Clinical study Number in "Fondazione IRCCS Istituto Nazionale dei Tumori di Milano": INT 147/22

TITLE: I^{3}LUNG: Integrative science, Artificial Intelligence data platform for Individualized LUNG cancer care with Immunotherapy (prospective)

Version 1.0 of 22-06-2022

PATIENT INFORMATION FORM

This form, which will be provided before your final decision,
exhibits the essential information of the study you have been asked to take part in.
It is important that you read this information and discuss with your physician
before you sign this consent.
Only patients who accept and sign this consent will participate in the study.
You can withdraw this consent whenever you decide.

The Disease

Dear Mr/Mrs,

As you might know, the disease diagnosed to you is called 'lung cancer', a tumor that arises from lung cells but can spread to other organs. You decided to receive treatment for this disease, which usually includes chemotherapy, immunotherapy and biologic agents, with a treatment plan that you decided with your physician.

Immunotherapy, which consists of drugs that help your immunological system recognize and fight against tumoral cells, allows patients with different cancers, including lung cancer to improve their quality of life and prolong life expectancy. Some tumors, however, cannot respond to these drugs, or develop some mechanisms to overcome the drug effect, such as bacteria do with antibiotics. These mechanisms are known as "resistance".

Aim of this study

This study is carried out under the Horizon Europe I^{3}LUNG project, funded by the European Commission in 2022 and aims to identify factors, or a combination of factors (clinical, analytical, molecular, radiological) related to your response to treatment and/or able to influence the course of your disease (progression or resistance). These factors could also represent other potential treatment targets. The main reason why the identification of these factors could be useful is to help physicians learn the mechanisms underlying growing, evolution and spreading of cancer cells and, finally, immunotherapy resistance, in order to prevent or counteract it.

This study could help physicians select patients to be treated with immunotherapy and, finally give the right treatment at the right time for the right patient.

I^{3}LUNG Partners

Fondazione IRCCS Istituto Nazionale dei Tumori (INT, Italy); (Coordinator)
Politecnico di Milano (POLIMI, Italy);
Istituto di Ricerche Farmacologiche Mario Negri (IRFMN, Italy);
Istituto Europeo di Oncologia (IEO; Milano, Italy);

ML Cube (ML3 Italy);
LungenClinic Grosshansdorf GmbH (GHD, Germany);
Universitaetsklinikum Hamburg-Eppendorf (UKE, Germany);
Vall d'Hebron Institute of Oncology (VHIO, Barcelona, Spain);
Medica Scientia Innovation Research S.L. (MEDSIR, Spain);
Metropolitan Hospital (MH, Greece);
Shaare Zedek Medical Center (SZMC, Israel);
Katholieke Universiteit Leuven (KUL, Belgium);
Institutet for Halso-OCH Sjukvardsekonomi Aktiebolag (IHE, Sweden);
University of Chicago (UOC, Illinois, USA);
Aalborg Universitet (AAU, Denmark);
Lung Cancer Europe (LUCE, Bern, Swiss).

Design of this study and data collection

This is a multicenter study that involves different oncologic centers all over the world. It consists of two parts: retrospective and prospective. As defined by the National Cancer Institute, in a retrospective cohort study, "medical records of groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) are compared for a particular outcome (such as lung cancer)."[1] A prospective cohort study, "follows over time groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) and compares them for a particular outcome (such as lung cancer)."[2]

This informed consent refers to the prospective clinical study within the I^{3}LUNG project.

The prospective part of the study plans to collect information from your clinical medical record related to your disease and tumor biological information, the same information as for the retrospective study. In particular, your pseudo-anonymized personal data (for example age, gender, smoke habits, height and body weight, drugs that you use to take), *except for your name,* and data regarding your disease (stage, histology, molecular alterations, treatments that you received, response and how you tolerated it) will be collected and registered on a web-based platform. Moreover, all images from your radiological exams (CT scan and FdG-PET) that you performed (if you did it) will be gathered in a shared collection system. Finally, specific and innovative analysis will be conducted on your biological samples. In particular, the tumor tissue taken for your cancer diagnosis will be analyzed to extrapolate the DNA and RNA from tumor cells and the immune cells surrounding the tumor. The biopsy procedures (collection of tumor tissue samples) will be performed as per clinical practice, no additional biopsy for tissue collection will be performed. Additionally, within the prospective phase, 32 ml of peripheral blood samples will be collected at the start of the immunotherapy. Also, stool samples will be collected from you at the start of immunotherapy in order to analyze your microbiota.

New methodologies like Artificial Intelligence, in particular, deep and machine learning methodologies (DL and ML) will be used to analyze your data, in order to create models useful to identify patients who will benefit from the immunotherapy treatment and possible resistance mechanisms. This will help physicians to further personalize treatment of lung cancer patients.

[1] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/retrospective-cohort-study
[2] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/prospective-cohort-study

Because several years are usually required to obtain meaningful improvement in cancer diagnosis and treatment, you may not be able to directly benefit from this study participation. However, identification of clinical, molecular and immunologic predictive factors and mechanisms of response will probably provide substantial benefit in the treatment of patients with lung cancer.

Before taking your final decision, we invite you to take into account that what we actually know about your disease and its treatment is based on previous research on patients with conditions similar to yours.

Consent, data handling and confidentiality

By signing this informed consent, you agree that researchers from your oncologic centre use your biological samples and your pseudonymized personal data for being used in the clinical study of the I^{3}LUNG project.

Your data will be collected strictly in the scope of the present study and will be processed in a confidential manner. Your data will be identified by means of a code, and any information that could lead to your identification will not be included. Only your physician/study collaborators will be able to link this data to you and your clinical history. Therefore, your identity will not be disclosed to any other person except the health authorities, when required, or in case of a medical emergency. The Research Ethics Committees, the representatives of the Health Authority involved in matters of inspections, and the personnel authorized by the study coordinator will only be able to access the data in order to verify personal information, clinical study procedures and to ensure that the rules of good clinical practice are being followed (always respecting the confidentiality of the information).

Your data will be collected during the study duration (5 years) and will remain available in an encrypted manner for 25 years, and then will be anonymized. Promotional material without reference to identifiable information may be kept after the conclusion of the I^{3}LUNG project.

Anonymized research results will be published in journal articles, conference presentations and via any other mode of scientific exchange and dissemination that will be seen as appropriate by your physician and the study researchers, while protecting your anonymity

Transfer of data

Your encrypted data and samples are authorized to be transferred from your cancer center to other involved centers to be analyzed. In order to conduct this research, your encrypted data will be transferred to research centers belonging to the I^{3}LUNG project in different locations in the following manner:

- The study will involve exporting of CT scans and PET images from EU cancer centers (Italy, Germany, Spain, Greece) and US to Israel to perform radiomics analysis;
- Clinical data will be exported from all the EU cancer centers and Israel to US for AI analyses.
- Biological samples (tissue, blood and stool samples) will be collected from Israel and will be imported in EU countries (Italy, Germany, Spain) for pathological, genomic, circulating and microbiome analyses.

In all cases when the codified data are transferred to a third party and to other countries, additional steps will be taken to protect your information from being linked to you.

In case the third parties are not established in the European Union (EU), appropriate safeguards will be taken in order to ensure the protection of personal data and to make effective legal remedies available.

Insurance coverage

Due to the observational relevance of the study, i.e. because no medical additional intervention is planned, the insurance coverage stipulated from this Center guarantees adequate coverage, according to the applicable law.

Guarantee to the Patient taking part of this study

This study was approved by an Independent Ethics Committee at "Fondazione IRCCS Istituto Nazionale Tumori di Milano".

Your personal data and your biological samples will be processed, stored, and analyzed under the supervision and responsibility of:

Dr. Prelaj Arsela
Department of Medical Oncology 1
Fondazione IRCCS, Istituto Nazionale dei Tumori, via Venezian, 1 Milano

Voluntary participation and right to withdraw

Your participation in this study is free and voluntary and you will not receive any economic compensation for his/her participation in the study. This means that your participation in the research is entirely voluntary. You are free to choose not to participate, or to withdraw your participation at any moment without any consequence.
If you should choose to stop your participation in the middle of the study, no further new data will be collected from you but the information collected up to the time you decide to leave the study will remain a part of the study data. One copy of this form and one copy of the signed informed consent will be given to you to keep if you decide to participate in the trial.

Contacts

The study will last 5 years. The collected data can be stored and used for 25 years.

On the same way, it is possible that this information, as well as your biological samples and/or medical data is used and processed in research related to this study. If you request, you could be informed with general information about research studies in which your samples were used.

If you need more information about this study, please don't hesitate to contact our team at the address below. At the same time, we will promptly inform you whether new details that could encourage your decision will be available.

INFORMED CONSENT ABOUT PERSONAL DATA TREATMENT
AND ABOUT SPECIFIC DATA CATEGORIES FOR CLINICAL PROPOSAL

Clinical study Number at "Fondazione IRCCS Istituto Nazionale dei Tumori di Milano": …

TITLE: I^3LUNG: Integrative science, Artificial Intelligence data platform for Individualized LUNG cancer care with Immunotherapy (Prospective Phase)

Study Code: …..

Dear Mr/Mrs,
In accordance with the European regulations in terms of personal data protection, in particular in light of the "Regulation" (UE) 2016/679 of 27th April 2016 (General Regulation on data protection), we inform You that:

1) Data Controller and DPO
Istituto Nazionale dei Tumori di Milano, as the study promoter, is the Controller of your personal Data and this Center, in the figure of Dr.Prelaj, is the supervisor of your Data. Single Centers will manage your Data for the issues of competence and in accordance with obligations established by the law.

The rights reported in this document can be exercised addressing:

- Data Controller, that is, Fondazione I.R.C.C.S. Istituto Nazionale dei Tumori in Milan, via Giacomo Venezian 1, 20133 (MI), in the person of the General Director:
  e-mail: direttore.generale@istitutotumori.mi.it

- Data Protection Officer (or DPO):
  e-mail: DPO@istitutotumori.mi.it

  PEC: formazione.privacy@pec.istitutotumori.mi.it

2) Data processed, legal basis of the processing and purpose

The IRCCS Foundation National Cancer Institute of Milan acquires, directly and through third parties, personal data and particular categories of data (including data related to your health, origin, lifestyles and genetic data) that it processes in paper and digital form, for clinical research purposes, as described in the study, in order to promote the prevention and improvement of therapeutic treatments.

By agreeing with the treatment described here, your data may be used for the purpose of improving knowledge of oncological pathologies, developing new treatments, medical devices and diagnostic methods, to finally ensure better patient care. Your consent to the processing of data for the purposes of this study is voluntary and optional and your refusal to provide it will not preclude you from accessing other medical/health services requested and prescribed by oncologists and/or other specialists.

Your consent may be revoked at any time, in which case the revocation will only have value for the future, remaining valid for the processing carried out up to that moment.

3) Nature and consequences of providing data
As mentioned above, your consent to the processing of data for the purposes of this study is voluntary and optional but is a necessary and indispensable condition to participate in this study.

4) Processing methods and storage times
Your data will be processed with suitable technical and organizational security measures.

They will be processed without specifying your name but associated with an identification code (pseudo-anonymization). This will avoid your direct identification when the study data will be used. Only the physician and authorized persons will be able to link this code to your name.

The data you provide will be stored during the study duration (5 years) and will remain available in an encrypted manner for 25 years, and then will be anonymized. In the field of scientific research, in fact, constant technological development makes it possible to obtain new and very important results thanks to the analysis of data which, due to the lack of current medical and technological knowledge at the time of their initial collection, could not be examined. Furthermore, with the progress of the research activity, data collected, even in very ancient periods, could be useful for new studies. The conservation of your data therefore represents an essential phase for research.

5) Confidentiality

For the purposes outlined above, your data will be processed by authorized personnel duly designated by the Foundation, such as: healthcare, technical, administrative personnel and any external companies that perform on behalf of and authorized by the Foundation, in Italy, in the European Union or in non-EU countries. In the latter case, the transfer to each of these countries will take place on the basis of the legitimacy of the transfer in relation to each country or on the basis of the consent that you provided. The promoter will take all possible measures to ensure compliance with current legislation in relation to the information collected. The updated list of third parties including analysis laboratories is available and it will be provided by your physician at your request.

The data, processed also through electronic means, will be shared only in aggregate form and in an absolutely anonymous way and may be published in scientific and/or statistical journals or disclosed during scientific conferences.

6) Exercise of Rights

At any time, you can access the data concerning you, know how they were acquired, check if they are exact, complete, updated and secure and assert your rights to request the rectification of your data, as well as the limitation of the processing that concerns you, as expected pursuant to and within the limits of articles 15, 16, 18 of the GDPR Regulation. You may also exercise the right to object to the processing of your data pursuant to and within the limits of art. 21 of the Regulation and request the portability of your data, within the limits of art. 20 of the Regulation.

You also have the right to withdraw your consent at any time, without prejudice to the lawfulness of the processing based on consent before the withdrawal. These rights can be exercised by contacting the Data Controller as indicated in point 1.

Pursuant to article 77 of the Regulation, if you believe that the processing that concerns you violates the legislation on the protection of personal data, you have the right to lodge a complaint with the Italian Data Protection Authority or with the supervisory authority of the EU Member State in which you habitually reside, work or in the place where the alleged violation occurred.

CONSENT ACQUISITION*

This form must be signed only in the case you decide to take part in the study.
It is important that you have discussed this with your physician before you sign this consent.
Only patients who accept and sign this consent will participate in the study.
You can withdraw this consent at any given moment in time.

I declare that I have been fully informed about this study, that I have received a copy of the information form and that I have adequately discussed it with the physicians who are responsible for it at this institution.

I give my free and informed consent:

To take part in the clinical prospective study phase within I^3LUNG project, meaning that data, imaging and biological samples (tissue, blood and stool at baseline therapy), as well as self-report measures (i.e., questionnaires regarding your quality of life and information regarding your decision about treatments), will be collected, stored and used to carry out research under the conditions previously detailed.	YES □ NO □
I agree to the processing of data concerning me, in paper and electronic format, in compliance with the regulations in force pursuant to, among other things, the Legislative Decree 196/2003 and subsequent amendments to supplement the consent already signed by me for the processing of sensitive data at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan	YES □ NO □
I agree with the transfer of my personal Data and those owning to special categories even those from outside of the European Union for research purposes within I^3LUNG project and with modalities and limitations indicated in the patient information form provided with this document.	YES □ NO □
I agree with the possibility that my personal data and those owning to special categories will be transferred outside of the European Union, if it will be necessary, for research purposes and with modalities and limitations indicated in the patient information form provided with this document.	YES □ NO □

**In particular cases, the consent could be provided by the tutor/support administrator.*

Any determination that is not specified in the attached information sheet cannot be made until after new approval by the Independent Ethics Committee, which will decide whether it is necessary to issue a new consent on my part.

The results of the determinations carried out will be published only in an anonymous and aggregated form with the results of the determinations concerning other patients. I have the right to request the destruction of the samples, if not already used, and limited to the period in which this is technically possible, in particular until they have not yet been made completely anonymous.

It is not planned to provide information to me or my physicians about the results of the determinations carried out on biological samples, but I can request (even from now) to be informed about the results of the study.

Full name of the Person conducting the consent discussion ……

Signature of the Person conducting the consent discussion ……

Date …../…../…….

Full name of the Patient ……

Signature of the Patient ……

Date …../…../…….

Full name of the legal representative (if appropriated) ……

Signature of the legal representative ……

Date …../…../…….

Full name of the impartial witness (if appropriated) ……

Signature of the witness ……

Date …../…../…….