi biomarcatori per la diagnosi del cancro ovarico, simultaneamente in campioni bioptici, di biopsia liquida e urine di pazienti con tumore ovarico.

Publications

1. Perrone MG, Luisi O, De Grassi A, Ferorelli S, Cormio G, Scilimati A. Translational Theragnosis of Ovarian Cancer: where do we stand? Curr Med Chem. 2020;27(34):5675-5715. doi: 10.2174/0929867326666190816232330. PMID: 31419925.
2. Dellino M, Cascardi E, Leoni C, Fortunato F, Fusco A, Tinelli R, Cazzato G, Scacco S, Gnoni A, Scilimati A, Loizzi V, Malvasi A, Sapino A, Pinto V, Cicinelli E, Di Vagno G, Cormio G, Chiantera V, Laganà AS. Effects of Oral Supplementation with Myo-Inositol and D-Chiro-Inositol on Ovarian Functions in Female Long- Term Survivors of Lymphoma: Results from a prospective Case-Control Analysis. J Pers Med. 2022 Sep 19;12(9):1536. doi: 10.33907jpm12091536. PMID: 36143320; PMCID: PMC9505907.

Rechallenge con Doxorubicina Liposomale Pegilata in aggiunta alla Trabectedina nella recidiva di Tumore Ovarico: studio prospettico multicentrico (REPRAB study - MITO 36)

Funding source - Start and end dates:
Funding source: Agostino Gemelli University Polyclinic Foundation, Pharma Mar S.A.
Study start and end: 09 August 2023 - December 2023
Study type: prospective multicenter phase II no-profit study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Prof. Giovanni Scambia; Prof. Gennaro Cormio
Proposing Institute: IRCCS FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI
Other institutions involved: 16 Italian centers
- Cardinal Massaia Hospital
- IRCCS - IRST Meldola Dino Amadori
- IRCCS National Cancer Institute
- Veneto Oncology Institute IRCCS AO - Ordine Mauriziano
- S. Anna Hospital
- S. Maria di Ca' Foncello Hospital
- ULSS 3 Serenissima - Mirano District - Dolo
- New Hospital of Prato
- A. Gemelli Polyclinic Foundation
- "Regina Elena" National Cancer Institute
- University Campus Bio - Medical
- La Sapienza University Umberto I Polyclinic
- A.O. Universitaria Consorziale Policlinico di Bari
- Vito Fazzi Hospital Presidio ASL Lecce
- AORN Cardarelli
- National Cancer Institute IRCCS Fondazione Pascale

Aims
Demonstrate that rechallenge with the combination of pegylated liposomal doxorubicin (PLD) and trabectedin (Yondelis®) is active (objective response rate) in patients with ovarian cancer recurrence who have already received PLD and have relapsed within 6-12 months after the end of the last platinum or more than 12 months after the last platinum and are unable or unwilling to receive other platinum treatments.

Study of the mechanism of cross-talk between tumor cells and TAM in ovarian tumour

Funding source - Start and end dates:
Funding source: AIRC Foundation, IG grant 26340 entitled "Unraveling the metabolic cross-talk between cancer cells and macrophages in ovarian cancer" (PI: Alessandra Castegna)
Study start and end: September 01, 2023 - September 01, 2027
Study type: nonprofit bi-centered prospective observational study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Prof. Gennaro Cormio
Proposing Institute: IRCCS Cancer Institute "Giovanni Paolo II," Bari
Other institutions involved: Department of Biosciences, Biotechnology and Environment, University of Bari ALDO MORO

Status of patient enrollment
17 enrolled patients

Aims
- To identify markers of immunosuppression of patients' MAs in order to validate the results obtained from in-vitro models, in which the cross-talk mechanisms, mediated by the phenotype of tumor cells, that determine their expression will also be studied
- To help define new diagnostic pathways based on the phenotype of AMs and outline new innovative therapeutic pathways, based on metabolic immunotherapy, which, through targeting immunosuppressive markers or cross-talk mechanisms, could limit tumor progression and metastasis formation.

Publications
1. Menga A, Favia M, Spera I, Vegliante MC, Gissi R, De Grassi A, Laera L, Campanella A, Gerbino A, Carrà G, Canton M, Loizzi V, Pieri CL, Cormio G, Mazzone M, Castegna A. N-acetylaspartate release by glutaminolytic ovarian cancer cells sustains protumoral macrophages. EMBO Rep. 2021 Sep 6;22(9):e51981. doi: 10.15252/embr.202051981. Epub 2021 Jul 14. PMID: 34260142; PMCID: PMC8419692.
2. De Nola R, Menga A, Castegna A, Loizzi V, Ranieri G, Cicinelli E, Cormio G. The Crowded Crosstalk between Cancer Cells and Stromal Microenvironment in Gynecological Malignancies: Biological Pathways and Therapeutic Implication. Int J Mol Sci. 2019 May 15;20(10):2401. doi: 10.3390/ijms20102401. PMID: 31096567; PMCID: PMC6567055.

Study of the mechanism of cross-talk between tumor cells and TAM in ovarian tumour

Comprehensive, Open-label, Randomized, Controlled, Phase 3 Clinical Trial of Telisotuzumab Vedotin (ABBV-399) versus Docetaxel in Subjects with Previously Treated, EGFR Wild-type, Locally Advanced/Metastatic, Non-Squamous Non-Small Cell Lung Carcinoma with c-Met Overexpression.

Funding source - Start and end dates:

Funding source: PROFIT STUDY (ABBVIE)
Study start and end: 01/23/2023 - ongoing
Study type: multicenter extra-EU phase III interventionist study

Principal investigator - proposing institution - other institutions involved

Principal Investigator: Domenico Galetta
Proposing Institution: ABBVIE
Other Institutes Involved: 5 Italian Centers; 240 Global Centers

Status of patient enrollment

Active enrollment. 14 patients prescreened

Aims

The primary objective is to determine whether telisotuzumab vedotin improves progression-free survival (PFS), based on ICR assessments and/or overall survival (OS) compared with docetaxel in the following nested populations:

- NSCLC subjects with high overexpression of c-Met, wild-type EGFR, nonsquamous
- All NSCLC subjects with overexpression of c-Met, EGFR wildtype, nonsquamous

Phase 3 Randomized, Open-label Study of Pralsetinib Compared with Standard Of Care For First-Line Treatment Of Ret-Fusion-Positive Metastatic Non-Small-Cell Lung Carcinoma - Acceleret-Lung

Funding source - Start and end dates:
Funding source: Study Profit - Sponsor: F. Hoffmann-La Roche Ltd
Start and end of study: 10/06/2020 - ONGOING
Study type: Phase III International Multicentric Interventional Study.

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Dr. DOMENICO GALETTA
Proposing Institution: F. Hoffmann-La Roche Ltd
Other institutions involved: No. 116 Global Institutes; No. 15 National Institutes

Status of patient enrollment
No. 8 pcs screened; No. 3 pcs in treatment

Aims
- To evaluate whether pralsetinib improves PFS compared with the investigator's chosen platinum-based SOC anticancer therapeutic regimen in participants with RET fusion-positive metastatic NSCLC
- To evaluate the efficacy of pralsetinib compared with the investigator's chosen platinum-based SOC anticancer therapeutic regimen
- To evaluate OS

International phase III, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of adjuvant osimertinib versus placebo in participants with EGFR mutation-positive stage IA2- IA3 non-small cell lung cancer following complete tumor resection (ADAURA2)

Funding source - Start and end dates:
Funding source: for-profit study (ASTRAZENECA)
Start and end of study: DDG No. 555 of 10/26/2022 - ONGOING (open enrollment)
Study type: Interventional Multicentric Extra EU, Phase 3

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Domenico Galetta
Proposing Institution: ASTRAZENECA
Other institutions involved: 10 Italy, 182 global

Status of patient enrollment
No. subjects screened: 4
No. subjects enrolled: 1

Aims
- Primary end-point: to evaluate the efficacy of osimertinib compared with placebo with assessment of Disease Free Survival (DFS) in the high-risk patient population.
- Secondary end-point: DFS and OS (Overall Survival) in all participating subjects, Safety, Quality of Life and pharmacokinetics.
- Primary endpoints: Demonstrate efficacy of osimertinib compared with placebo, evaluation of DFS in participants.

International multicenter phase III, double-blind, placebo-controlled, multicenter study with Durvalumab in Neoadjuvant/Adjuvant for the treatment of patients with resectable stage II and III non-small cell lung cancer. Protocol Code: D9106C00001(AEGEAN)

Funding source - Start and end dates:
Funding source: Profit study (ASTRAZENECA)
Study start and end: DDG No. 553, 07/17/2020 - ongoing (closed enrollment)
Study type: Interventional Multicenter Extra EU, PHASE 3

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Domenico Galetta
Istituto proponente: ASTRAZENECA
Altri istituti coinvolti: 8 Italia, 228 Globale

Status of patient enrollment
No. of subjects screened: 5
No. of subjects enrolled: 4

Aims
Primary objective: Endpoint/variable: Compare the efficacy of durvalumab + pre-surgical chemotherapy and post-surgical durvalumab compared with placebo + pre-surgical chemotherapy and post-surgical placebo in terms of EFS EFS Compare the activity of durvalumab + pre-surgical chemotherapy compared with placebo + pre-surgical chemotherapy in terms of mPR

Publications
Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, Winder T, Zukov R, Garbaos G, Gao S, Kuroda H, Ostoros G, Tran TV, You J, Lee KY, Antonuzzo L, Papai-Szekely Z, Akamatsu H, Biswas B, Spira A, Crawford J, Le HT, Aperghis M, Doherty GJ, Mann H, Fouad TM, Reck M; AEGEAN Investigators. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 2;389(18):1672-1684. doi: 10.1056/NEJMoa2304875. Epub 2023 Oct 23. PMID: 37870974. (Galetta D in appendice)

Activity of Osimertinib in NSCLC Patients with Uncommon EGFR Mutations: Italian Retrospective Observational Study (ARTICUNO)

Funding source - Start and end dates:
Funding Source: Nonprofit Study
Study Start and End: 5/27/2022
Study type: National Multicenter Observational Study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Michele Montrone
Proposing Institution: ASST Grande Ospedale Metropolitano Niguarda, Milan
Other Institutions Involved: No. 31 Centers Involved

Status of patient enrollment
No. of subjects enrolled: 5

Aims
To evaluate the activity of Osimertinib in patients with metastatic or unresectable NSCLC with uncommon EGFR mutations (excluding exon 20 insertions), not pretreated with EGFR tyrosine kinase inhibitors.

Breath analysis in lung and pleural neoplasms. Prospective observational study for the assessment of volatile organic compounds (VOCs) in the exhaled breath - BALP

Funding source - Start and end dates:

Funding Source: Nonprofit Study
Study start and end: 04/30/2022 - ongoing
Study type: National Multicenter Observational

Principal investigator - proposing institution - other institutions involved

Principal Investigator: Annamaria Catino, Domenico Galetta
Proposing Institute: IRCCS Cancer Institute “Giovanni Paolo II”
Other institutions involved: 2 Italian centers.

Status of patient enrollment

Active enrollment:
24 patients enrolled in 2021
86 patients enrolled in 2022
95 patients enrolled in 2023

Aims

The primary objective of the study is to chemically identify a pattern of VOCs (Volatile Organic Compounds) capable of characterizing Lung Cancer and Pleural Mesothelioma patients compared with healthy subjects and subjects with prior asbestos exposure

Publications

- Di Gilio A, Palmisani J, Ventrella G, Facchini L, Catino A, Varesano N, Pizzutilo P, Galetta D, Borelli M, Barbieri P, Licen S, de Gennaro G. Breath Analysis: Comparison among Methodological Approaches for Breath Sampling. Molecules. 2020 ;25(24):5823. doi: 10.3390/molecules25245823. PMID: 33321824; PMCID: PMC7763204.
- Di Gilio A, Catino A, Lombardi A, Palmisani J, Facchini L, Mongelli T, Varesano N, Bellotti R, Galetta D, De Gennaro G, Tangaro S. Breath Analysis for Early Detection of Malignant Pleural Mesothelioma: Volatile Organic Compounds (VOCs) Determination and Possible Biochemical Pathways. Cancers 2020, 12, 1262; doi:10.3390/cancers12051262
- Catino A, De Gennaro G, Di Gilio A, Facchini A, Galetta D, Palmisani J, Porcelli F, Varesano N. Breath Analysis: A Systematic Review of Volatile Organic Compounds (VOCs) in Diagnostic and Therapeutic Management of Pleural Mesothelioma . Cancers 2019, 11, 831; doi:10.3390/cancers11060831
- Catino A, Di Gilio A, Nisi M, D'Alonzo G, Palmisani J, Varesano N, Bafunno D , De Summa S, De Gennaro G, Galetta D. Volatile Organic Compounds in exhaled breath as biomarkers for lung cancer.A screening-based study in high-risk participants. Trial in progress . J Thor Oncol suppl 11, S454, 2023

Randomized, noncomparative phase II trial investigating the best sequence of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR mutations - (CAPLAND)

Funding source - Start and end dates:
Funding source: nonprofit study
Start and end of study: DDG No. 593 of 07/31/2020 - ONGOING (open enrollment)
Study type: Interventional, phase 2

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Domenico Galetta
Proposing Institution: Foundation for Translational Research (FoRT)
Other institutions involved: National Multicenter, 20 Italy

Status of patient enrollment
No. Subjects Screened: 6
No. Subjects Enrolled: 6

Aims
To evaluate the best sequence of treatments in patients with advanced or metastatic EGFR mutation-positive NSCLC. By including patients with classic or uncommon activating EGFR mutations, the study will allow the efficacy of dacomitinib or osimertinib to be investigated in this population. The ability to enroll patients with asymptomatic or controlled brain metastases will allow the efficacy of dacomitinib to be defined in this particular population.

Observational study of patients with advanced non-squamous NSCLC treated with first-line combination of chemo-immunotherapy. Chemo-Immuno-REAL

Funding source - Start and end dates:
Funding Source: Nonprofit Study
Study Start and End: 04/30/2021 Enrollment Closed
Study Type: National Multicenter Observational Study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Michele Montrone
Proposing Institution: University Hospital of Parma
Other Institutions Involved: No. 42 Centers Involved

Status of patient enrollment
No. 45 enrolled patients

Aims
The primary objective of the study is to measure overall survival (OS) in the Italian "real-life" of patients with advanced nonsquamous NSCLC treated with the combination of carbo/cisplatin + pemetrexed + pembrolizumab in the first-line setting. Secondary objectives are to measure progression-free survival (PFS), objective response rate (ORR), and incidence of treatment-related adverse events.

Two-cohort, randomized phase 2 trial comparing standard therapy and chemoimmunotherapy combinations in patients with relapsed non-small cell lung cancer after chemoradiation therapy and durvalumab for stage III disease (CONDOR)

Funding source - Start and end dates:
Funding Source: Nonprofit Study
Study Start and End: 04/30/2021 Enrollment Closed
Study Type: National Multicenter Observational Study

Principal investigator - proposing institution - other institutions involved
Principal Investigator: Michele Montrone
Proposing Institution: Translational Research Foundation
Other institutions involved: 29

Status of patient enrollment
Active enrollment: 3 patients enrolled.

Aims
Primary objectives:
1. To investigate whether durvalumab prolongs survival when added to single-agent chemotherapy (ARM A) versus single-agent chemotherapy alone (ARM B) in patients who progress during durvalumab administered as maintenance therapy in stage III disease.
2. Whether, after chemoimmunotherapy, the addition of olaparib to durvalumab (ARM C) improves survival compared with durvalumab alone (ARM D) in patients with relapse after completing maintenance therapy with durvalumab for stage III disease.

Randomized phase II trial comparing atezolizumab versus atezolizumab plus bevacizumab as first-line treatment in patients with PD-L1 overexpression with advanced non-small cell lung cancer - FoRT 05-BEAT

Source of funding
Non-PROFIT Study

Start date:
January 2020

Type of study:
National Phase II Multicenter Interventional Study
P.I. Domenico Galetta

Proposing Institute:
Foundation for Translational Research (FoRT)

Other institutions involved
No. 35 Centers Involved

Status of patient enrollment
No. 13 pcs screened
No. 0 pcs in treatment
No.4 pcs in follow-up

Aims
To evaluate whether the combination of atezolizumab and bevacizumab increases overall survival (OS) compared with atezolizumab as monotherapy in patients with high PD-L1 expression with untreated metastatic NSCLC. To evaluate the response rate (RR), progression-free survival (PFS) and safety profile of the combination compared with monotherapy. Evaluate whether the combination of atezolizumab and bevacizumab increases overall survival (OS) compared with atezolizumab monotherapy when bone and/or liver metastases are present, considering their potential predictive value (Landi WCLC 2018). Perform exploratory analyses on predictive biomarkers of efficacy.

HERTHENA-Lung02: Phase 3, randomized, open-label study of patritumab deruxtecan compared with platinum-based chemotherapy in metastatic or locally advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor mutation (EGFRm) after failure of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy

Source of funding
Daiichi Sankyo, inc

Start date:
February 2023

Type of study:
Extra-EU multicenter phase III interventional
P.I. Domenico Galetta

Proposing Institute:
IRCCS Istituto Tumori "Giovanni Paolo II" Bari

Other institutions involved
Global study at approximately 200 study centers located in North America; Asia, including Japan; Australia; and Europe, including the United Kingdom

Status of patient enrollment
Screening: 12 patients
Enrolled: 7 patients

Aims
Primary objective: To compare the efficacy of patritumab deruxtecan versus platinum-based chemotherapy, as measured by PFS, in subjects with metastatic or locally advanced nonsquamous NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R)

Phase III randomized, double-blind, placebo-controlled trial of selpercatinib as adjuvant therapy following definitive locoregional treatment in participants with RET fusion-positive stage IB-IIIA NSCLC" - BOOK 432

Source of funding
Profit Study

Start date:
April 2022

Type of study:
Extra-EU multicenter phase III interventional
P.I. Domenico Galetta

Proposing Institute:
LILLY

Other institutions involved
6 Italy, 99 Global

Status of patient enrollment
Nº 12 prescreened patients including 1 patient screened, randomized and under treatment

Aims
Primary: Compare the EFS of participants in the primary analysis population with stage II-IIIA RET fusion-positive NSCLC treated with selpercatinib versus placebo.
Secondary: Compare the EFS of participants in the overall population with stage IB-IIIA RET fusion-positive NSCLC treated with selpercatinib versus placebo.
Compare other efficacy outcomes achieved with selpercatinib versus placebo in the primary analysis and in the overall populations.
Assess the safety and tolerability of selpercatinib compared with placebo in the primary analysis and in overall populations.
To evaluate/evaluate the performance of RET assays from investigator-identified laboratories versus a single RET assay designated by Lilly.
To compare the onset or worsening of NSCLC symptoms in participants treated with selpercatinib versus placebo.

Phase III, Randomized, Controlled, Multicenter 3-arm Study with Osimertinib as Neoadjuvant in Monotherapy or in Combination with Chemotherapy Compared with Standard Chemotherapy Alone for the Treatment of Patients with Resectable, Non-Small Cell Lung Carcinoma Positive for Epidermal Growth Factor Receptor Mutation (NeoADAURA)

Source of funding
Profit Study

Start date:
April 2021

Type of study:
Extra-EU Multicenter Interventionist, PHASE 3
P.I. Domenico Galetta

Proposing Institute:
ASTRAZENECA

Other institutions involved
8 Italy, 223 Global

Status of patient enrollment
No. Subjects Screened: 7
No. Subjects Enrolled: 1

Aims
Primary objective: To determine the efficacy of osimertinib as monotherapy or in combination with chemotherapy compared with chemotherapy alone as neoadjuvant treatment.
Secondary Aim: To further evaluate the efficacy of osimertinib as monotherapy or in combination with chemotherapy versus chemotherapy alone as neoadjuvant treatment by evaluation of pathologic complete response, event-free survival, disease-free survival, under staging, and overall survival.

Phase 3, open-label, randomized trial of lazertinib with amivantamab administered subcutaneously by hand injection versus amivantamab administered intravenously or amivantamab administered subcutaneously with a body-applied delivery system in patients with advanced or metastatic non-small cell lung cancer with EGFR mutations after progression to treatment with osimertinib and chemotherapy. PALOMA 3

Source of funding
Profit Study

Start date:
March 2023

Type of study:
Diagnostic
P.I. Domenico Galetta

Proposing Institute:
Janssen Research & Development, LLC

Other institutions involved
9 Italy, 186 Global

Status of patient enrollment
No. Subjects Screened: 3
No. Subjects Enrolled: 3

Aims
Primary objectives: to evaluate the pharmacokinetic noninferiority of amivantamab SC-CF by manual injection compared with amivantamab EV (Part 1) and to evaluate the bioequivalence of amivantamab SC-CF by manual injection and amivantamab SC-CF OBDS (Part 2).
Primary secondary objectives are to evaluate the efficacy (objective response rate [Objective Response Rate, ORR] and progression-free survival [Progression-Free Survival, PFS] and safety of the different administrations.

Prospective, multicenter, randomized nonprofit screening clinical trial entitled: "Multicenter randomized trial of lung cancer screening with low-dose chest CT (LDCT) associated with primary prevention and comorbidity reduction in high-risk heavy smokers - RISP clinical trial"

Source of funding
Non-PROFIT Study (with grant only for tac)

Start date:
July 2022

Type of study:
Diagnostic
P.I. Domenico Galetta

Proposing Institute:
IRCCS National Institute of Tumors Foundation of Milan

Other institutions involved
17 in Italy

Status of patient enrollment
1460 applications for participation in the project were received. All subjects were contacted, of whom 945 were made eligible. At present n.767 have been enrolled, signed consent and performed tac baseline.

Aims

- Definition of individual risk profile, based on the set of epidemiological and radiomic data obtained at the time of the first LDCT examination: coronary calcifications, lung damage (COPD, emphysema, fibrosis);
- Identification of optimal screening intensity (LDCT interval) according to individual risk, and evaluation of the cost/benefit of a longer interval (≧ 2 years) bei low-risk subjects;
- Significant reduction in the percentage of smokers in the high-risk group as a result of the data obtained from LDCT screening and direct involvement of the Smoking Center present at the site.

Publications

- Cani M., Mercadante E., Cardellicchio S., Zuccatosta L., Pattacini P., Milanese G., Bafunno D., DeFilippis A., Del Giudice T., Trussardo S., Riglietta M., Franzese N., Aloè T., Caffo O., Camerano F.,Cammarota A., DiPieri M., Papale M. Primary prevention strategies within the Italian Lung Cancer Screening Program (RISP): a first update. Tumori Journal 2023, Vol. 109(2S) p.64 (Accepted as POSTER at AIOM 2023).
- Ferrari G., Cani M., Garbo E., Passiglia F., Capelletto E., Bertaglia V., Bironzo P., Tinivella M., Pasqualini G., Mogavero A., Gasparro M., Bernardi G., Mangiapane F., Butticè S., Baldan S., Biffi D., Bafunno D., D'Alonzo G., Barbieri V., Novello S. Diet and lifestyle habits among participants to the lung cancer Italian screening program. Tumori Journal 2023, Vol. 109(2S) p.70 (Accepted as POSTER at AIOM 2023).

Retrospective observational study on the outcome of mediastinal consolidation radiotherapy in patients with microcytoma, extensive disease treated with chemoimmunotherapy. (MEDIASTINAL RT)

Source of funding
Non-PROFIT Study

Start date:
March 2023

Type of study:
National Multicenter Observational Study
P.I. Longo Vito

Proposing Institute:
SSD Medical Oncology for Thoracic Pathology - IRCCS Istituto Tumori "Giovanni Paolo II" - Bari, Italy

Other institutions involved
Total Patients: 16

Status of patient enrollment
1460 applications for participation in the project were received. All subjects were contacted, of whom 945 were made eligible. At present n.767 have been enrolled, signed consent and performed tac baseline.

Aims
To evaluate the safety of the use of mediastinal consolidation radiotherapy in patients treated with chemo-immunotherapy by analyzing the type and frequency of any adverse reactions in current clinical practice. To evaluate the impact of mediastinal consolidation radiotherapy in patients with disease-extended microcytoma treated with chemo-immunotherapy on the overall efficacy of care by measuring progression free survival and overall survival.

Publications
Longo V, Della Corte CM, Russo A, Spinnato F, Ambrosio F, Ronga R, Marchese A, Del Giudice T, Sergi C, Casaluce F, Gilli M, Montrone M, Gristina V, Sforza V, Reale ML, Di Liello R, Servetto A, Lipari H, Longhitano C, Vizzini L, Manzo A, Cristofano A, Paolelli L, Nardone A, De Summa S, Perrone A, Bisceglia C, Derosa C, Nardone V, Viscardi G, Galetta D, Vitiello F. Consolidative thoracic radiation therapy for extensive-stage small cell lung cancer in the era of first-line chemoimmunotherapy: preclinical data and a retrospective study in Southern Italy. Front Immunol. 2024 Jan 18;14:1289434. doi: 10.3389/fimmu.2023.1289434. PMID: 38304255; PMCID: PMC10830694.

First-line efficacy study of Osimertinib in patients with EGFR-mutated NSCLC based on TP53 mutational status (TEMPLE-2)

Source of funding
Fondazione Policlinico Universitario Agostino Gemelli IRCCS with registered office in Rome

Start date:
December 2022

Type of study:
'Nonprofit' Clinical Trials
P.I. Domenico Galetta

Proposing Institute:
Agostino Gemelli IRCCS University with registered office in Rome

Other institutions involved
Total Patients: 10

Status of patient enrollment
1460 applications for participation in the project were received. All subjects were contacted, of whom 945 were made eligible. At present n.767 have been enrolled, signed consent and performed tac baseline.

Aims
Primary objective: To determine the PFS efficacy of Osimertinib in treating patients with EGFR mutated NSCLC based on TP53 mutational status.
Secondary Aim: To evaluate secondary indices of clinical efficacy including overall survival (OS), overall response rate (ORR), disease control rate (DCR) and duration of response (DoR), adverse events (AEs) based on TP53 mutational status.

Forest therapy integrated with immunotherapy treatment of patients with pulmonary neoplasm

Source of funding
Non-PROFIT Study

Start date:
March 2023

Type of study:
Prospective, single-center observational
P.I. Longo Vito

Proposing Institute:
IRCCS Istituto Tumori Giovanni Paolo II - Bari

Other institutions involved
1 involved

Status of patient enrollment
Total Patients: 11
Patients in Treatment: 11

Aims
Evaluation of the impact of forest therapy on different psychological aspects of patients, such as stress, depression and anxiety.
Analysis of changes related to lymphocyte population on peripheral blood.
Analysis of changes related to expression of pro-inflammatory cytokines.

- Evaluation of change in spirometric parameters.
- Modification of values detectable by bioimpedance analysis, with special reference to phase angle, FM and FFM.
- Impact on fatigue and algie control.
- Number of progressions following integrated therapeutic intervention

Phase 2 study of Translational approach to first-line cHemoimmunotherapy followed by maintenance with pembrOlizumab and olaparib in extensive stage small cell lung caRcinoma (THOR-TRIAL)

Source of funding
Non-PROFIT Study

Start date:
April 2023

Type of study:
Phase II National Multicenter Interventional Study
P.I. Longo Vito

Proposing Institute:
IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l Via Piero Maroncelli, 40/42 - 47014 Meldola (FC)

Other institutions involved
13 Institutes involved

Status of patient enrollment
No.2 pazients screened; No.2 patients in treatment

Aims
To evaluate the efficacy of induction of chemo-immunotherapy followed by maintenance with pembrolizumab and olaparib in terms of progression-free survival (PFS) from registration.

Prospective, multicenter, phase II, single-arm study of the combination Niraparib + Dostarlimab in patients with advanced non-small cell lung cancer and/or malignant pleural mesothelioma positive for PD-L1 expression and germline or somatic mutations in homologous recombination repair (HRR) genes - UNITO

Source of funding
Non-PROFIT Study

Start date:
July 2022

Type of study:
Phase II National Multicenter Interventional Study
P.I. Domenico Galetta

Proposing Institute:
Università Degli Studi di Torino

Other institutions involved
13 Institutes involved

Status of patient enrollment
N. TOT. 20 patients screened
No. 1 patient in treatment

Aims
Primary: Progression-free survival
Secondary: Objective response rate; duration of objective responses; disease control rate; overall survival; tolerability.

Phase 3, randomized, open-label trial of Dato-DXd plus pembrolizumab versus pembrolizumab as monotherapy in treatment-naïve subjects with advanced or metastatic non-small cell lung cancer expressing high levels of PD-L1 (TPS ≥50%) without "actionable" genomic alterations (TropionLung08)

Source of funding
PROFIT Study

Start date:
January 2023

Type of study:
Interventional Multicenter Extra-EU, Phase 3
P.I. Domenico Galetta

Sponsor:
Daiichi Sankyo, Inc.

Other institutions involved
Centers tot: 226; centers in Italy: 9

Status of patient enrollment
Total Prescreened and Screened Patients: 15
Patients In Treatment: 3

Aims
To compare the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab in monotherapy, as measured by progression-free survival (PFS) by blinded independent central review (BICR). To compare the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab as monotherapy, measured by overall survival (OS).

Phase 2, multicenter, open-label, single-arm study to evaluate the efficacy and safety of Taletrectinib in patients with ROS1-positive NSCLCL and other advanced or metastatic solid tumors - AB106G208

Source of funding
PROFIT Study

Start date:
January 2023

Type of study:
Interventional Multicenter Extra-EU, Phase 2
P.I. Domenico Galetta

Sponsor:
AnHeart Therapeutics Inc.

Other institutions involved
9 Italy, Global Unk

Status of patient enrollment
Nº Subjects Screened: 3
Nº Subjects Enrolled: 3

Aims
Primary Objective: To evaluate the efficacy of taletrectinib according to objective response rate (ORR) in patients with advanced or metastatic ROS1-positive NSCLC Secondary Efficacy Objectives: 1. To evaluate efficacy according to duration of response (DOR) 2. To evaluate efficacy according to progression-free survival (PFS) 3. Assess efficacy according to time to failure (TTF) 4. Assess efficacy according to time to response (TTR) 5. Assess efficacy according to overall survival (OS) 6. Evaluate efficacy endpoints (ORR, DOR and PFS) assessed by investigators 7. Evaluate the intracranial efficacy of taletrectinib.

Open-label, randomized Phase II trial with BNT111 and cemiplimab in combination or as single agents in patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma

Source of funding
PROFIT Study

Start date:
April 2021

Type of study:
Multicenter, open-label, randomized, phase II study
P.I. Michele Guida

Sponsor:
BIONTECH

Other institutions involved
60 centers in 15 countries

Status of patient enrollment
We have enrolled 16 patients, 3 patients are currently in follow-up. Enrollment is closed.

Aims
To demonstrate the antitumor activity of the drug trials BNT111 + Cemiplimab, compared with Cemiplimab alone in patients progressing after anti PD-1 in terms of objective response and survival.

Adjuvant Therapy with Pembrolizumab versus Placebo in Resected Highrisk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)

Source of funding
PROFIT Study

Start date:
December 2018

Type of study:
Multicenter, randomized, phase III, double-blind study
P.I. Michele Guida

Sponsor:
Merck Sharp & Dohme Corp

Other institutions involved
166 centers in 16 countries

Status of patient enrollment
We enrolled 14 patients who completed the planned year of treatment. 12 patients are in follow-up. Enrollment is closed.

Aims
Adjuvant treatment with pembrolizumab in patients with high-risk melanoma (stage IIB and IIC) to compare disease-free survival in the treatment arm versus placebo. That trial led to registration of the drug for this stage of disease in 2023.

A Phase 3, Randomized, Double-blind, Active-Comparator-Controlled Clinical Study of Adjuvant MK-7684A (Vibostolimab with Pembrolizumab) Versus Adjuvant Pembrolizumab in Participants with High-risk Stage II-IV Melanoma (KEYVIBE010)

Source of funding
PROFIT Study

Start date:
September 2024

Type of study:
Multicenter, international, randomized, double-blind study
P.I. Michele Guida

Sponsor:
MSD

Other institutions involved
225 centers including 9 centers in Italy

Status of patient enrollment
We have enrolled 10 patients, 7 of whom are on treatment. Enrollment is open and will close in May 2024.

Aims
Primary objective: To evaluate the superiority in terms of RFS (disease-free time)of the combination therapy of Pembrolizumab + MK-7684A compared with pembrolizumab in melanoma patients in the adjuvant setting (stage IIB to IV rececate). Secondary objectives: to evaluate OS in the seperimental arm compared with the standard and safety.

A phase 3 trial of fianlimab (anti-lag-3) and cemiplimab versus pembrolizumab in the adjuvant setting in patients with completely resected high-risk melanoma

Source of funding
non-profit study

Start date:
August 2024

End date:
ongoing

Type of study:
Multicenter, international, randomized, double-blind study
P.I. Michele Guida

Sponsor:
REGENERON

Other institutions involved
200 centers around the world

Status of patient enrollment
9 patients, 7 of whom were on treatment. Enrollment is open.
Enrollment is scheduled to close in March 2025.

Aims
Primary objective: To evaluate the superiority in terms of RFS (disease-free time) of the combination therapy of CEMIPLIMAB + FIANLIMAB compared with pembrolizumab in melanoma patients in the adjuvant setting (stage IIC to stage IV rececate). Secondary objectives: to evaluate OS in the experimental arm compared with the standard and safety.

Sequential Combo Immuno and Target therapy (SECOMBIT) study.
A three arms prospective, randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) and combo target therapy (LGX818/MEK162) in patients with metastatic melanoma and BRAF mutation

Source of funding
non-profit study

Start date:
December 2016

Type of study:
Multicenter, prospective, randomized phase II study
P.I. Michele Guida

Proposing institution:
Istituto dei Tumori IRCCS "Fondazione Pascali", Napoli

Other institutions involved
37 centers in 9 European countries

Status of patient enrollment
We enrolled 7 patients, of whom 1 patient is still in treatment.
Enrollment is closed.

Aims
To evaluate the best sequential approach with the combination of target therapy (LGX818 plus MEK162) and the combination of immunotherapy (ipilimumab plus nivolumab) in patients with metastatic melanoma and BRAF V600 mutation.

Publications

1 Ascierto PA, Casula M, Bulgarelli J, Pisano M, Piccinini C, Piccin L, Cossu A, Mandalà M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, Arance A, Guida M, Maiello E, Gogas H, Richtig E, Fierro MT, Lebbe C, Helgadottir H, Queirolo P, Spagnolo F, Tucci M, Del Vecchio M, Cao MG, Minisini AM, De Placido S, Sanmamed MF, Mallardo D, Paone M, Vitale MG, Melero I, Grimaldi AM, Giannarelli D, Dummer R, Sileni VC, Palmieri G. Sequential immunotherapy and targeted therapy for metastatic BRAF V600 mutated melanoma: 4-year survival and biomarkers evaluation from the phase II SECOMBIT trial. Nat Commun. 2024 Jan 2;15(1):146. doi: 10.1038/s41467-023-44475-6. PMID: 38167503; PMCID: PMC10761671.
2 Ascierto PA, Mandalà M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, Arance A, Guida M, Maiello E, Gogas H, Richtig E, Fierro MT, Lebbè C, Helgadottir H, Queirolo P, Spagnolo F, Tucci M, Del Vecchio M, Gonzales Cao M, Minisini AM, De Placido S, Sanmamed MF, Mallardo D, Curvietto M, Melero I, Palmieri G, Grimaldi AM, Giannarelli D, Dummer R, Chiarion Sileni V. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): A Randomized, Three-Arm, Open-Label Phase II Trial. J Clin Oncol. 2023 Jan 10;41(2):212-221. doi: 10.1200/JCO.21.02961. Epub 2022 Sep 1. PMID: 36049147.

Evaluation of clinical outcomes of chemotherapy (or androgen receptor therapy) in combination with hormone therapy in metastatic hormone-sensitive stage prostate cancer (ECHOS)

Source of funding
non-profit study

Start date:
July 2021

End date:
December 2025

Type of study:
Multicenter observational study
P.I. Emanuele Naglieri

Proposing institution:
Ospedale Santa Chiara, Trento

Other institutions involved
92 italian centers

Status of patient enrollment
11 patients enrolled

Aims
To evaluate: the clinical outcome (in terms of progression free survival - PFS) of treatment with docetaxel or ARTA for mHSPC in an unselected population in clinical practice; the criteria for selecting patients for chemotherapy treatment or ARTA; the other clinical outcomes, prognostic-predictive factors of response and toxicity profile; to analyze the therapies administered at the time of progression to treatment and their clinical outcome.

Phase 3, randomized, double-blind, placebo-controlled clinical trial to study the efficacy and safety of Pembrolizumab (MK-3475) in combination with chemoradiation therapy (CRT) versus chemoradiation therapy alone in subjects with muscle-invasive bladder cancer (MIBC) (KEYNOTE-992)

Source of funding
Merck Sharp & Dohme Corp.

Start date:
April 2020

End date:
June 2029

Type of study:
Randomized double-blind phase III study
P.I. Emanuele Naglieri

Proposing institution:
Merck Sharp & Dohme Corp.

Other institutions involved
131 global centers, of which 8 are Italian

Status of patient enrollment
11 patients enrolled

Aims
Compare event-free survival, with intact bladder, in participants in arm A (pembrolizumab + chemoradiotherapy) and arm B (placebo + chemoradiotherapy), based on cystoscopy, biopsy with centralized pathologic evaluation (where applicable), urinary cytology, and radiographic evaluation by independent blinded central review.

Multicenter phase III, randomized, open-label study to determine the efficacy and safety of durvalumab in combination with tremelimumab and enfortumab vedotin or durvalumab in combination with enfortumab vedotin for perioperative treatment in patients ineligible for cisplatin who undergo radical cystectomy for muscle-invasive bladder cancer. VOLGA

Source of funding
Labcorp Drug Development Inc.

Start date:
January 2023

End date:
September 2028

Type of study:
Randomized phase III study
P.I. Emanuele Naglieri

Proposing institution:
Astrazeneca AB

Other institutions involved
260 global centers, of which 16 are Italian

Status of patient enrollment
2 patients enrolled

Aims
To evaluate the safety and tolerability of durvalumab + tremelimumab + EV in participants with MIBC ineligible for cisplatin treatment; to evaluate the efficacy of durvalumab + tremelimumab + EV on pCR rate and Event-free Survival (EFS).

Multicenter, randomized, open-label, phase 3 study with blinded endpoint evaluation aimed at comparing the effect of abelacimab versus apixaban on venous thromboembolism (VTE) recurrence and bleeding events in patients with cancer-associated VTE (ASTER)

Type of study:
Multicenter, randomized, open-label, phase 3 study
P.I. Stefano Oliva

Sponsor:
Anthos Therapeutics

Other institutions involved
Coordinating center: SS. Annunziata di Chieti, General Medicine 2 -G. D'Annunzio University, Department of Innovative Technologies in Medicine and Dentistry

Background
Cancer is a strong risk factor for venous thromboembolism (VTE). Apixaban equals low-molecular-weight heparin in preventing VTE recurrence and has a similar rate of major bleeding in cancer-associated venous thrombosis, but is associated with an increase in clinically relevant nonmajor bleeding. Abelacimab is a fully human monoclonal antibody shown in experimental models to prevent carotid artery thrombosis by dose-dependent prolongation of activated thromboplastin partial time.

Aims
The primary objective of this study is to evaluate whether abelacimab is noninferior to apixaban for the prevention of VTE recurrence 6 months after randomization in oncology patients and newly diagnosed VTE patients.

Multicenter, randomized, open-label, phase 3 study with blinded endpoint evaluation aimed at comparing the effect of abelacimab versus dalteparin on venous thromboembolism (VTE) recurrence and bleeding events in patients with gastrointestinal/genitourinary cancer

Type of study:
Multicenter, randomized, open-label, phase 3 study
P.I. Stefano Oliva

Sponsor:
Anthos Therapeutics

Other institutions involved
Coordinating center: SS. Annunziata di Chieti, General Medicine 2 -G. D'Annunzio University, Department of Innovative Technologies in Medicine and Dentistry

Background
Direct oral anticoagulants have shown at least similar efficacy to dalteparin in preventing recurrence of venous thromboembolism (VTE) during cancer; however, they have been associated with an increased risk of bleeding, especially in patients with cancers of the gastrointestinal and genitourinary tracts.

Aims
The primary objective of the study is to determine whether abelacimab is noninferior to dalteparin in preventing recurrence of venous thromboembolism 6 months after randomization in patients with gastrointestinal or genitourinary carcinoma.

Philadelphia-positive adult acute lymphoblastic leukemia at diagnosis. Sequential treatment with ponatinib and the bispecific monoclonal antibody blinatumomab vs. chemotherapy and imatinib

Source of funding
Non-PROFIT Study

Start date:
2021

Type of study:
Interventional, randomized, multicenter phase III trial drug delivery
P.I. Crescenza Pasciolla

Proposing institution:
Fondazione GIMEMA

Other institutions involved
15 involved

Status of patient enrollment
Total Patients: 4

Aims
To evaluate the efficacy of a first-line therapeutic strategy with chemo-free induction/consolidation (ponatinib+blinatumomab) and compare it with control arm (chemotherapy+imatinib), in terms of event-free survival defined as: non-negativity (complete molecular remissions and unquantifiable positives) of minimal residual disease, death, toxicity, and resistance in adult patients with Philadelphia+ Acute Lymphoblastic Leukemia.

Multicenter study of immune system cell phenotype during therapy by anti-CD19/CD3 monoclonal antibodies in patients with acute B lymphoblastic leukemia

Source of funding
Non-PROFIT Study

Start date:
2020

Type of study:
Spontaneous, observational, prospective, noninterventional, multicenter, national.
P.I. Crescenza Pasciolla

Proposing institution:
AOU Policlinico S.Orsola-Malpighi, UO of Hematology, Dr. Antonio Curti

Other institutions involved
Centers at the Regional (Emilia-Romagna) and National (CAMPUS ALL Group) levels.

Status of patient enrollment
Total Patients: 3. Enrolled 3 patients and they are in follow-up.

Aims
The study proposes to evaluate the immunologic response in patients with ALL undergoing therapy by anti-CD19/CD3 monoclonal antibodies and to identify biomarkers predictive of response to anti-CD19/CD3 monoclonal antibody therapy and their possible correlation with conventional prognostic criteria.

Publications
Blinatumomab differentially modulates peripheral blood and bone marrow immune cell repertoire: A Campus ALL study Br J Haematol. 2023 Nov;203(4):637-650. doi: 10.1111/bjh.19104.
Darina Ocadlikova, Federico Lussana, Nicola Fracchiolla, Massimiliano Bonifacio, Lidia Santoro, Mario Delia, Sabina Chiaretti, Crescenza Pasciolla, Alessandro Cignetti, Fabio Forghieri, Francesco Grimaldi, Giulia Corradi, Letizia Zannoni, Stefania De Propris, Gian Maria Borleri, Ilaria Tanasi, Jayakumar Vadakekolathu, Sergio Rutella, Anna Rita Guarini, Robin Foà, Antonio Curti

Prospective observational study on infectious complications in patients with Acute Myeloid Leukemia treated with first-line demethylating agents in 2019-2020" (Study Code LAM_SEIFEM)

Source of funding
Non-PROFIT Study

Start date:
2020

Type of study:
Spontaneous, observational, prospective, noninterventional, multicenter, national.
P.I. Crescenza Pasciolla

Proposing institution:
Udine Integrated ASU, Hematology Clinic, Dr. Anna Candoni

Other institutions involved
No.28 Centers nationwide

Status of patient enrollment
Total Patients: 8. They are in follow-up.

Aims
To assess the incidence of clinically or microbiologically documented infectious (bacterial, fungal, viral) complications in patients with AML treated with first-line Demethylating Agents (Azacytidine, Decitabine, Guadecitabine). Evaluate the impact of these complications on the treatment schedule and survival.
Evaluate the type of anti-infective prophylaxis performed by these patients (type of drugs and timing of administration) and its efficacy (comparing incidence of infections in prophylactic versus nonprophylactic patients). Assess the hospitalization rate determined by intercurrent infectious complications and attributable mortality.

Publications
Prospective multicenter study on infectious complications and clinical outcome of 230 unfit acute myeloid leukemia patients receiving first-line therapy with hypomethylating agents alone or in combination with Venetoclax Am J Hematol. 2023 Apr;98(4):E80-E83. doi: 10.1002/ajh.26846.
Anna Candoni, Davide Lazzarotto, Cristina Papayannidis, Matteo Piccini, Giampaolo Nadali, Michelina Dargenio, Marta Riva, Nicola Fracchiolla, Lorella Mellillo, Giulia Dragonetti, Maria Ilaria Del Principe, Chiara Cattaneo, Manuela Stulle, Crescenza Pasciolla, Roberta De Marchi, Mario Delia, Maria Chiara Tisi, Valentina Bonuomo, Mariarita Sciumè, Antonio Spadea, Chiara Sartor, Davide Griguolo, Elisa Buzzatti, Claudia Maria Basilico, Chiara Sarlo, Anna Lina Piccioni, Elisa Cerqui, Federica Lessi, Attilio Olivieri, Renato Fanin, Mario Luppi, Livio Pagano.

istituto tumori

IRCCS - Bari

dirscientifica@oncologico.bari.it

https://www.sanita.puglia.it/web/irccs

Viale Orazio Flacco 65 - 70124 Bari

+39 080 555 5111

Social Networks