APOLLO 11 Project, Consortium in Advanced Lung Cancer Patients Treated With Innovative Therapies: Integration of Real-World Data and Translational Research

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Abbreviations: AI, artificial intelligence; CPS, combined positive score; ctDNA, circulating tumor DNA; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; DL, deep learning; FACS, fluorescence activated cell sorting; ICIs, immune checkpoint inhibitors; ML, machine learning; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non–small cell lung cancer; PBMC, Peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SCLC, small cell lung cancer; TKIs, thyrosine kinase inhibitors; TMB, tumor mutational burden; TPS, tumor proportion score.

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Abstract

Introduction: Despite several therapeutic efforts, lung cancer remains a highly lethal disease. Novel therapeutic approaches encompass immune-checkpoint inhibitors, targeted therapeutics and antibody-drug conjugates, with different results. Several studies have been aimed at identifying biomarkers able to predict benefit from these therapies and create a prediction model of response, despite this there is a lack of information to help clinicians in the choice of therapy for lung cancer patients with advanced disease. This is primarily due to the complexity of lung cancer biology, where a single or few biomarkers are not sufficient to provide enough predictive capability to explain biologic differences; other reasons include the paucity of data collected by single studies performed in heterogeneous unmatched cohorts and the methodology of analysis. In fact, classical statistical methods are unable to analyze and integrate the magnitude of information from multiple biological and clinical sources (eg, genomics, transcriptomics, and radiomics). **Methods and Objectives:** APOLLO11 is an Italian multicentre, observational study involving patients with a diagnosis of advanced lung cancer (NSCLC and SCLC) treated with innovative therapies. Retrospective and prospective collection of multiomic data, such as tissue- (eg, for genomic, transcriptomic analysis) and blood-based biologic material (eg, ctDNA, PBMC), in addition to clinical and radiological data (eg, for radiomic analysis) will be collected. The overall aim of the project is to build a consortium integrating different datasets and a virtual biobank from participating Italian lung cancer centers. To face with the large amount of data provided, AI and ML techniques will be applied will be applied to manage this large dataset in an effort to build an R-Model, integrating retrospective and prospective population-based data. The ultimate goal is to create a tool able to help physicians and patients to make treatment decisions. **Conclusion:** APOLLO11 aims to propose a breakthrough approach in lung cancer research, replacing the old, monocentric viewpoint towards a multi-comprehensive, multiomic, multicenter model. Multicenter cancer datasets incorporating common virtual biobank and new methodologic approaches including artificial intelligence, machine learning up to deep learning is the road to the future in oncology launched by this project.

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Introduction

For more than 50 years, cytotoxic chemotherapy has been the only treatment able to modestly prolong survival in advanced patients with both Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC).[1] In the last decade, advances in the understanding of cell biology have led to the identification of specific genetic alterations in NSCLC, known as "driver" alterations, including mutations in *EGFR, KRAS,* and *BRAF* and rearrangements of *ALK, ROS1, NTRK,* and *RET* genes. The use of "target therapies" is the preferred treatment choice in the subgroup of patients with oncogenic alterations. *EGFR* mutations, observed in about 15% of NSCLC patients, became the first target for which a tailored treatment was approved. Different TKIs (eg, gefitinib, erlotinib, and osimertinib) are commonly used in clinical practice as they demonstrated superiority over chemotherapy in the first-line setting.[2] Immunotherapy has further changed the therapeutic landscape in both NSCLC without "driver" alteration and SCLC. Several ICIs have been approved over the past decade for the treatment of lung cancer, halving the risk of death and promising long-term tumor control in some patients. In particular, antibodies engineered to counter CTLA-4 (eg, Ipilimumab), PD-1 (eg, Pembrolizumab) expressed by immune cells, and PD-L1 (eg, Atezolizumab) expressed by cancer cells and microenvironment, were developed and tested in locally advanced and metastatic NSCLC and SCLC.[3,4] However, not all patients significantly benefit from ICIs, as in the case of patients with *EGFR* mutations or *ALK/ROS1* rearrangements; furthermore, there is a subgroup of patients (13%-26%) in which ICIs can be even detrimental, therefore called "hyperprogressors".[5,6] In NSCLC patients, specifically, the expression level of PD-L1, detected by immunohistochemistry and calculated through specific formulas such as TPS and CPS, still remains the only approved biomarker to predict patients' outcome to ICIs. This test is the basis for choosing the modality of ICI administration, in combination with other clinical factors (eg, monotherapy for tumor expressing PD-L1 $\geq$ 50% in absence of other risk factors, or combination with platinum-based chemotherapy for patients with <50% and/or high disease burden); it is also useful to predict the benefit of maintenance therapy with Durvalumab (anti-PDL1) after definitive chemoradiation for locally advanced NSCLC patients.[7] Because the predictions of efficacy are limited by PD-L1 status alone, other biomarkers including TMB or NLR have been tested, with unsuccessful results in terms of prediction.[8-10]

The lack of a single biomarker reflects the complexity of NSCLC biology, which cannot be explained by a single predictor in a "1 size fits all" model. Today it is possible to obtain a great deal of information about the tumor, the microenvironment and the immune system due to the wide range of new techniques available (genomics, transcriptomics, and radiomics).[11-14] However, generating trustworthy biomarkers applicable in clinical practices from all these biological and clinical inputs remains a concern, also for the difficulty to validate it in large datasets. In addition, integrating existing and new potential biomarkers into a comprehensive model is not feasible with classical statistic methodologies. In the era of big data, classical statistic methods would not be able to tackle this complexity. AI and Machine Learning/Deep Learning (ML/DL) processes are more potent instruments with the capacity to synthesize and correlate information from enormous amounts of data from multiple

sources provided in different formats. This methodology of analysis would allow to integrate multiomics data and finally implement the model obtained from their joint combined analysis to a real-life setting.

The APOLLO11 project aims to fill this knowledge gap with a design philosophy that is highlighted in its catchphrase "Unity is strength". The milestone of the project is the integration of both clinical data and biological specimens from multiple centers in order to avoid the dispersion of data, which risks remaining stored in single institutions and unused. Some hypotheses remain unexploited or unanswered due to the limited population number, lack of significance and limited statistical power of single institution-initiated studies. To do this, APOLLO11 aims to build up a network formed by a large number of Italian lung cancer care centers sharing standardized clinical datasets and procedures of biological sample collection and storages. This effort could help identify and combine different types of biomarkers (clinical, radiologic, genetic, molecular, and immunological) across different lung cancer stages and subtypes, to address specific scientific questions (eg, baseline prediction of response to therapy, discovery of primary or secondary resistance mechanisms, prediction of relapse in advanced disease treated with multimodal curative approaches, and prevention of toxicities).

Discussion

Study Design

APOLLO11 is an Italian, multicenter, retrospective and prospective, observational study involving patients with a diagnosis of lung cancer (NSCLC and SCLC) treated with innovative therapies. These include not only ICIs, but also target therapies and other novel anticancer treatments, such as metabolic modulators, inhibitors of tumor microenvironment and next-generation immunomodulators.

The study will include patients candidate to these treatments (prospective patients), but also those who already received them (retrospective). The latter group will allow the registration in a standardized platform of all the available clinical, radiological, and genomic data, whereas for prospective patients biological samples will also be collected following standardized procedures, registered in the same database and made available for future research.

This project will build an infrastructure for the collection, harmonization, storage, and sharing of lung cancer patients' data and biological samples, in a homogenized but centre-distributed database (Figure 1). Of note, clinical and research centers with expertise in the management of lung cancer will be the final owners of their data for internal purposes, but can easily share -anonymized data with other centers to address specific aims that may emerge during the study conduction. Moreover, patients advocacy were involved to actively revise the scientific design of the study and the informed consent.

The first research question, called "APOLLO11-BRI" (Figure 2) has been proposed by "Istituto Nazionale Tumori" of Milan, the Coordinating Center, with the aim to identify biomarkers of ICIs response in NSCLC. Clinical real-world and available translational and radiomics data in more than 1000 patients will be collected and integrated with a prospective translational analysis, including single cell transcriptomic data obtained from blood samples of 30 patients receiving ICIs as first-line treatment. A total of 120 plasma samples from different centers involved in the network analyzed with FACS analysis will be used as validation cohort. The data will be then integrated using AI pipelines methods to develop a decision-making tool for treatment individualization, avoiding unnecessary cost, and undue toxicities.

A central steering committee analyzes scientific proposal from the centers and determines which projects to prioritize based on clinical applicability, scientific relevance, and data availability. Further scientific purposes are currently under evaluation and will be implemented in the next future.

Study Population

Inclusion criteria of this study are the cytological or histological diagnosis of NSCLC or SCLC lung and having received or being candidate to receive an innovative therapy (eg, targeted therapy, immune-checkpoint inhibitors, and next-generation therapy as per clinical practice or within a compassionate use program). Will be excluded lung cancer patients not treated with innovative therapies, eg, chemotherapy only, patients who received only locoregional therapies (eg, surgery or radiotherapy alone) and patients who received treatments considered innovative before 2010 (eg, Bevacizumab).[15]

Study Objectives

APOLLO11 network has multiple purposes stated in a data driven master protocol. First of all, the development and maintenance of a multicentric distributed real-world REDCap platform for lung cancer treated with innovative therapy by integrating multiple "heterogeneous" data sources (eg, clinical, biochemical, radiological, and translational data). Innovative treatments analysed in this study include, but are not limited to, immunotherapies (eg, anti-PD1 monoclonal antibody, anti-PDL1, anti-CTLA4, anti-LAG3, and other immune-checkpoint inhibitors), monoclonal antibodies and small molecules targeting specific protein (eg, *EGFR, ALK, ROS1, BRAF, NTRK, KRAS, RET*, and *MET*), antibody-drug conjugates (eg, Trastuzumab Deruxtecan, Sacituzumab Govitecan, and Datopotamab Deruxtecan), and drug interacting with specific cellular processes (eg, PARP inhibitors, CDK4/6 inhibitors), Simultaneously, foundation of a national "virtual biobank" through the collection of biological specimens stored in participating centers; in particular, samples will be stored, managed and owned by centers involved in their collection, but data obtained from them will be made available in a standardized way to the other network members, creating a virtual knowledge repository of multiomics data. Consequently, APOLLO11 will promote the ideation, design and sharing of clinical trial proposals, multicentric research projects and funding applications, to secure its sustainability in the long term as well as to foster opportunities for research in smaller or local hospitals which can greatly benefit from access and participation to a study with this specific setup. The development of this network would be instrumental to provide answers to questions coming from all the Italian centers involved. Results obtained to test the formulated hypotheses will be used for the construction of decision-making tools, favoring an individualized prediction of response to treatments in lung cancer patients.

Figure 1 APOLLO11 master protocol data and biobank driven research in lung cancer patients treated with innovative therapies.

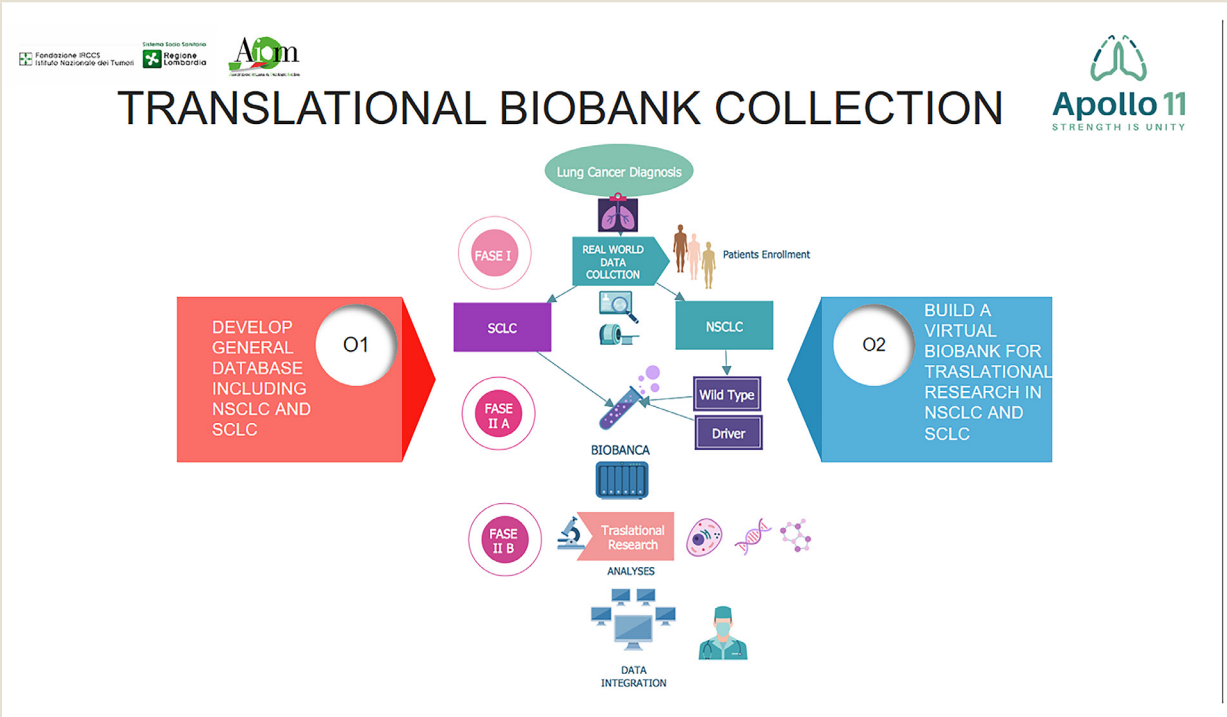
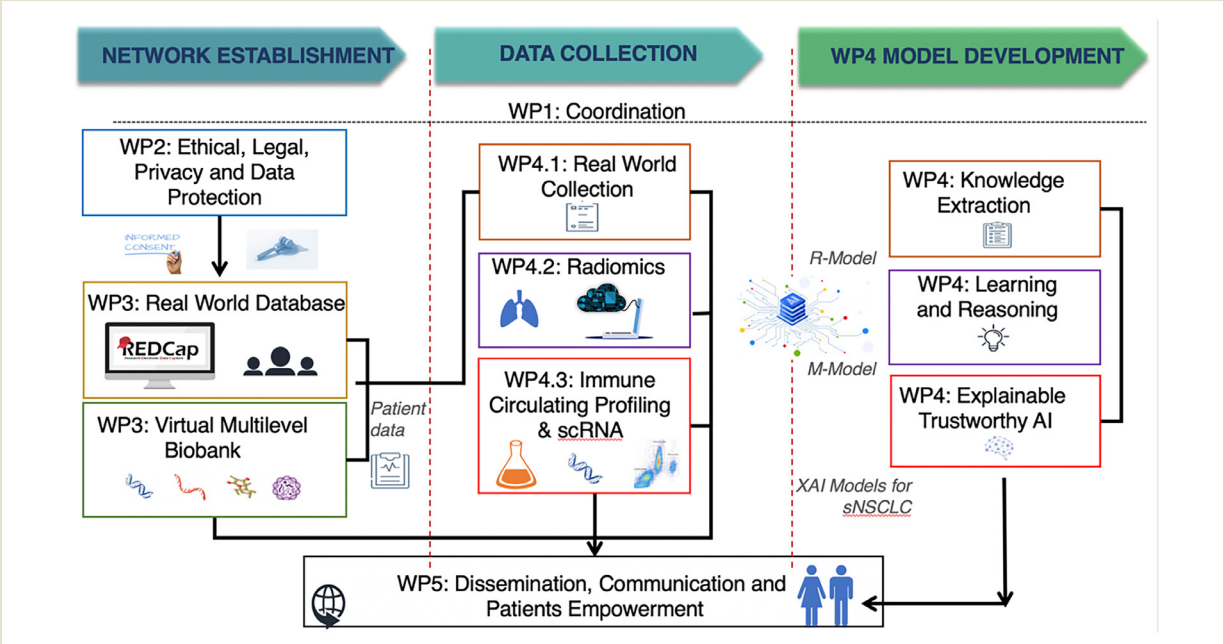


Figure 2 APOLLO11-BRI, first research question design to be solved among the network.



Statistical Analysis

To cope with the massive amount of data provided by a coordinated national database, AI and ML techniques will be applied. As a general principle, the first step of the analysis will be knowledge extraction through techniques like Principal Component Analysis, Filter methods, Autoencoder methods, in order to select the features that can better feed the predictive models (eg, Support Vector Machines, Extratrees, and Neural Networks[14]). If necessary, techniques coming from literature will be extended to better suit the specific setting we are facing. The "retrospective" patients, ie, who already received the therapy, will be divided into 2 cohorts for the AIs training and testing. Afterwards, the entire set of "retrospective" patients will be used for a second knowledge extraction and model training phase, which will produce the final R-model, and their predictive capabilities will finally be tested on "prospective" cases.

Conclusion

APOLLO11 strives to establish a new approach in lung cancer "data and biobank driven" research, through a transition from classic "1 size fits all" approaches to a multicomprehensive, multiomics, multicenter model. Cooperation between centers, sharing expertise, knowledge, and the aptitude in using new methodologic approach is the key to reach these objectives, admittedly ambitious and yet vital to carry clinical and translational research over to the next step.

Disclosures

Arsela Prelaj certifies that all conflicts of interest reported can be considered outside the present paper: consulting or advisory role for BMS, AstraZeneca; had travel, accommodations, or other expenses paid or reimbursed by Roche, Italfarmaco; principal investigator of Spectrum Pharmaceuticals. Alessandra Laura Giulia Pedrocchi holds shares of Agade srl. Giuseppe Lo Russo has received fees for acting as a consultant from Roche, Novartis, BMS, MSD, AstraZeneca, Takeda, Amgen, Sanofi, Italfarmaco, Pfizer; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Roche, Novartis, BMS, MSD, AstraZeneca, Takeda, Amgen, Sanofi, has received support for attending meetings and/or travel from Roche, BMS, MSD; has participated on data safety monitoring board or advisory board for Roche, Novartis, BMS, MSD, AstraZeneca, Sanofi, has acted as principal investigator in sponsored clinical trials for Roche, Novartis, BMS, MSD, AstraZeneca, GSK, Amgen, Sanofi. Rossana Berardi has received fees for acting as a consultant, for lectures and/or for participating to advisory board from BI, EISAI, GSK, Italfarmaco, Otsuka, Lilly, MSD; has received funding to Institution from AZ, BMS, Pfizer, Novartis, Roche; AMGEN. Giulia Galli declares the following conflicts of interest: Italpharma (advisory board); Roche (travel accommodation); Astra Zeneca, BMS, MSD (honoraria for lectures). Federica Bertolini has received consultant fees from MSD, Astra-Zeneca, Lilly, Eisai, Sanofi and speakers fee from BMS, MSD, Astra Zeneca. Filippo de Braud reports a patent for PCT/IB2020/055956 pending and a patent for IT201900009954 pending; and Roche, EMD Serono, NMS Nerviano Medical Science, Sanofi, MSD, Novartis, Incyte, BMS, Menarini Healthcare Research & Pharmacoepidemiology, Merck Group, Pfizer, Servier, AMGEN, Incyte. No disclosures were reported by the other authors.

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