

Introduction:

- **NSCLC remains a leading cause of cancer mortality**, with therapeutic resistance limiting durable treatment responses^{1,2}.
- **Patient-derived organoids (PDOs)** preserve many histologic, genomic, and transcriptomic features of their tumors and support personalized drug selection³.
- Clinical implementation remains challenging due to **variable culture methods, drug-exposure selection, and limited prospective validation**.
- Integrating **multiomic profiling with functional drug testing** may improve therapy selection for actionable drivers such as **ALK, EGFR, and KRAS**.
- **MyOncoPM** is a precision-medicine platform using minimally cultured NSCLC PDOs, molecular characterization, and PK-informed drug screening.
- This study evaluates **PDO-tumor concordance, assay reproducibility, and correlation between PDO classifications and clinical outcomes**, with particular emphasis on barriers to achieving high positive predictive value.

MyOncoPM Functional Precision-Oncology Platform:

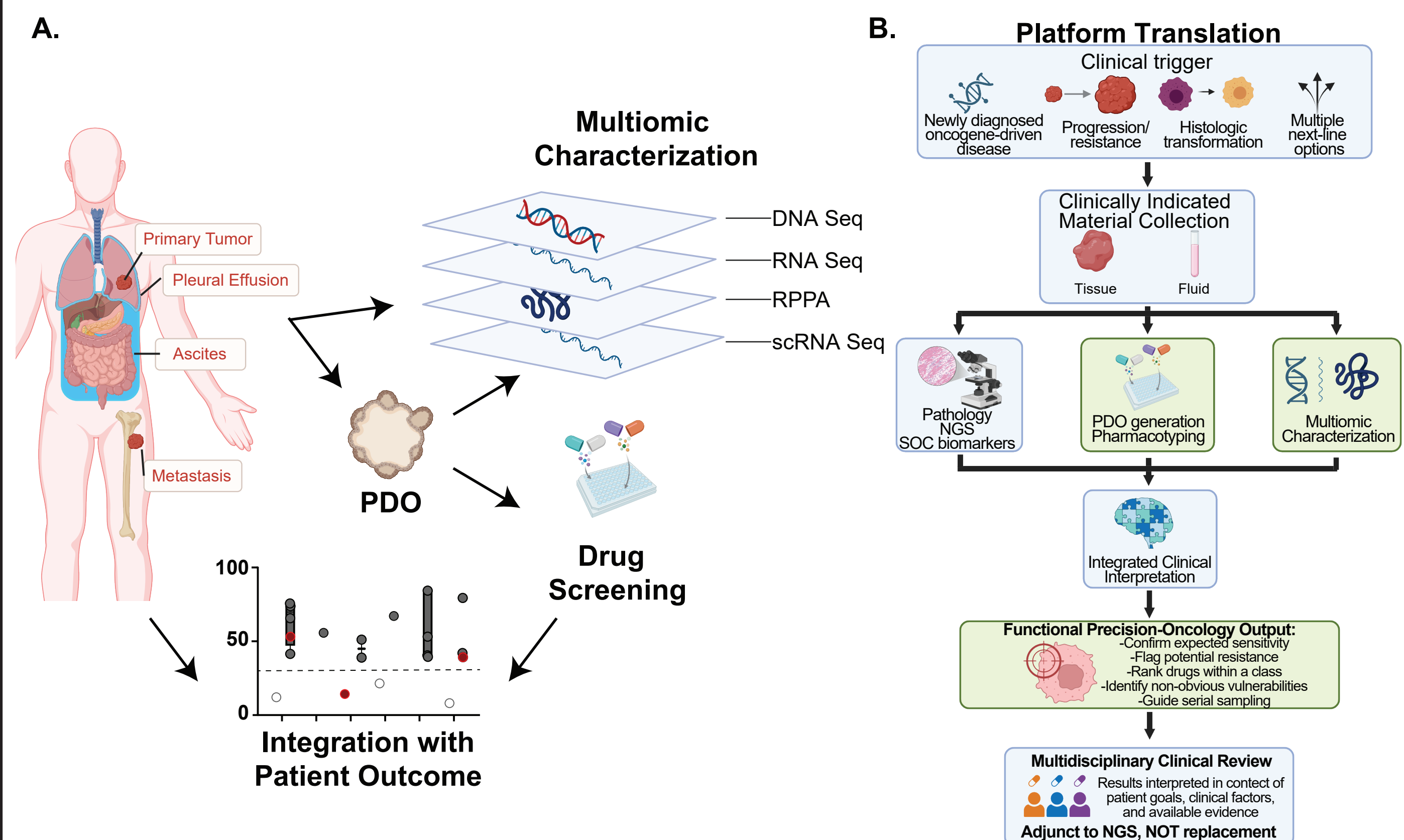


Figure 1. A. Workflow integrating clinical specimens, short-term patient-derived organoid (PDO) generation, drug screening, multiomic profiling, and clinical outcomes. **B.** Integration of PDO pharmacotyping with standard molecular testing to inform treatment prioritization in oncogene-driven lung cancer.

Genomic Concordance Between Matched Tumors and PDOs:

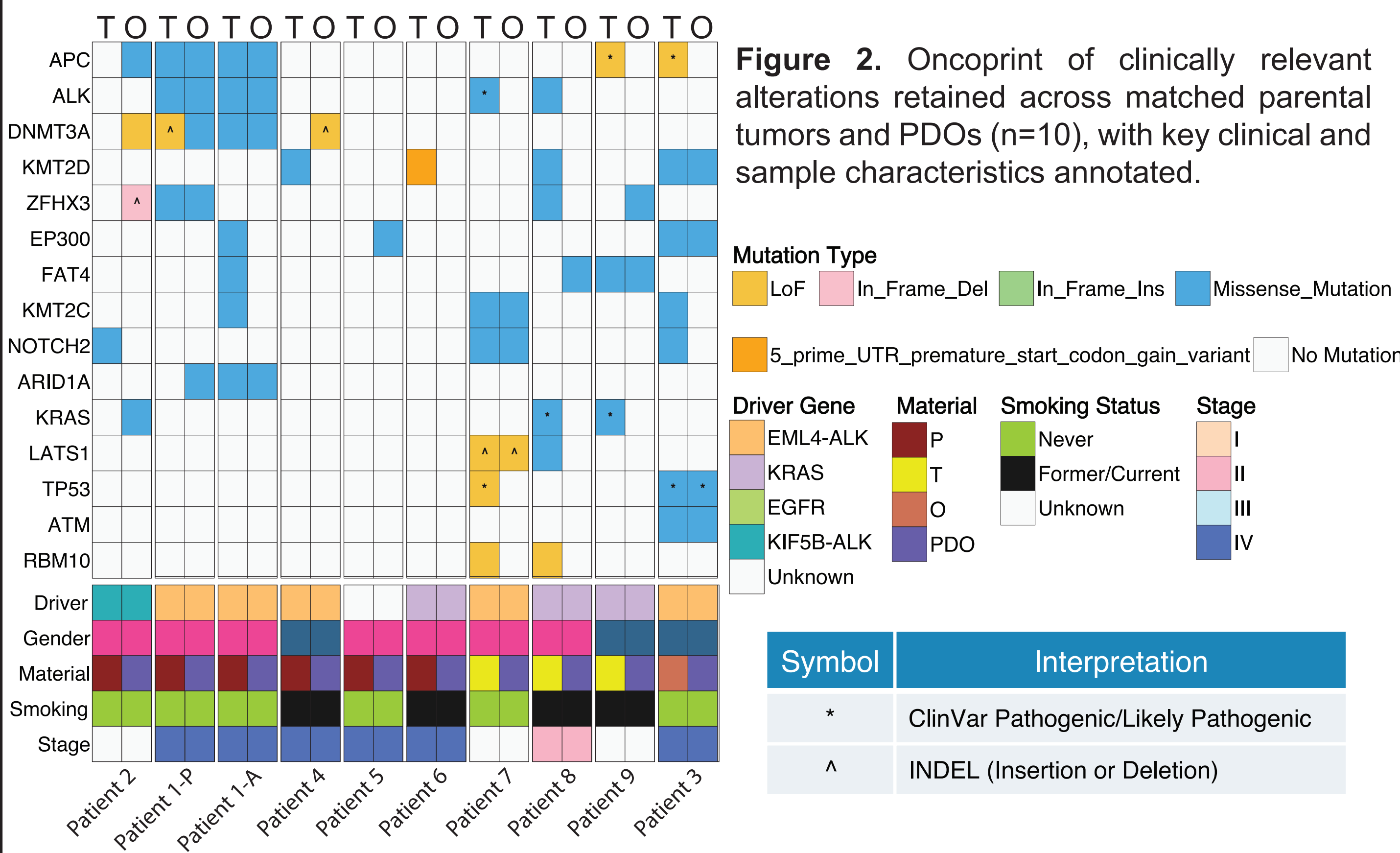


Figure 2. Oncoprint of clinically relevant alterations retained across matched parental tumors and PDOs (n=10), with key clinical and sample characteristics annotated.

Conclusions:

- **MyOncoPM provides rapid, reproducible pharmacotyping and multiomic profiling from tissue and malignant fluids.**
- **PDO testing complements genomic analysis by identifying resistance and additional therapeutic vulnerabilities.**
- **Functional and scRNA analyses expose clinically relevant heterogeneity, supporting prospective evaluation of PDO-guided therapy selection.**

PDO Drug Responses Correlates With Clinical Outcomes:

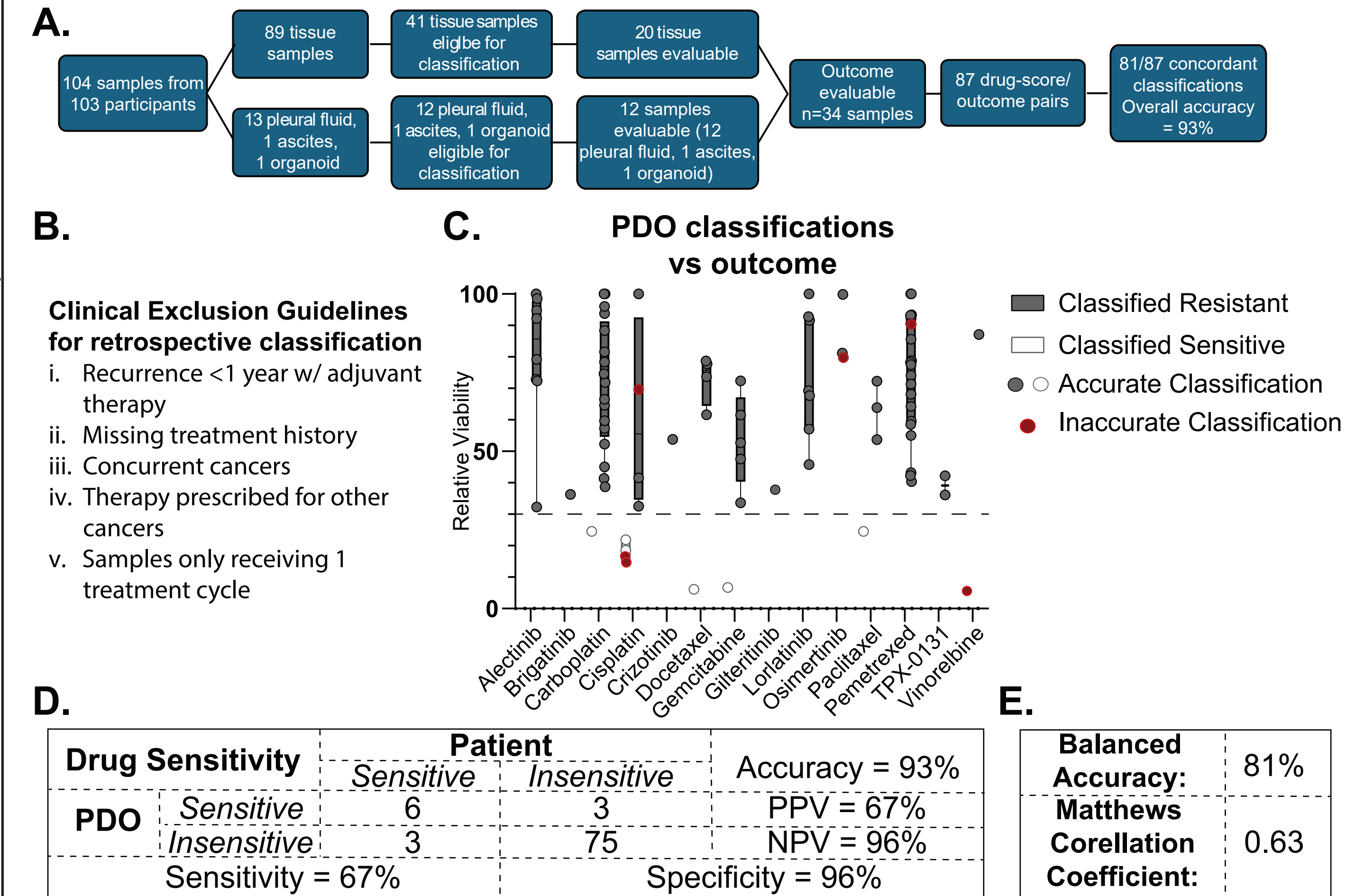


Figure 3. A-B. Selection of evaluable patient-PDO comparisons. **C.** PDO sensitivity at clinically relevant drug concentrations, using a 30% viability threshold. **D-E.** Predictive performance summarized by confusion matrix, PPV, NPV, balanced accuracy, and MCC.

Concordant Pharmacotyping Across Anatomically Distinct Malignant Fluids:

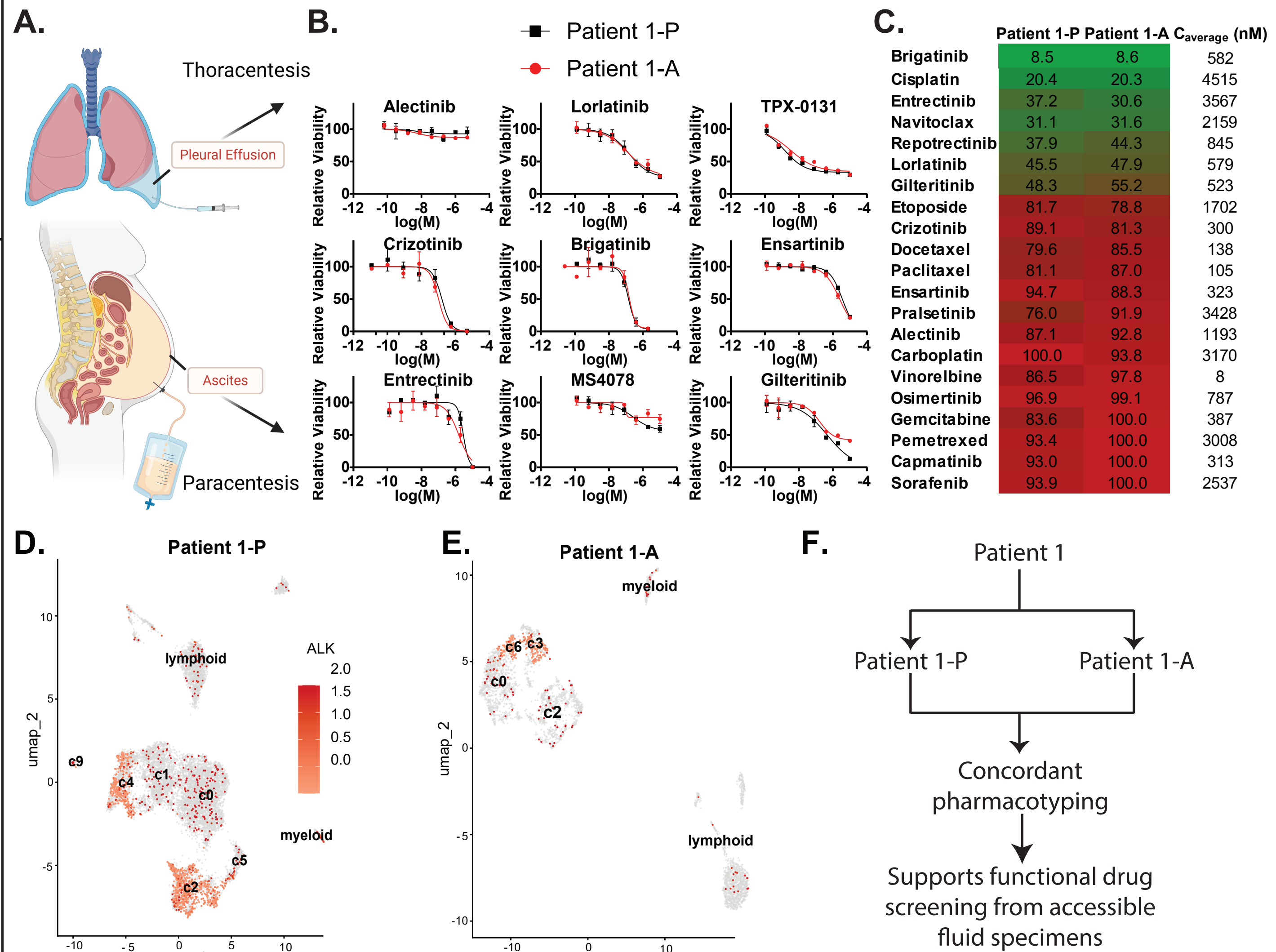


Figure 4. A. Pleural effusion and ascites collection. **B-C.** Samples showed similar responses to ALK TKIs and chemotherapy and recapitulated prior clinical resistance. **D-E.** scRNA seq identified tumor and immune populations, including tumor clusters with differing ALK expression. **F.** Concordant responses support functional drug testing using accessible malignant fluids.

Functional Testing and scRNA Profiling Reveal Therapeutic Challenges and Tumor Heterogeneity:

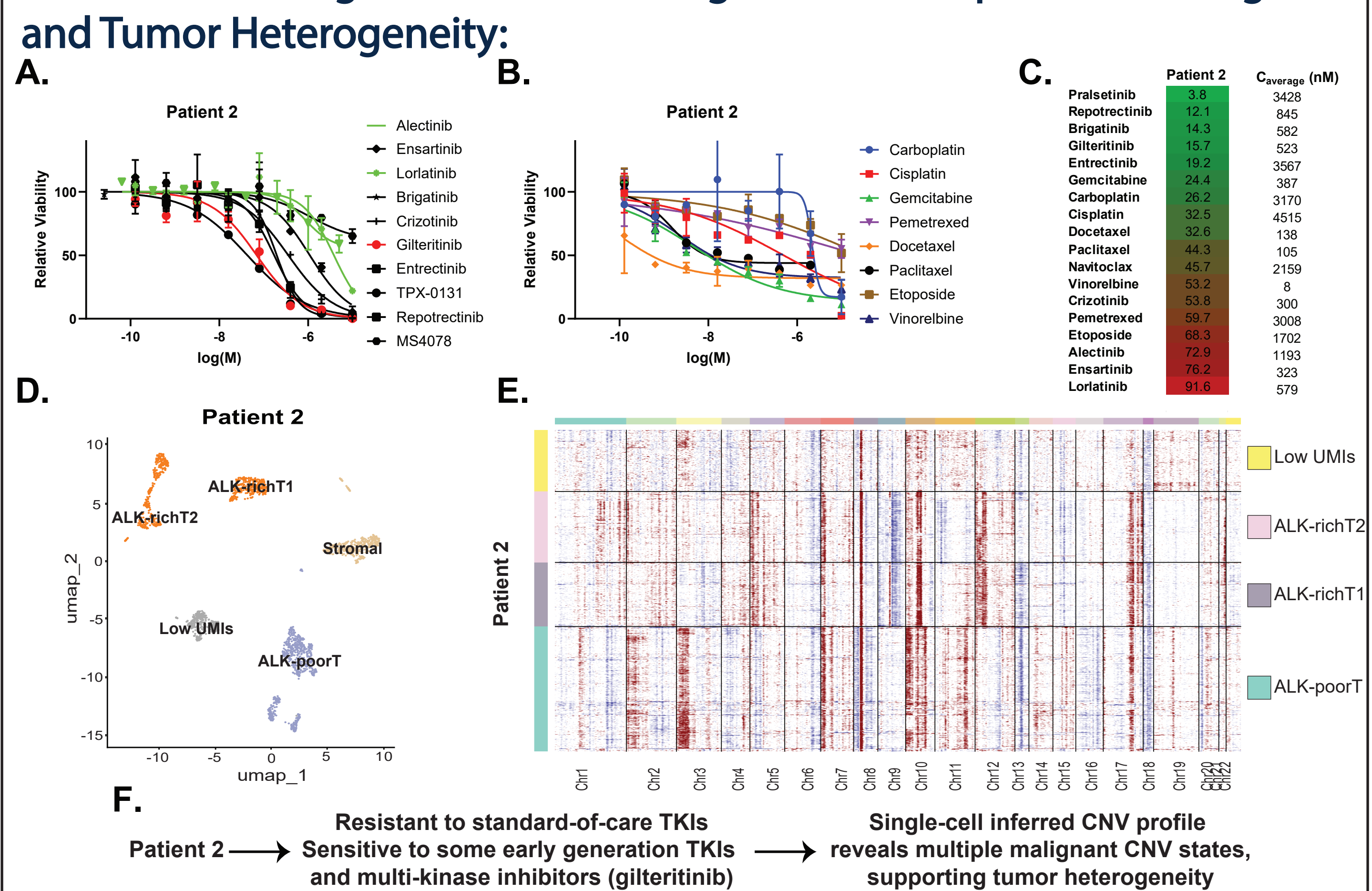


Figure 5. A-C. PDO showed reduced sensitivity to standard ALK TKIs and variable sensitivity to alternative targeted agents and chemotherapies. **D-E.** scRNA seq identified heterogeneous tumor populations with distinct ALK expression and inferred CNV profile. **F.** Integrated functional and scRNA seq revealed therapeutic opportunities and heterogeneity not captured by bulk profiling.

MyOncoPM Identifies Vulnerabilities After Small-Cell Transformation:

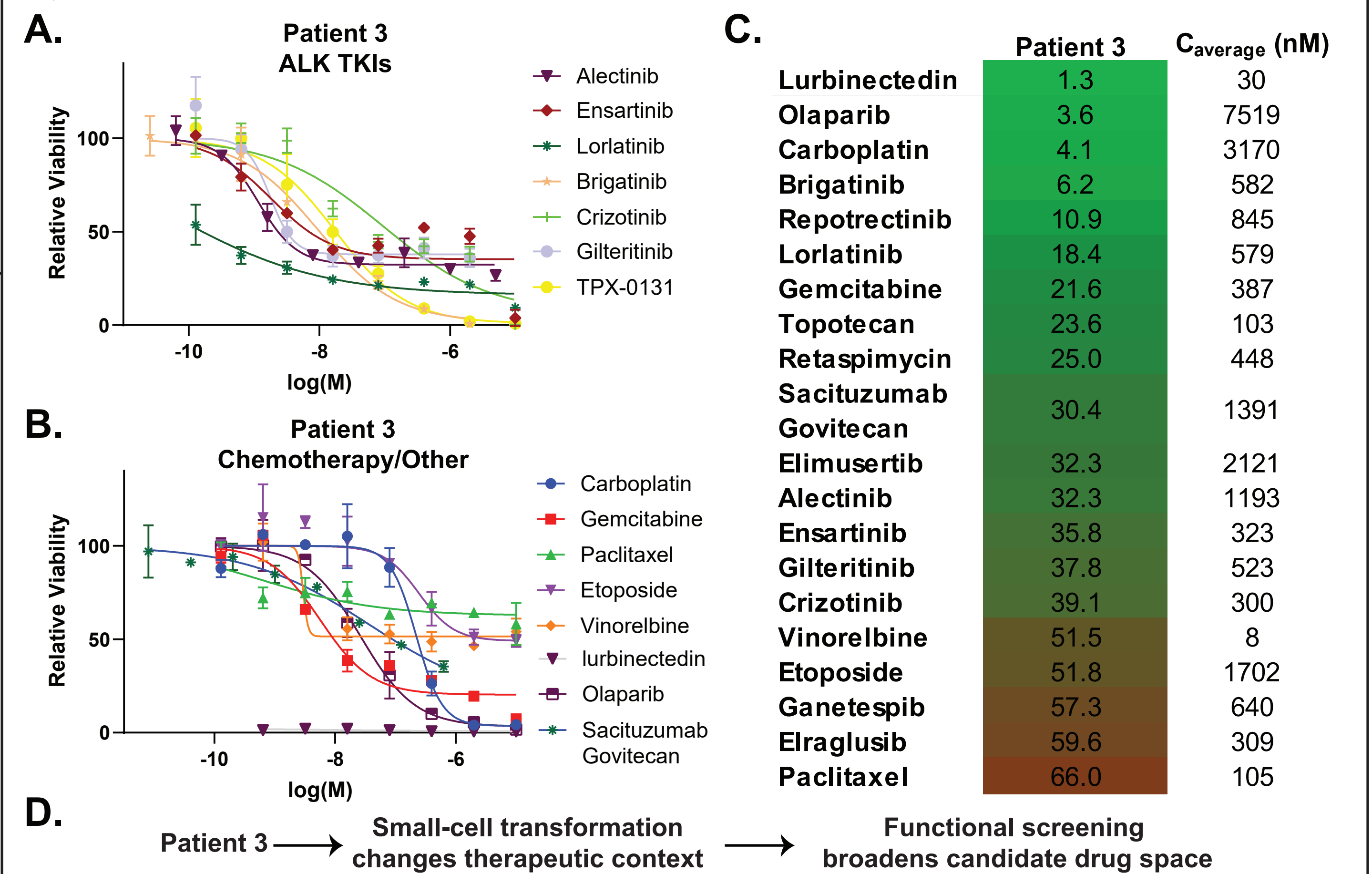


Figure 6. A-C. Functional testing showed variable ALK TKI sensitivity and identified additional non-ALK targeted vulnerabilities, including responses to therapies not typically prioritized for EML4-ALK NSCLC. **D.** Pharmacotyping revealed broadened therapeutic opportunities with small-cell transformation.

References:

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- Lin, Y. T., Yu, C. J., Yang, J. C. & Shih, J. Y. Anaplastic Lymphoma Kinase (ALK) Kinase Domain Mutation Following ALK Inhibitor(s) Failure in Advanced ALK Positive Non-Small-Cell Lung Cancer: Analysis and Literature Review. *Clin Lung Cancer* **17**, e77-e94, doi:10.1016/j.clcc.2016.03.005 (2016).
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Artificial Intelligence Use Disclosure: U-M GPT (GPT-5.6 Sol, OpenAI) was used to assist with language editing, condensation, and formatting of poster text. Claude assisted in scRNA analysis code creation, under the guidance of an experienced informatician. AI was not used directly in study data design, analysis or interpretation. All AI-assisted content was reviewed and verified by the authors, who retain responsibility for the final material.