# Gemini-NSCLC Study - Integrated Longitudinal Multi-Omic Biomarker Profiling of Non-Small Cell Lung Cancer (NSCLC) Patients

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## INTRODUCTION

- Lung cancer is the global leading cause of cancer deaths. Despite treatment advances, NSCLC outcomes remain poor.
- The molecular landscape of NSCLC has identified various subtypes allowing targeted therapies, but some tumors lack a biomarker-directed therapy. For these patients, agnostic IO in first-line represents the standard of care, but no known biomarkers of IO response or resistance are currently available.
- **Identifying improved surrogates of immunotherapy (IO) response is key to stopping ineffective treatments and empowering patients to switch therapies more rapidly.** Combining next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) technologies with high-resolution multi-omic data may revolutionize NSCLC management by enabling non-invasive monitoring, personalized treatment strategies, and the development of next-generation therapies to improve patient outcomes.

## ENDPOINTS

- For **Cohort 1 (Resectable),** the primary endpoint is real-world disease-free survival (rwDFS).
  - Secondary endpoints include pathologic complete response (pCR) rate, and real-world overall survival (rwOS) stratified by ctDNA status.
  - Molecular endpoints include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of minimal residual disease (MRD) assay vs. conventional imaging.
- For **Cohort 2 (Metastatic),** the primary endpoint is rwOS, with rwPFS as a secondary endpoint.
  - Molecular endpoints include description of evolving genomic variants as resistance mechanisms.

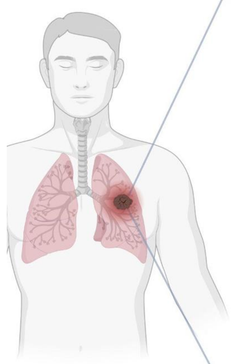
## METHODS

- The **Gemini-NSCLC Study** is a multicenter, real-world observational study profiling patients with NSCLC undergoing IO standard-of-care (SOC) therapy.
- **Cohort 1 (Resectable)** includes patients with early-stage disease treated with curative intent therapies.
- **Cohort 2 (Metastatic)** includes patients with late-stage disease receiving first-line IO excluding those with targetable genomic drivers.
- Patients will have blood and tissue collected at study entry and longitudinally. They will undergo testing with DNA and RNA sequencing and novel assays, including baseline spatial transcriptomic profiling, serial tumor-informed ctDNA profiling, and scRNA sequencing with T Cell receptor seq of peripheral immune cells.
- All patients will be assessed with cohort-relevant real-world endpoints, allowing correlation with longitudinal multi-omic data for biomarker discovery. Information from novel multi-omic assays will be descriptive and hypothesis-generating. Patients in Cohort 1 will be followed until recurrence or five years post-therapy. Patients in whom disease recurs may roll over to C2 for continued data collection.

## STUDY STATUS

The study is currently open at 53/60 US sites to comprise a mix of both community and academic sites.

| Accruals | To Date: | Target |
|---|---|---|
| **Cohort 1** Resectable | 80 | 500 |
| **Cohort 2** Metastatic | 96 | 700 |



| | Target Accrual: 500 | Target Accrual: 700 |
|---|---|---|
| | **Cohort 1** | **Cohort 2** |
| **Inclusion** | Newly diagnosed resectable early stage NSCLC (stage II-IIIB) with neoadjuvant, adjuvant or perioperative IO mono or combination therapy intention<br><br>EGFR/ALK WT | Stage IV NSCLC in the first line metastatic setting<br><br>EGFR/ALK WT<br><br>Patients intended to receive 1L mono or combination IO |
| **Exclusion** | Exclude patients with another malignancy within <2 years | Exclude patients with another malignancy within <2 years |
| **Primary endpoint** | Real-world disease-free survival (rwDFS) | rwOS |
| **Secondary Endpoint** | pathologic complete response (pCR) rate and real-world overall survival (rwOS) stratified by ctDNA status | rwPFS |

| | ID Pharmacodynamic Biomarkers | | ID Predictive Biomarkers | | | |
|---|---|---|---|---|---|---|
| | **ctDNA** | **single cell RNAseq** | **Global and targeted protomics, IHC** | **Tissue H&E segmentation** | **Tissue spatial transcriptomics** | **Tissue xT xR assays** |
| Rationale | **Surrogate of PDx response**: identify patients who are most likely to respond or progress to SoC IO/IO +chemo. Categorize patients into RECIST-like groups, e.g. CR, PR, SD, PD. | **IO PD and benchmark for IO bispec**: determine longitudinal correlatives of response and resistance to PDx SoC. Utilze the dataset to benchmark IO studies | **Target ID and Prevalence**: inform novel drug targets in IO-resistant/ histopathology groups. Inform future IO-combos and/or novel drug developments | **MoR and patient selection**: inform mechanisms of IO/IO +chemo resistance, identify predictive imaging-based correlatives of response to inform patient selections strategy | **MoR and patient selection**: inform mechanisms of IO/IO +chemo resistance, identify predictive stratified gene expression and cell neighborhood correlatives of response to inform patient selection strategy | **MoR and patient selection**: inform genomics correlatives of IO/IO+chemo resistance and response to inform patient selections strategy |
| Outcome | ctDNA longitudinal changes will be compared to clinical RWD outcomes like PFS, OS to assess its utility as a response proxy and benchmark ctDNA for AZ NSCLC studies. | scRNA longitudinal changes will be compared to clinical RWD outcomes like PFS, OS and ctDNA-defined surrogates of response like CR/PR/ SD/PD. Potential to benchmark PD for IO-based therapies in NSCLC | Prevalance of each target will be contrasted against clinical outcomes, PFS/ OS and stratas based on ctDNA. Morphological groups will also be used for stratification | Each segmentation H&E group will be contrasted against clinical outcomes, PFS/ OS and stratas based on ctDNA. Morphological groups will also be used for stratification | Features collected from STx will be contrasted against clinical outcomes, PFS/OS and stratas based on ctDNA. Morphological groups will also be used for stratification | Genomics and expression bulk features will be contrasted against clinical outcomes, PFS/ OS and non-response group based on ctDNA. Morphological groups will also be used for stratification |

**Digital Spatial Profiling: Description of Immune Composition**

**Figure 1.** H&E Annotated Tumor Area

**Figure 2.** Predicted Cancer Cells

**Figure 3.** Inflamed Case

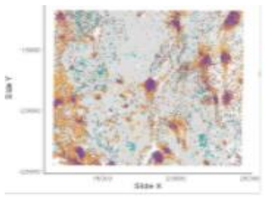
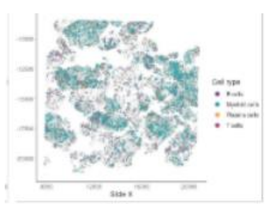


**Figure 4.** Non-Inflamed Case



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