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# A viable human lung cancer tissue collection (LCTC) to accelerate translational research

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ABSTRACT

*Background:* The collection of clinical data and patient tumor specimens in institutional repositories is essential to accelerate translational research in lung cancer, linking laboratory findings with patient outcomes. These resources allow investigators to explore tumor heterogeneity, analyze therapeutic profiles and, more recently, generate patient-derived models of cancer. Given the plethora of therapies in clinical use or under investigation, it is critical to establish tissue collection programs that support the identification of predictive biomarkers of drug sensitivity to define patient subgroups that may benefit from tailored therapeutic strategies. However, access to high-quality viable specimens remains limited.

*Methods:* We established a multidisciplinary program -the Lung Cancer Tissue Collection (LCTC) study- to prospectively collect viable human specimens and clinical data. Samples can be collected post-diagnosis and at multiple treatment time points, preserving material for future studies.

*Results:* In the first 24 months of the LCTC study, we enrolled 158 patients and collected over 700 specimens from patients with lung cancer. *EGFR* and *KRAS* mutations were the most frequently identified oncogenic drivers, mirroring frequencies reported in public datasets. We achieved a 60 % success rate in cryopreservation

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-measured by the proportion of patient-derived organoids growing after tissue thawing and processing- highlighting the feasibility of our program.
*Conclusions:* The LCTC biobank captures the molecular and clinical diversity of lung cancer, providing a clinically annotated resource of viable tissue and longitudinal blood specimens. This platform enables patient-derived modeling and multi-omic and functional studies to investigate tumor biology, treatment response, and resistance, supporting biomarker discovery and precision medicine.

## Introduction

Availability of clinical data and tumor specimens of patient tumors serves as a substantial resource to generate and validate hypotheses related to cancer biology, progression, and prediction of therapeutic response. With the goal to personalize treatments, patients can be actively engaged in tissue collection programs to gain a comprehensive understanding of the heterogeneity and pathophysiology of tumors from patient-derived models of cancer (PDMCs). By closely recapitulating the human disease, these models have emerged as valuable tools to gain insights into how to best target each subset of tumors, particularly those that do not display sensitivity to standard approaches. A clear example of tailored cancer treatment is represented by targeted therapies that selectively inhibit the growth of cancer cells characterized by specific overactivated molecular pathways [1,2]. In lung cancer, mutant EGFR was the first druggable oncogenic driver and tyrosine kinase inhibitors (TKIs) targeting mutant EGFR replaced chemotherapy improving the overall survival (OS) with a objective response rate (ORR) in the treatment-naïve setting of up to 80 % [2,3]. In the following two decades, targeted therapies have transformed the treatment landscape for subsets of patients with metastatic lung cancer harboring oncogenic driver alterations, such as those in *ALK, RET, MET, BRAF, ERBB2/HER2, ROS1, NTRK* and more recently *KRAS* [3,4]. Clinical studies showed that biomarker-based therapies strikingly improved patient outcomes. However, a limited fraction of patients with lung cancer benefits from a targeted therapy and, as treatment rarely leads to a complete response, drug resistance will eventually emerge constituting a major clinical challenge [5]. Overall, this highlights that 'one-target one-therapy' does not always apply and further tumor stratification, based on unique tumor molecular properties, may help refine treatments based on specific biomarkers.

Collecting, storing, and analyzing clinical data require intense efforts and collaboration among several departments and setting up an efficient workflow is key to keep track of patients enrolled in a study. A successful example of data collection and analysis of tumor samples is indeed *The Cancer Genome Atlas (TCGA)* that was launched towards the end of 2005 and brought together the first dataset on lung cancer published in 2014 [6]. Importantly, this type of study uncovered previously overlooked altered genes enabling further refinement in sub-classification to personalize lung cancer treatment. In the same year, the prospective study *TRACERx (TRAcking non-small cell lung Cancer (NSCLC) Evolution through therapy [Rx])* was launched in Europe to define and monitor trajectories of NSCLC evolution during progression at different sites of disease [7]. More recently, cryopreservation of tumor specimens led to the establishment of PDMCs that enabled the investigation of genomic and non-genomic human tumor data, including reconstituting the tumor microenvironment and testing potential strategies to improve clinical outcomes [8]. These living biobanks of PDMCs allow recapitulating somatic copy number and mutational spectra found in patient tumors and are amenable to high-throughput drug screening [9]. When multiple tissue collections are possible at different sites of disease and/or time points during treatment and time of relapse, PDMCs enable the assessment of each tumor cell population contribution and studying the evolution of a tumor by evaluating synchronous metastases [10]. Despite tissue-specific requirements, it has been possible to establish different histological subtypes (*i.e.,* in lung cancer) and maintain primary tissue in culture during long-term expansion *in vitro*. Considering the short length of time from successful biobanking to drug testing, these models are proving to be useful for predicting patient-specific drug responses [11–13]. Overall, this shows the results of fruitful collaborative teams, further supporting this type of intra- and inter-institutional translational research program initiative.

We decided to build on these efforts and contribute to the field by gaining more information from human lung cancer specimens. Here, we introduce our lung cancer tissue living biobank that we established with the engagement of patients diagnosed with lung cancer and treated at our Institute. We launched the Lung Cancer Tissue Collection (LCTC) program in our national Scientific Institute for Research, Hospitalization, and Healthcare (IRCCS) with the support of our University, and crucial efforts of many teams within the Institute. Indeed, this program could have not been possible without the financial support of research foundations, highlighting the importance of the consistent support of funding agencies. From 24 months of active collection, we showed that our cohort recapitulated the clinical information represented in larger datasets. Importantly, all patients that were asked to be enrolled in our program agreed to sign the informed consent. This underlines the trust and support that patients and their families are willing to offer to clinicians and translational researchers.

Samples from lung adenocarcinoma -the most common subtype of NSCLC- in our cohort consisted of specimens from all stages of disease including early-stage tumors. Importantly, we are learning how adjuvant therapy can strikingly improve the outcomes in early settings as well [14]. Thus, translational research leveraging these samples will enable comprehensive profiling of early-stage tumors to glean information about tumor evolution and inform clinical follow-up strategies. So far, our collaboration enabled us to establish an institutional living biobank collection and set up a comprehensive toolset that covers a diverse spectrum of therapeutically relevant oncogenic drivers and non-oncogene addicted tumors. Functional studies and therapeutic testing of these unique settings will help us investigate genotype-specific vulnerabilities that could lead to identify novel therapeutic biomarkers. This new resource will also serve as a foundation for inter- and intra-collaborations that will be able to strengthen our impact in solid tumor research.

## Material and methods

### *Patient enrollment and collection workflow*

Owing to the tight collaboration of the Medical Oncology and Thoracic Surgery Departments, the Radiology Department and the Pathology Unit, we launched the institutional LCTC program to enroll patients diagnosed with lung cancer that are evaluated at the IRCCS San Raffaele Scientific Institute (Milan, Italy) and have their tumors analyzed by the Pathology Unit. Notably, this program allows us to collect tumor and adjacent non-tumor (peritumor) tissue when available -both selected by expert pathologists during intraoperative consultation session (*i.e.,* from therapeutic resections)- and, blood samples. Samples obtained for routine diagnostic or monitoring purposes are processed and stored by the institutional biobank Biological Resource Center (CRB-OSR; Fig. 1**A**). Importantly, the clinical information collected at the CRB-OSR are also made publicly available on Biobanking and BioMolecular Resources Infrastructure (BBMRI) at https://directory.bbmri-eric.eu/ERIC/directory/#/collection/bbmri-eric:ID:IT_1383758011993

577:collection:f3d9c80e23bc462?search=lctc and updated yearly [15]. Our prospective collection study is conducted following clinical practice and has been reviewed and approved by the Internal IRCCS San Raffaele Hospital Ethical Committee (protocol number 62/INT/2022) and subsequently by The Territoriale Lombardia 1 Ethical Committee (protocol number CET Em. 229–2025). Upon enrollment, patients are monitored through clinical follow ups to report any clinical activity including treatment, surgery, and occurrence of relapse. All procedures were performed as the standard of care and thus at the discretion of the treating physician and could have occurred at time of diagnosis or progression. According to clinical practice, patients were included if they had any stage of lung cancer and excluded when they had a different primary tumor than lung. Demographic data including sex and age at time of tumor collection are recorded during routine follow-up and were extracted in Table 1.

*Specimen processing and storage*

Tumor and peritumor tissue specimens are collected in a *transfer solution* which is composed by RPMI supplemented with 2 % penicillin/streptomycin (final concentration: 200 U/ml and 0.2 mg/ml, respectively) and 0.04 % Amphotericin B (0.1 μg/ml). When processed, viable tissue samples are stored in freezing media composed by 90 % fetal bovine serum and 10 % DMSO and stored at −80° for 24 h and then transferred to liquid nitrogen for long-term storage. Frozen tumor and peritumor tissues are stored at −80°. All specimens are selected and reviewed by the Pathologist for quality check. Paraffin-embedded specimens are available for routine histology and further investigation. Blood samples are collected in EDTA blood collection tube to prevent blood coagulation preserving cellular integrity and allowing plasma separation and PBMC isolation from whole blood using density-gradient centrifugation. Plasma samples and PBMCs, the latter transferred to freezing media, are stored in liquid nitrogen. Summary information regarding biological specimen that can be collected in LCTC together with numbers of vials that can be stored are reported in Table 2. 712 samples were collected between year 2022 and year 2024 under written informed consent in agreement with the Declaration of Helsinki. Collected specimens include viable tumor tissue (21 %), frozen tumor tissue (6 %), and frozen peritumor tissue (10 %) covering all stages of disease (Fig. 1**B** and **C**). Because of up to 5/6 aliquots could be retrieved from each patient blood withdrawal, peripheral blood mononuclear cells (PBMCs) and plasma samples represented the 28 % and 35 % of LCTC, respectively (Fig. 1**B**). All specimens are processed in compliance with UNI ISO 20,387:2019 Biotechnology –"Biobanking"– General requirements for biobanking and with GCP/GCLP standards.

## Results

*Heterogeneity of LCTC specimens recapitulates lung cancer statistics*

Lung cancer is the second most diagnosed cancer worldwide and remains the leading cause of cancer-related death [16]. NSCLC accounts for 85 % of the lung cancer cases while small cell lung cancer (SCLC) represents the remaining 15 %. NSCLC can be further histologically classified in adenocarcinoma (LUAD), squamous cell carcinoma (SCC), and other less common lung cancer histological subtypes such as large cell carcinoma (LCC), pulmonary pleomorphic carcinoma (PPC), and a recently characterized thoracic SMARCA4-deficient undifferentiated tumors. Among these tumor histologies, LUAD is the most common subtype representing 40–60 % of cases [16–18].

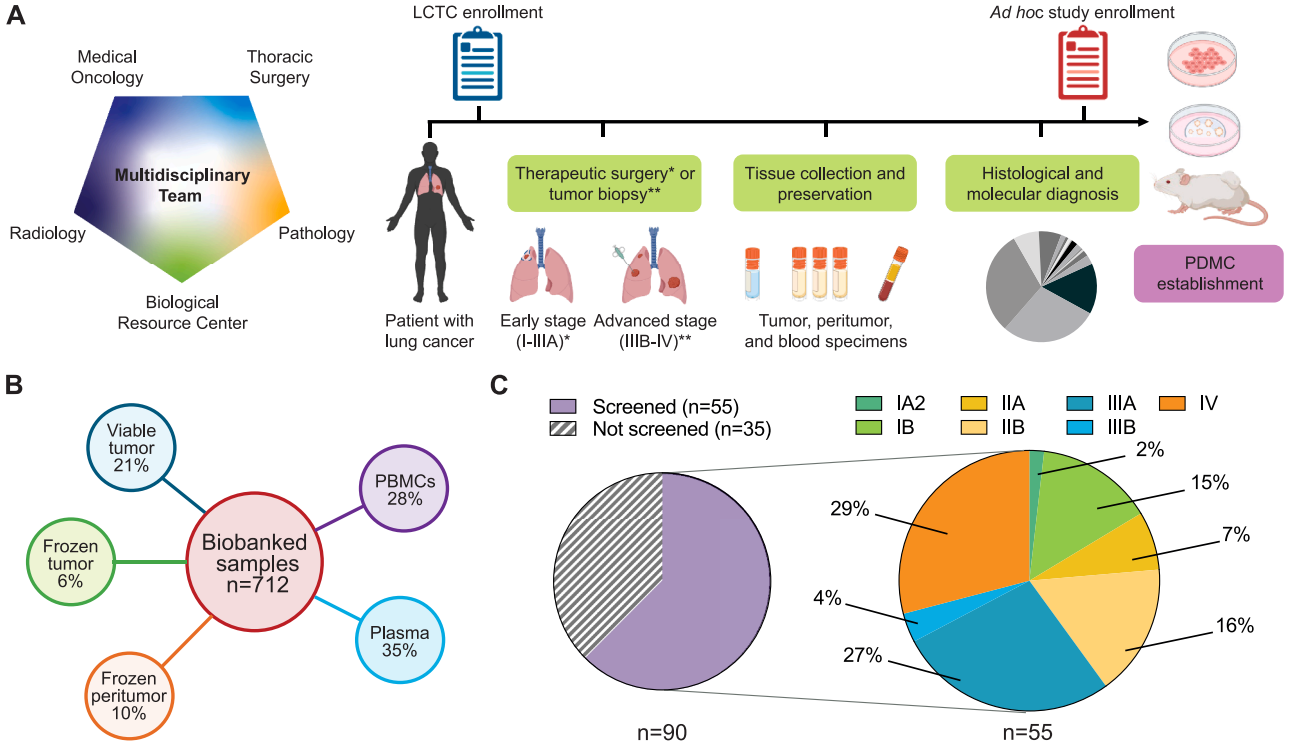


**Fig. 1. LCTC Overview. A.** Workflow and units involved in the LCTC program. Multidisciplinary team involved in this program includes the Medical Oncology including our laboratory, the Thoracic Surgery, and the Radiology Departments, the Pathology Unit and the Biological Resource Center (CRB-OSR). Patients diagnosed with lung cancer are enrolled by the Lung Disease Unit (within the Medical Oncology Department) or the Thoracic Surgery Department. After therapeutic surgery (I-IIIA)* or diagnostic tumor biopsy (IIIB-IV)**, the LCTC program allows the collection and cryopreservation of tumoral, adjacent non-tumor (peritumor), and blood samples at CRB-OSR. Following histological and molecular validation, tumor samples can be leveraged upon *ad hoc* study patient enrollment (*i.e.,* allowing PDMC generation). **B.** Samples collected in the LCTC biobank in 2 years. LCTC currently involves the storage of $n = 712$ biobanked samples including viable tumor tissue (21 %), frozen tumor tissue (6 %), frozen peritumor tissue (10 %), PBMCs (28 %) and plasma (35 %). **C.** LCTC molecularly screened lung adenocarcinomas ($n = 55/90$ total) displayed all stages of disease (from IA2 to IV) enabling translational research at different time points of tumor progression.

**Table 1**

**Patient Demographics.** Table summarizing information of patients enrolled in the LCTC cohort as patient age at tumor collection, type of procedure, and sex. Information about histology, oncogenic driver alteration, tumor stage, therapy and viable tissue availability of each relative tumor specimen collected in the LCTC program is also reported. (0 = not available, 1 = viable only, 2 = viable + frozen, 3 = frozen only). Treatment status at time of tumor/blood collection is also reported (0 = naïve, 1 = resistant, 2 = residual disease). Tissue and blood collections within six months are indicated by (+), whereas intervals > 6 months are indicated by (/).

| LCTC Code | Age at Collection | Sex | Procedure | Histology | Oncogenic Driver | Tumor Stage at Collection | Tissue Availability | Treatment naïve/ resistant |
|---|---|---|---|---|---|---|---|---|
| LCTC_001 | 67 | M | surgery | Adenocarcinoma | NRAS | IIB | 0 | 0 |
| LCTC_002 | 77 | F | surgery | Adenocarcinoma | not screened | IA2 | 3 | 0 |
| LCTC_003 | 57 | F | surgery | Adenocarcinoma | not screened | IA1 | 0 | 0 |
| LCTC_004 | 59 | F | surgery | Adenocarcinoma | KRAS | IIIA | 2 | 0 |
| LCTC_005 | 69 | M | surgery | Squamous cell carcinoma | not screened | IA2 | 1 | 0 |
| LCTC_006 | 73 | F | surgery | Adenocarcinoma | EGFR | IIIA | 2 | 0 |
| LCTC_007 | 44 | M | surgery | Squamous cell carcinoma | unknown driver | IIIC | 1 | 0 |
| LCTC_008 | 64 | F | surgery | Adenocarcinoma | KRAS | IIB | 1 | 0 |
| LCTC_009 | 76 | M | surgery | Adenocarcinoma | KRAS | IB | 1 | 0 |
| LCTC_010 | 78 | M | surgery | Adenocarcinoma | KRAS | IIIA | 1 | 0 |
| LCTC_011 | 71 | M | surgery | Adenocarcinoma | EGFR | IVA | 2 | 1 |
| LCTC_012 | 59 | F | surgery | Large cell carcinoma | not screened | IIIA | 2 | 0 |
| LCTC_013 | 65 | M | surgery | Other - colic adenocarcinoma metastasis | | | 0 | |
| LCTC_014 | 86 | M | surgery | Adenocarcinoma | unknown driver | IIIA | 2 | 0 |
| LCTC_015 | 71 | M | surgery | Other - colic adenocarcinoma metastasis | | | 2 | |
| LCTC_016 | 68 | M | surgery | Carcinoid | not screened | IA3 | 1 | 0 |
| LCTC_017 | 80 | M | surgery | Adenocarcinoma | unknown driver | IIIA | 0 | 0 |
| LCTC_018 | 58 | F | surgery | Adenocarcinoma | EGFR | IB | 2 | 0 |
| LCTC_019 | 77 | M | surgery | Adenocarcinoma | not screened | IA3 | 1 | 0 |
| LCTC_020 | 72 | F | surgery | Carcinoid | not screened | IA2 | 0 | 0 |
| LCTC_021 | | | surgery (postponed) | | | | | |
| LCTC_022 | 76 | F | surgery | Adenocarcinoma | not screened | IA2 | 0 | 0 |
| LCTC_023 | 68 | M | surgery | Adenocarcinoma | not screened | IA2 | 1 | 0 |
| LCTC_024 | 55 | F | surgery | Squamous cell carcinoma | not screened | IA2 | 1 | 0 |
| LCTC_025 | 54 | F | surgery | Squamous cell carcinoma | PIK3CA | IIB | 2 | 0 |
| LCTC_026 | 76 | F | biopsy | Squamous cell carcinoma | EGFR | IV | 0 | 1 |
| LCTC_027 | 68 | M | surgery | Adenocarcinoma | KRAS | IB | 1 | 0 |
| LCTC_028 | 70 | M | surgery | Adenocarcinoma | not screened | IA2 | 1 | 0 |
| LCTC_029 | 76 | F | surgery | Adeno-squamous carcinoma | not screened | IA3 | 1 | 0 |
| LCTC_030 | 70 | M | surgery | Adenocarcinoma | KRAS | IIA | 2 | 0 |
| LCTC_031 | 71 | M | surgery | Adenocarcinoma | not screened | IA3 | 1 | 0 |
| LCTC_032 | 69 | M | surgery | Adenocarcinoma | not screened | IA3 | 1 | 0 |
| LCTC_033 | 77 | M | surgery | Squamous cell carcinoma | PIK3CA | IIIA | 1 | 0 |
| LCTC_034 | 68 | M | surgery | Adenocarcinoma | unknown driver | IIA | 1 | 0 |
| LCTC_035 | 60 | M | surgery | Mucinous cystadenoma | not screened | not required | 0 | 0 |
| LCTC_036 | 78 | F | surgery | Adenocarcinoma | not screened | IA2 | 2 | 0 |
| LCTC_037 | 76 | M | surgery | Adenocarcinoma | not screened | TNx | 2 | 0 |
| LCTC_038 | 68 | M | surgery | Adenocarcinoma | CTNNB1 | IIB | 1 | 0 |
| LCTC_039 | 74 | F | surgery | Carcinoid | not screened | IIB | 1 | 0 |
| LCTC_040 | 82 | M | surgery | Adeno-squamous carcinoma | not screened | IIB | 2 | 0 |
| LCTC_041 | 66 | F | surgery | Adenocarcinoma | not screened | IA2 | 0 | 0 |
| LCTC_042 | 70 | M | biopsy | Adenocarcinoma | EGFR | IV | 0 | 1 |
| LCTC_043 | 56 | F | surgery | Adenocarcinoma | KRAS | IIIA | 1 | 0 |
| LCTC_044 | 57 | M | surgery | Adenocarcinoma | not screened | IIB | 2 | 0 |
| LCTC_045 | 77 | M | surgery | Other - colic adenocarcinoma metastasis | | | 0 | |
| LCTC_046 | 73 | M | biopsy + blood | Adenocarcinoma | EGFR | IV | 1 | 1 |
| LCTC_047 | 76 | M | surgery | Adenocarcinoma | not screened | IA2 | 0 | 0 |
| LCTC_048 | 79 | F | surgery | Adenocarcinoma | EGFR | IB | 2 | 0 |
| LCTC_049 | 74 | M | surgery | Squamous cell carcinoma | not screened | IA2 | 0 | 0 |
| LCTC_050 | 63 | F | surgery | Adenocarcinoma | not screened | IA1 | 0 | 0 |
| LCTC_051 | 76 | M | surgery/blood | Adenocarcinoma + Large cell carcinoma | KRAS | IV | 1 | 0 |
| LCTC_052 | 64 | M | biopsy | Small cell lung cancer | EGFR | IV | 0 | 1 |
| LCTC_053 | 77 | M | surgery | Adenocarcinoma | unknown driver | IB | 2 | 0 |
| LCTC_054 | 74 | F | surgery | Adenocarcinoma | unknown driver | IA2 | 2 | 0 |
| LCTC_055 | 85 | M | surgery | Other - chronic inflammation | | | 1 | |
| LCTC_056 | 63 | F | surgery | Adenocarcinoma | unknown driver | IIA | 2 | 0 |
| LCTC_057 | 81 | M | surgery | Adenocarcinoma | KRAS | IIB | 2 | 0 |
| LCTC_058 | 81 | M | surgery/blood | Adenocarcinoma | KRAS | IIB | 2 | 0 |

(*continued on next page*)

**Table 1** (*continued*)

| LCTC Code | Age at Collection | Sex | Procedure | Histology | Oncogenic Driver | Tumor Stage at Collection | Tissue Availability | Treatment naïve/ resistant |
|---|---|---|---|---|---|---|---|---|
| LCTC_059 | 47 | F | biopsy | Adenocarcinoma | EGFR | IV | 0 | 1 |
| LCTC_060 | 70 | F | surgery | Large cell carcinoma | unknown driver | IIB | 2 | 0 |
| LCTC_061 | 75 | M | surgery | Adenocarcinoma | not screened | TNx | 1 | 0 |
| LCTC_062 | 62 | F | surgery | Other - chronic inflammation | | | 0 | |
| LCTC_063 | 72 | M | surgery | Squamous cell carcinoma | not screened | IA3 | 2 | 0 |
| LCTC_064 | 59 | F | surgery | Adenocarcinoma | KRAS | IIIA | 1 | 0 |
| LCTC_065 | 73 | M | surgery | Adenocarcinoma | NRAS | IIIB | 2 | 0 |
| LCTC_066 | 64 | F | biopsy + blood | Adenocarcinoma | EGFR | IV | 0 | 1 |
| LCTC_067 | 77 | F | surgery | Adenocarcinoma | EGFR | IIB | 0 | 0 |
| LCTC_068 | 54 | F | surgery | Adenocarcinoma | unknown driver | IB | 0 | 0 |
| LCTC_069 | 55 | F | biopsy + blood | Adenocarcinoma | EGFR | IV | 0 | 1 |
| LCTC_070 | 74 | M | surgery | Adenocarcinoma | unknown driver | IVA | 1 | 0 |
| LCTC_071 | 78 | F | surgery | Carcinoid | not screened | TNx | 2 | 0 |
| LCTC_072 | 73 | M | surgery | Adenocarcinoma | KRAS | IIIA | 2 | 0 |
| LCTC_073 | 43 | F | surgery | Adenocarcinoma | not screened | IA3 | 1 | 0 |
| LCTC_074 | 80 | M | surgery | Squamous cell carcinoma | unknown driver | IIB | 1 | 0 |
| LCTC_075 | 53 | M | surgery | Carcinoid | not screened | IIB | 1 | 0 |
| LCTC_076 | 68 | F | surgery | Carcinoid | not screened | IA2 | 0 | 0 |
| LCTC_077 | 72 | M | blood | Adenocarcinoma | WT | IV | 0 | 0 |
| LCTC_078 | 78 | F | surgery | Adenocarcinoma | not screened | IA3 | 1 | 0 |
| LCTC_079 | 75 | M | surgery | Squamous cell carcinoma | unknown driver | IIB | 2 | 0 |
| LCTC_080 | | | surgery (postponed) | | | | | |
| LCTC_081 | 55 | M | surgery | Adenocarcinoma | unknown driver | IVA | 0 | 0 |
| LCTC_082 | 75 | M | blood (not collected) | Squamous cell carcinoma | WT | IV | 0 | 0 |
| LCTC_083 | 78 | F | blood (not collected) | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_084 | 79 | F | blood (not collected) | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_085 | 61 | M | surgery | Pleomorphic carcinoma | KRAS | IIIB | 2 | 0 |
| LCTC_086 | 70 | M | surgery | Adenocarcinoma | EGFR | IIIA | 0 | 0 |
| LCTC_087 | 57 | M | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_088 | 83 | F | surgery | Other - ovaric carcinoma metastasis | | | 0 | |
| LCTC_089 | 78 | M | surgery | Adenocarcinoma | KRAS | IB | 0 | 0 |
| LCTC_090 | 82 | M | biopsy + blood | Squamous cell carcinoma | not screened | IIIA | 1 | 0 |
| LCTC_091 | 79 | M | surgery | Adenocarcinoma | not screened | IA2 | 0 | 0 |
| LCTC_092 | 62 | M | surgery | Adenocarcinoma | not screened | IA2 | 0 | 0 |
| LCTC_093 | 77 | M | surgery | Other - fibro-necrotic nodule | | | 0 | |
| LCTC_094 | 87 | M | surgery | Pleomorphic carcinoma | KRAS | IIIA | 2 | 0 |
| LCTC_095 | 63 | M | surgery | Adenocarcinoma | EGFR | IIIA | 2 | 0 |
| LCTC_096 | 78 | M | surgery | Adenocarcinoma | not screened | IB | 2 | 0 |
| LCTC_097 | 76 | M | surgery | Adenocarcinoma | unknown driver | IIIA | 2 | 0 |
| LCTC_098 | 55 | F | surgery | Adenocarcinoma | unknown driver | IIIA | 2 | 0 |
| LCTC_099 | 75 | M | surgery | Other - chronic inflammation | | | 0 | |
| LCTC_100 | 77 | F | surgery | Tumorlet | not screened | not required | 0 | 0 |
| LCTC_101 | 82 | F | surgery | Adenocarcinoma | not screened | IA | 0 | 0 |
| LCTC_102 | 80 | M | surgery | Pleomorphic carcinoma + adenocarcinoma | unknown driver | IB | 0 | 0 |
| LCTC_103 | 69 | M | biopsy | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_104 | 62 | F | surgery | Adeno-squamous carcinoma | unknown driver | IIB | 2 | 0 |
| LCTC_105 | 66 | F | surgery | Other - melanoma metastasis | | | 2 | |
| LCTC_106 | 88 | M | surgery | Adenocarcinoma | unknown driver | IIIA | 0 | 0 |
| LCTC_107 | 71 | M | surgery | Tumorlet | not screened | not required | 0 | 0 |
| LCTC_108 | 64 | F | surgery | Adenocarcinoma | KRAS | IIIA | 0 | 0 |
| LCTC_109 | 63 | M | surgery | Large cell carcinoma | not screened | IA3 | 1 | 0 |
| LCTC_110 | 86 | M | surgery | Adenocarcinoma | not screened | IB | 1 | 0 |
| LCTC_111 | 65 | F | biopsy | Adenocarcinoma | EGFR | IV | 2 | 1 |
| LCTC_112 | 59 | M | surgery | Adenocarcinoma | KRAS | IIIB | 2 | 0 |
| LCTC_113 | 76 | M | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_114 | 78 | F | surgery | Adenocarcinoma | not screened | IB | 0 | 0 |
| LCTC_115 | 50 | F | surgery | Other - chronic inflammation | | | 0 | |
| LCTC_116 | 58 | F | surgery | Adenocarcinoma | not screened | IA2 | 1 | 0 |

(*continued on next page*)

**Table 1** (*continued*)

| LCTC Code | Age at Collection | Sex | Procedure | Histology | Oncogenic Driver | Tumor Stage at Collection | Tissue Availability | Treatment naïve/ resistant |
|---|---|---|---|---|---|---|---|---|
| LCTC_117 | 75 | M | blood | Squamous cell carcinoma | not screened | IIIA | 0 | 0 |
| LCTC_118 | 81 | M | biopsy + blood | Adenocarcinoma | EGFR | IV | 0 | 0 |
| LCTC_119 | 60 | F | surgery | Adenocarcinoma | not screened | IB | 0 | 0 |
| LCTC_120 | 52 | F | surgery | Adenocarcinoma | EGFR | IIB | 2 | 0 |
| LCTC_121 | 53 | M | biopsy + blood | Adenocarcinoma | ALK | IV | 1 | 1 |
| LCTC_122 | 69 | F | biopsy + blood | Adenocarcinoma | EGFR | IV | 1 | 1 |
| LCTC_123 | 67 | M | surgery | Adenocarcinoma | KRAS | IIB | 1 | 0 |
| LCTC_124 | 68 | M | surgery | Adeno-squamous carcinoma | unknown driver | IIA | 0 | 0 |
| LCTC_125 | 31 | F | biopsy + blood | Adenocarcinoma | ALK | IV | 3 | 1 |
| LCTC_126 | 74 | M | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_127 | 48 | M | surgery | Other - chronic inflammation | | | 0 | |
| LCTC_128 | 66 | M | surgery | Adenocarcinoma | not screened | IB | 0 | 0 |
| LCTC_129 | 77 | M | biopsy + blood | Adenocarcinoma | EGFR | IV | 1 | 1 |
| LCTC_130 | 84 | F | blood | Adenocarcinoma | KRAS | IIIB | 0 | 0 |
| LCTC_131 | 68 | F | surgery/blood | Squamous cell carcinoma | unknown driver | IIIB | 1 | 2 |
| LCTC_132 | 28 | M | surgery | Carcinoid | not screened | IB | 2 | 0 |
| LCTC_133 | 81 | M | surgery | Adenocarcinoma | not screened | IA2 | 1 | 0 |
| LCTC_134 | 73 | M | biopsy | Adenocarcinoma | KRAS | IIIA | 0 | 0 |
| LCTC_135 | 67 | M | blood | Adenocarcinoma | KRAS | IIB | 0 | 0 |
| LCTC_136 | 49 | F | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_137 | 73 | M | blood | Squamous cell carcinoma | not screened | IV | 0 | 0 |
| LCTC_138 | 73 | M | surgery | Adenocarcinoma | not screened | IB | 1 | 0 |
| LCTC_139 | 72 | F | surgery | Adenocarcinoma | not screened | IA1 | 0 | 0 |
| LCTC_140 | 64 | M | blood | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_141 | 76 | M | blood | Adenocarcinoma | KRAS | IIIA | 0 | 0 |
| LCTC_142 | 70 | F | surgery | Adenocarcinoma | not screened | IB | 2 | 0 |
| LCTC_143 | 71 | M | blood | Adenocarcinoma | KRAS | IIIA | 0 | 0 |
| LCTC_144 | 37 | F | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_145 | 77 | M | blood | Squamous cell carcinoma | KRAS | IV | 0 | 0 |
| LCTC_146 | 66 | F | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_147 | 67 | F | surgery | Adenocarcinoma | not screened | IB | 0 | 0 |
| LCTC_148 | 55 | F | blood | Adenocarcinoma | KRAS | IIIA | 0 | 0 |
| LCTC_149 | 71 | M | blood | Adenocarcinoma | unknown driver | IIIC | 0 | 0 |
| LCTC_150 | 74 | F | surgery | Adenocarcinoma | not screened | IA1 | 0 | 0 |
| LCTC_151 | 85 | M | blood | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_152 | 65 | M | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_153 | 73 | M | blood | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_154 | 68 | M | surgery | Adenocarcinoma | not screened | IA3 | 2 | 0 |
| LCTC_155 | 65 | M | blood | Adenocarcinoma | unknown driver | IV | 0 | 0 |
| LCTC_156 | 73 | M | blood | Adenocarcinoma | unknown driver | IIIB/C | 0 | 0 |
| LCTC_157 | 60 | F | blood | Adenocarcinoma | KRAS | IV | 0 | 0 |
| LCTC_158 | 81 | M | blood | Adenocarcinoma | KRAS | IIIB | 0 | 0 |

**Table 2**

**Specimen Collection, Processing, and Storage.** Information related to type of tissue, timepoint and method of collection, and transfer, processing, and storage condition for each type of specimen is reported in the table. The maximum number of vials and their content for each specimen type are also indicated. All specimens are processed by our institutional CRB-OSR in compliance with UNI ISO 20,387:2019 and GCP/GCLP standards.

| Biological Specimen | Type of Tissue | Transfer Solution | Type of Storage | Storage Condition | Timepoint of Collection | Aliquots (n) | Quantity/ vial |
|---|---|---|---|---|---|---|---|
| Tissue | Tumor | RPMI+2 % Penicillin/ streptomycin+0.04 % Amphothericin B | Viable | 90 % FBS + 10 % DMSO; Liquid nitrogen | Baseline, Progression | 3 | case-specific |
| Tissue | Tumor | RPMI+2 % Penicillin/ streptomycin+0.04 % Amphothericin B | Frozen | −80° | Baseline, Progression | 3 | case-specific |
| Tissue | Peritumor | RPMI+2 % Penicillin/ streptomycin+0.04 % Amphothericin B | Frozen | −80° | Baseline, Progression | 3 | case-specific |
| Blood | Plasma | EDTA blood collection Tube | Frozen | Liquid nitrogen | Baseline, First treatment evaluation, Progression | 6 | 2 ml |
| Blood | PBMC | EDTA blood collection Tube | Viable | 90 % FBS + 10 % DMSO; Liquid nitrogen | Baseline, First treatment evaluation, Progression | 5 | $10 \times 10^{\wedge}6$ cells |

We spearheaded the generation of a comprehensive repository at our Institute to collect samples and data from lung tumor patients before and after treatment with any therapy. In 24 months, we collected tumor specimens from patients diagnosed with oncogene- and non-oncogene-addicted lung cancer. Importantly, out of the 158 patients enrolled in LCTC and underwent surgery or biopsy, 76 % of cases displayed a LUAD histotype, reflecting the histological frequency reported in publicly available human datasets (Fig. 2**A**). Other histological subtypes found in our cohort include SCC (10 %), carcinoid (6 %), LCC (3 %), pleomorphic carcinoma (2 %), tumorlet (2 %) and mucinous cystadenoma (1 %). Among these, the LCTC achieved a 64 % success rate in collecting and cryopreserving tumor specimens. This rate reflects the limited availability of excess tissue from diagnostic biopsies and the increasing use of minimally invasive robotic surgeries, which involves the resection of small early-stage tumors.

*Leveraging viable human specimens for translational research*

Tumor molecular diagnostic assessment through advanced next-generation sequencing panels allows the detection of the most frequent oncogenic alterations in LUAD (*e.g., KRAS, EGFR, BRAF, ALK*) guiding the selection of the standard therapeutic approach approved for clinical practice [18,19]. In the LCTC cohort, we found oncogenic alterations in *KRAS* and *EGFR* in 35 (38 %) and 19 (21 %) tumors for each driver, respectively (Table 1). These data are in agreement with the alteration frequencies reported in publicly available human datasets [20]. Importantly, our cohort is composed of human specimens including early-stage disease for which surgery represents the gold standard therapy (Fig. 1**C**). Clinical trials are showing a striking benefit for patients who are treated in the adjuvant setting with targeted therapy when an oncogenic driver such as mutant EGFR is found at diagnosis [14,21]. Thus, leveraging human specimens from early-stage tumors in the laboratory has become relevant to study mechanisms guiding tumor biology, investigate tumor evolution, and predict therapeutic response in case of relapse [22].

Immune checkpoint inhibitors that enhance anti-tumor immunity are now a cornerstone of systemic therapy for advanced NSCLC [4,18,23]. Importantly, PDMCs like organoids growing in three-dimensional

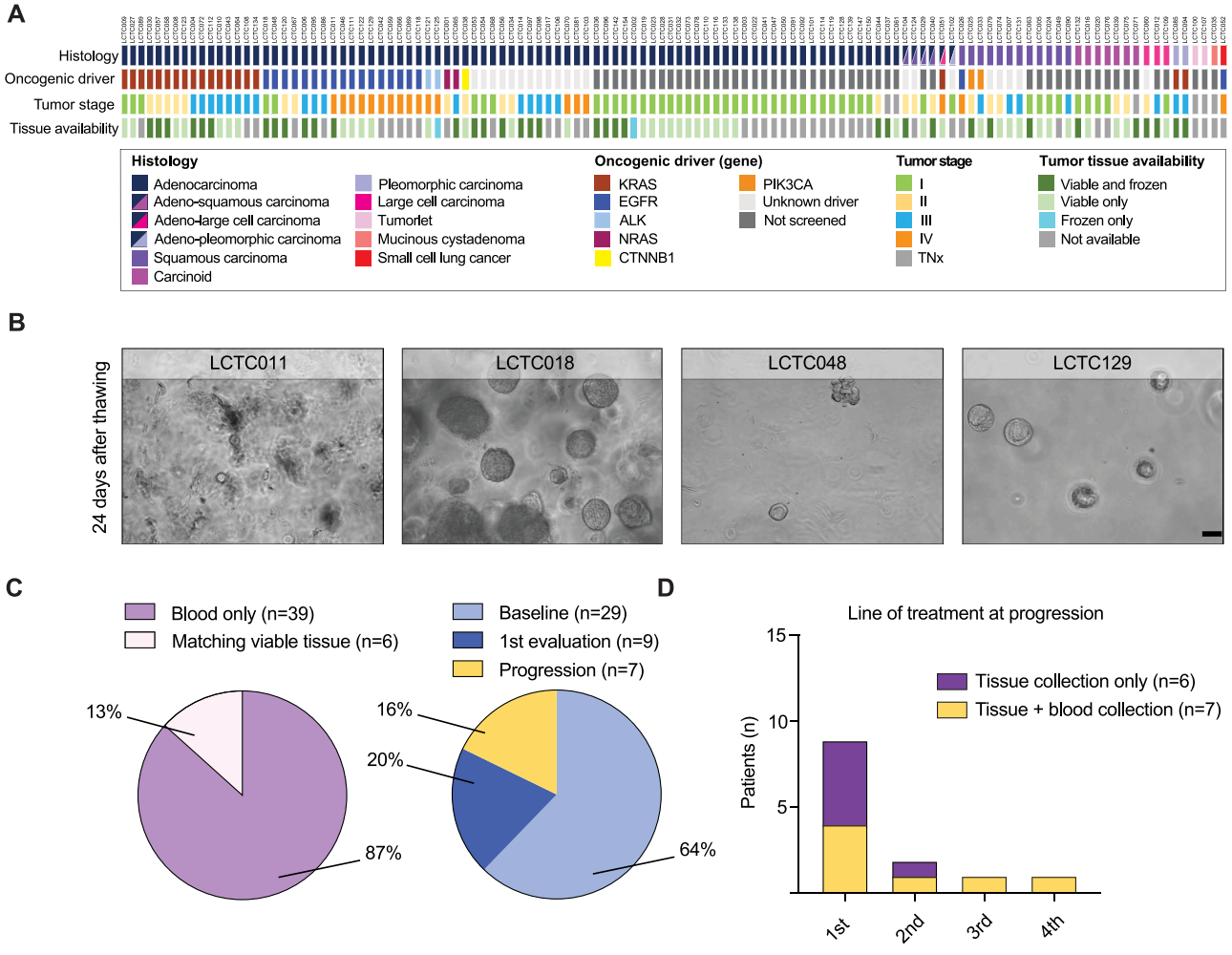


**Fig. 2. Tissue and Blood Specimen Availability and Characteristics. A.** LCTC oncoprint summarizing information about histology, oncogenic driver alteration, and tumor stage of each tumor sample from patients enrolled in LCTC for tissue collection ($n = 118$). If specimen was collected, information on viable and/or frozen tissue availability at CRB-OSR is reported. Sample information about tumor specimens from second surgeries ($n = 5$), collection attempted from different histology than lung cancer ($n = 11$), cases enrolled for blood collection only ($n = 27$), and cases of postponed surgery ($n = 2$) are not reported in the oncoprint. TNx = lymph nodes could not be measured. **B.** Patient-derived organoids at 24 days of culture. Representative images showing patient-derived organoids obtained from 4 cryopreserved tumor tissues stored at CRB-OSR, dissociated into single cells, and grown in 3D conditions (scale bar: 50μm). **C.** Information about blood collection in LCTC. 45 blood specimens were collected and 6 matched tissue samples ($n = 1$ frozen only) stored in CRB-OSR (left panel). Blood can be collected at different time points along the course of treatment or monitoring (*i.e.,* baseline, first evaluation, and progression; right panel). **D.** Histogram reporting line of treatment for patient samples collected at progression (tissue samples are indicated in purple while tissue + blood samples are in yellow). Number of total samples collected at progression in LCTC ($n = 13$).

(3D) conditions are more amenable to heterogeneous co-culture experiments for exploring tumor behaviors, including modeling tumor-immune interactions *in vitro* [23,24]. Importantly, we used 7 human tumor specimens retrieved from CRB-OSR to generate PDMCs and obtained a 60 % success rate, as measured by patient-derived organoids growing at 24 days of 3D culture after tissue thawing and processing (Fig. 2**B**). Our collection of blood samples includes storing viable PBMCs that can be leveraged for autologous co-culture assays with tumor organoids [25] allowing investigators to evaluate whether *in vitro* system matches clinical findings. Furthermore, these systems could be used to test the efficacy of combining immunotherapy with molecules that target pathways that are found to be enriched in the non-responders group. Ideally, blood specimens can be more easily collected at different time points along the course of treatment and monitoring thus granting investigators to set up *in vitro* models of tumor evolution across progression and therapy. As of today, we also collected and successfully stored 45 blood specimens including three time points (baseline, 1st evaluation, and progression at 1st or multiple line of therapy) and 13 % of these have matching viable tumor tissue stored in our biobank (Fig. 2**C** and **D**). Expanding this sample collection will support future studies to identify and detect novel tumor biomarkers that have the potential of being introduced in the clinic.

## Discussion

Cryopreserved tissue samples represent a valuable resource to study molecular mechanisms that can help predict tumor evolution and track response to available therapeutic approaches. To our knowledge, LCTC is one of the few publicly reported biobanks containing viable lung cancer tissue and blood samples, as most existing resources consist of frozen and/or formalin-fixed paraffin-embedded (FFPE) human specimens (Table 3). Through our LCTC program, we successfully established a lung cancer tissue biobank thanks to the active participation of patients and the cooperation of a multidisciplinary team. Indeed, LCTC is the result of a committed partnership and dedication of clinicians, researchers, data managers and patients and their families to develop a clinically meaningful institutional repository of unique specimens and data. Optimizing this type of study will further improve our way to understand lung cancer evolutionary processes and provide information to identify novel tumor specific vulnerabilities. Thus, large-scale longitudinal genomic and functional studies may become a central component to the delivery of precision cancer medicine.

When lung tumors are diagnosed at early stages and curative-intent surgery is performed, the addition of targeted therapy in the adjuvant setting has shown a striking impact in further delaying the occurrence of relapse [3]. A key example of this in lung cancer is represented by osimertinib treatment; it indeed revolutionized the outcome of patients with mutant EGFR lung cancer also as an adjuvant therapy (with or without post-operative chemotherapy) for surgically resected tumor stage IB to IIIA NSCLC, showing a OS greater than placebo (ADAURA trial) [14,26]. More recently, the LAURA trial showed that osimertinib significantly improved progression-free survival in patients with unresectable stage III mutant EGFR NSCLC following chemo-radiotherapy, compared to placebo [27]. These trials underscore the clinical benefit of targeted therapy at different stages of NSCLC, particularly in tumors harboring actionable mutations. However, cellular processes mediating a differential response to therapy or promoting resistance to therapy may limit long-term clinical benefits. Therefore, there is an increasing need to perform comprehensive molecular profiling of tumors at all stages of disease.

Collecting and storing patient-derived tissue samples offer the invaluable opportunity to gain insights in cancer evolutionary processes and observe tumor behavior in response to different therapeutic strategies. Leveraging PDMCs that accurately recapitulate the complexity of human tumors can contribute to investigate determinants of reduced drug response and define novel therapeutic targets [11]. Using commercial cell lines grown in two-dimensional (2D) conditions or *in vivo* studies can fail in achieving human tumor complexity. In contrast, PDMCs better preserve tumor heterogeneity allowing the validation of genotype-drug response associations and testing novel therapies, thereby informing clinical trial development aimed at extending OS and improving patient quality of life. LCTC was conceptualized to gather a multidisciplinary team and support this type of studies. More broadly, precision medicine-oriented initiatives like LCTC constitute a step forward in closing the gap between molecular profiling and clinical applications. By integrating translational research with clinical practice, these programs have the potential to accelerate the development of targeted therapies tailored to distinct subsets of tumors.

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## CRediT authorship contribution statement

**Virginia Guzzeloni:** Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Alessandra Bartolucci:** Writing – review & editing, Resources. **Samuele Valci:** Writing – review & editing, Validation. **Federica Pedica:** Writing –

**Table 3**
**Available Lung Cancer Tissue Biobanks.** Summary of existing literature reporting lung cancer tissue and blood biobanks. Notably, most resources consist of frozen human specimens.

| Reference | Study | Inclusion Criteria | Samples (n) | Tumor Tissue Collection | Blood Collection | Viable Tissue Availability | Additional Collection |
|---|---|---|---|---|---|---|---|
| [28] | Li et al. J Thorac Dis, 2009 | Lung cancer (NSCLC + SCLC) | 1054 cases, 20,356 biological samples | FFPE | plasma/serum, PBMC | No | |
| [29] | Yu et al. Thorac Cancer, 2015 | Lung cancer (NSCLC + SCLC) | 2000 cases, 100,000 biological samples | Frozen, FFPE | plasma/serum, buffycoat | No | |
| [30] | Washetine *et al.* Cancers, 2018 | Lung cancer (NSCLC + SCLC) | 3798 enrolled patients | Frozen, FFPE, | whole blood, plasma, serum, PBMC | No | |
| [31] | Wessels et al. Transl Lung Cancer Res, 2020 | IIIB-IV NSCLC | 183 enrolled patients | FFPE | plasma/serum | No | |
| [32] | Ceker *et al.* Turk J Biol, 2024 | Stage I-IIIA NSCLC, treatment naïve | 237 enrolled patients | Frozen, Viable | plasma/serum | Yes | urine, saliva, sputum, bronchoalveolar lavage, stool and exoxomes |

review & editing, Resources. **Pierluigi Novellis:** Writing – review & editing, Resources. **Piergiorgio Muriana:** Writing – review & editing, Resources. **Francesca Rita Ogliari:** Writing – review & editing, Resources. **Silvia Teresa Riva:** Writing – review & editing, Resources. **Nerina Shahi:** Writing – review & editing. **Arianna Limongelli:** Writing – review & editing. **Laura Bettini:** Writing – review & editing. **Francesca Rossetti:** Writing – review & editing, Resources. **Stefano Viscardi:** Writing – review & editing, Resources. **Carlo Di Giovannantonio:** Writing – review & editing, Resources. **Francesca Misceo:** Writing – review & editing, Resources. **Cinzia Scala:** Writing – review & editing, Resources. **Riccardo Di Fonzo:** Writing – review & editing, Resources. **Alberto Antonicelli:** Writing – review & editing, Resources. **Alessandro Bandiera:** Writing – review & editing, Resources. **Martina Bellantoni:** Writing – review & editing, Resources. **Simona De Santis:** Writing – review & editing, Resources. **Elisa Dieci:** Writing – review & editing, Data curation. **Angelo Carretta:** Writing – review & editing, Resources. **Paola Ciriaco:** Writing – review & editing, Resources. **Pau Mateo-Ramos:** Writing – review & editing, Resources. **Maria Giulia Cangi:** Writing – review & editing, Resources. **Emanuela Brunetto:** Writing – review & editing, Resources. **Lorenza Pecciarini:** Writing – review & editing, Resources. **Gilda Magliacane:** Writing – review & editing, Resources. **Gianluigi Arrigoni:** Writing – review & editing, Resources. **Claudio Doglioni:** Writing – review & editing, Resources. **Roberto Ferrara:** Writing – review & editing, Resources. **Sara Oresti:** Writing – review & editing, Resources. **Maria Grazia Viganò:** Writing – review & editing, Resources. **Antonio Nuccio:** Writing – review & editing, Resources. **Francesco Maria Venanzi:** Writing – review & editing, Resources. **Ludovica Mollica:** Writing – review & editing, Resources. **Giuseppe Damiano:** Writing – review & editing. **Elena Brioschi:** Writing – review & editing. **Michele Ferrara:** Writing – review & editing, Data curation. **Sara Guarnieri:** Writing – review & editing, Data curation. **Giacomo Lampertico:** Writing – review & editing, Data curation. **Nicola Fogale:** Writing – review & editing. **Michele Colombo:** Writing – review & editing, Resources. **Diego Palumbo:** Writing – review & editing, Resources. **Domenico Ghio:** Writing – review & editing, Resources. **Francesco De Cobelli:** Writing – review & editing. **Maurilio Ponzoni:** Writing – review & editing. **Giampiero Negri:** Writing – review & editing. **Michele Reni:** Writing – review & editing. **Alessandra Bulotta:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Giulia Veronesi:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Giorgia Foggetti:** Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

## Declaration of competing interest

V.G. has no disclosures; A.B. (Bartolucci) has no disclosures; S.V. (Valci) has no disclosures; F.P. has no disclosures; P.N. has no disclosures; P.M. has no disclosures; F.R.O. has been speaker for Roche, Amgen, and Sanofi; S.T.R has received payment honoraria for presentation from BMS and support for attending meeting from MSD, Amgen, and Daiichi Sankyo; N.S. has no disclosures; A.L. has no disclosures; L.B. has no disclosures; F.R. has no disclosures; S.V. (Viscardi) has no disclosures; C.D. (Di Giovannantonio) has no disclosures; F.M. has no disclosures; C.S. has no disclosures; R.D.F. has no disclosures; A.A. has no disclosures; A.B. (Bandiera) has no disclosures; M.B. has no disclosures; S.D.S. has no disclosures; E.D. has no disclosures; A.C. has no disclosures, P.C. has no disclosures; P.M.R has no disclosures; M.G.C. has no disclosures; E.B. (Brunetto) has no disclosures; L.P. has no disclosures; G.M. has no disclosures; G.A. has no disclosures; C.D. (Doglioni) has no disclosures; R.F. has received consulting fees from: MSD, Beigene, and AstraZeneca, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from: AstraZeneca and support for attending meetings and/or travel from: MSD; S.O. has no disclosures; M.G.V. has no disclosures; A.N. has no disclosures; F.M.V. has no disclosures; L.M. has no disclosures; G.D. has no disclosures; E.B. (Brioschi) has no disclosures; M.F. has no disclosures; S.G. has no disclosures; L.G. has no disclosures; N.F. has no disclosures; M.C. has no disclosures, D.P. has no disclosures; D.G. has no disclosures; F.D.C. has no disclosures; M.P. has no disclosures; G.N. has no disclosures; R.M. has received advisory board fees from LeoPharma, Viatris, and BMS and research funding from AstraZeneca; A.B. (Bulotta) has received consulting fees from: Roche, BMS, and AstraZeneca, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from: BMS, MSD, AstraZeneca and Eli Lilly; G.V. has received personal fees as a speaker and/or as an advisory board member from Roche, AstraZeneca, and MSD all outside the submitted work; G.F. has no disclosures.

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