Phase I/II study exploring safety and efficacy of APL-101 plus frontline osimertinib in EGFR-mutated metastatic non-small cell lung cancer

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Introduction

- Activation of MET signaling has been described as a driver of primary resistance to EGFR tyrosine kinase inhibitors (TKI)[1]
- Copy number gains in *MET* have been described in *EGFR* mutated non-small cell lung cancers (NSCLC) that are resistant to osimertinib and also treatment-naive samples[2]
- Combination of osimertinib with MET-TKIs has shown to be safe with encouraging antitumor activity following disease progression on osimertinib[3,4]
- APL-101 is a specific ATP-competitive small-molecule MET inhibitor that has shown favorable safety profile in advanced solid tumors with *MET* dysregulation (NCT03175224)

Hypothesis

- We hypothesize that combination therapy with MET inhibitor, APL-101, and EGFR-TKI osimertinib has the potential to induce deep and durable responses in patients with *EGFR* mutated lung cancer

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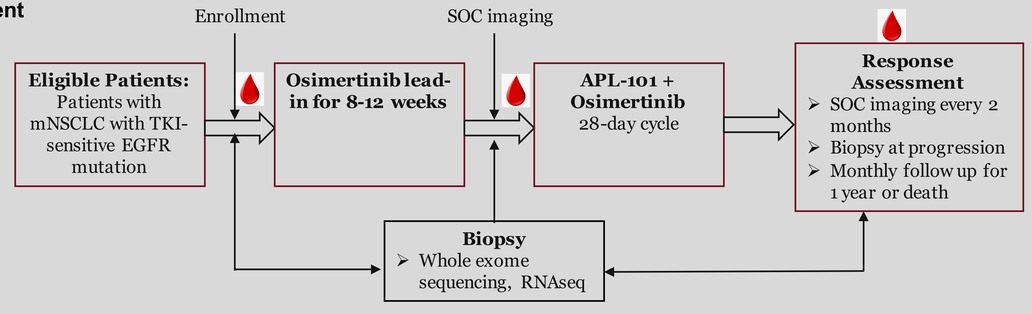
Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Metastatic NSCLC with TKI-sensitive *EGFR* mutations	Prior treatment with osimertinib in metastatic setting
Measurable disease by RECIST 1.1 with at least one lesion accessible for core biopsy	Prior immunotherapy treatment in metastatic setting
Planning to initiate treatment with osimertinib 80 mg daily	Presence of symptomatic and unstable brain metastasis

Treatment



- Tumor biopsies collected: at diagnosis, end of osimertinib lead-in, at progression
  - Biopsy after osimertinib lead-in and at progression are encouraged if feasible, but not mandatory
- ctDNA collected: at diagnosis, after osimertinib lead-in, at progression

Dose Level	APL-101 Dose (BID)	Osimertinib Dose
-1	200 mg daily (100 mg BID)	80 mg daily (option to start with 40mg, if dose reduction was pursued during lead-in phase)
0 (starting dose)	300 mg daily (100 mg AM, 200 mg PM)	
2	400 mg daily (200 mg BID)	

Study Objectives

- Phase I = dose escalation phase, determine maximum tolerated dose (MTD) and dose-limiting toxicities
  - Toxicity assessed by CTCAE v 5.0
  - Standard 3+ 3 design
- Phase II = MTD cohort expansion phase
  - Progression free survival at 1 year
  - Overall response rate, duration of response, overall survival
- Exploratory analyses will investigate genomic alterations underlying drug tolerance and identify biomarkers that are prognostic and predictive of treatment response

Study Information

- Status: Recruiting to dose level 2
- Protocol Number: 202104039
- ClinicalTrials.gov Identifier: NCT04743505

References
1. Benedettini et al. *Am J Pathol*. 2010
2. Roper et al. *Cell Rep Med*. 2020
3. Sequist et al. *Lancel Oncol*. 2020
4. E FS et al. *Future Oncol*. 2022

Acknowledgement
Funding: Apollomics Inc.