Dependence of EGFR-mutant NSCLC on MET as demonstrated by vebreltinib, a novel and selective brain-penetrating MET kinase inhibitor

AACR 2024
#6500

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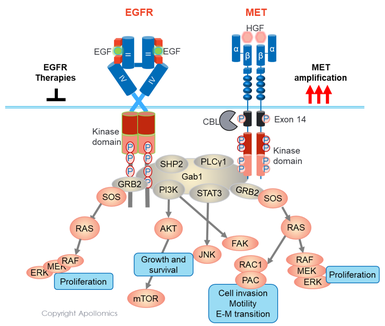
Introduction

Although EGFR inhibitors (EGFRi), preferably osimertinib, have offered substantial benefit for the classical plus T790M EGFR-mutant NSCLC patients, drug resistance develops and poses a critical challenge for long-term survival. The resistance is rooted to either on-target secondary EGFR mutations or compensatory oncogenic pathways bypassing EGFRi intervention, one of which appears to be treatment-acquired *MET* amplification (*MET*amp) potentially attributed to the cross-talk and overlapping signaling pathways between EGFR and MET. In this study we set out to understand the conditions when the tumor cells become dependent on MET.

MET amplification is a resistance mechanism to EGFR therapies
Cross-talk between EGFR and MET signaling pathways



Methods

Three types of patient-derived tumor models (PDX) carrying classical and T790M EGFR driver mutations were selected based on EGFR therapy treatment history and concurrent *MET* gene copy numbers or MET RNA expression levels to represent the following three types EGFR+ NSCLC:

- Type 1: Resistant to EGFRi with *MET*amp
- Type 2: Partially resistant to EGFRi with *MET*amp
- Type 3: Sensitive to EGFRi with low *MET* expression, no *MET*amp

These PDX xenograft mice were treated with vebreltinib (APL-101, Poster 597) at clinically relevant doses as single agent or in combination with osimertinib. The pharmacodynamic effects on EGFR and MET phospho (P)- and total proteins were analyzed from tumor samples harvested during and at the end of treatments.

Results

- Type 1 EGFR+ NSCLC:
  - APL-101 was effective on tumor growth inhibition as single-agent.
- Type 2 EGFR+ NSCLC:
  - APL-101 partially inhibited the tumor growth as single-agent and completely inhibited the tumor growth in combination with osimertinib.
- Type 3 EGFR+ NSCLC:
  - Addition of APL-101 suppressed tumor re-growth after stopping osimertinib dosing.
- The anti-tumor activity of APL-101 in type-1 and type-2 PDX was associated with pharmacodynamic inhibition of P-MET and P-EGFR and MET protein degradation.

Conclusion

EGFR+ NSCLC resistance to EGFR therapies may be dependent on MET pathway regardless of acquired *MET*amp, whereas *MET*amp may dictate the degree of MET dependence. Our data supports the hypothesis that adding APL-101 to EGFR therapies overcome MET dependent resistance with durable effect or preventing MET dependent resistance to maximize therapeutic benefits.

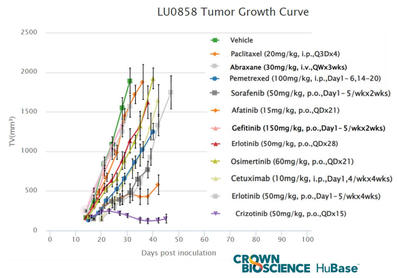
APL-101 is effective on Type 1 EGFR+ NSCLC as single-agent

A

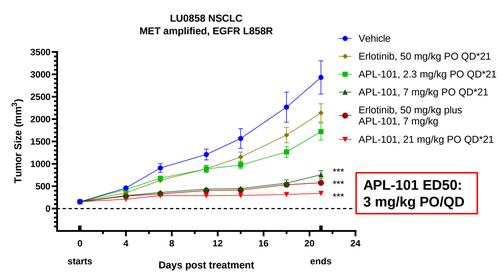
LU0858: EGFR+ NSCLC PDX, resistant to EGFRi with *MET* amplification

Cancer	Model	Genetic background	EGFRi outcome	*MET* amplified	*MET* RNA (FPKM)	*HGF* RNA (FPKM)
NSCLC	PDX	*EGFR* L858R	Resistant	Yes (GCN≥6)	744.4 (High)	1.4 (Low)

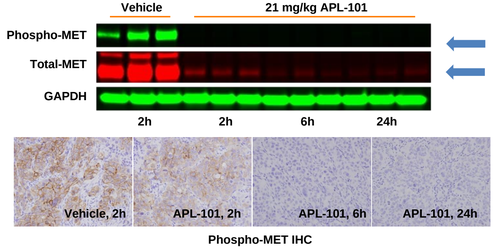
Resistant to Chemo, BRAFi, EGFRi (Osimertinib, etc.)



Inhibited effectively by APL-101 single-agent



APL-101 ED50: 3 mg/kg PO/QD



APL-101 PD effect:

- **MET Protein Degradation**
- **Phospho-MET inhibition**

B

LD1-0025-200662: EGFR+ NSCLC PDX, resistant to EGFRi with *MET* amplification

Cancer	Model	Genetic background	EGFRi outcome	*MET* amplified	*MET* RNA (FPKM)	*HGF* RNA (FPKM)
NSCLC	PDX	*EGFR* ex19del	Resistant	Yes (GCN=5)	748.3 (High)	0.06 (Low)

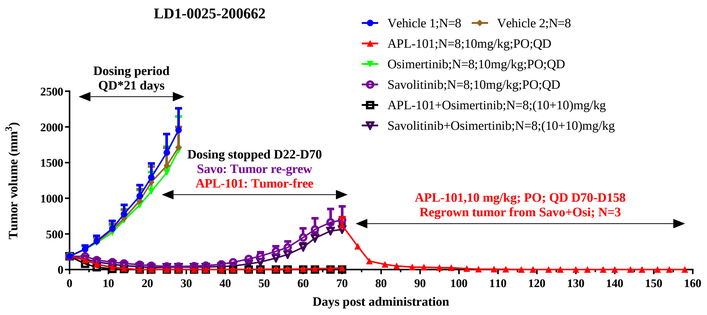
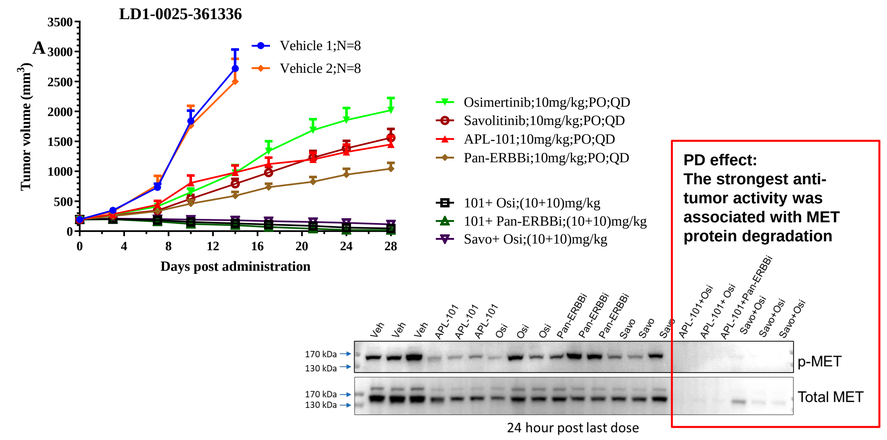


Figure 1. APL-101 single-agent effect on EGFR+ NSCLC PDX progressed from EGFR therapies with *MET*amp. **A**. LU0858, resistant to chemotherapies, BRAF inhibitor and EGFRi including osimertinib, was inhibited by APL-101 with ED50 of 3 mg/kg. **B.** LD1-0025-200662, resistant to osimertinib, appeared to be eradicated by APL-101 and the mice became tumor-free on Day 18 and remained so after dosing stop on day 21 with last observation at study end (Day 70). Savolitinib did not eradicate tumor growth at the same dose as APL-101 or in combo with osimertinib. Regrown tumor after savolitinib/osimertinib combo dosing stop was inhibited completely by APL-101 follow-on treatment. FPKM: Fragments Per Kilobase of transcript per Million mapped reads, an RNA expression unit by RNAseq; GCN: Gene Copy Number, *MET* amplification is defined as GCN ≥ 5 in this study.

APL-101 is effective on Type 2 EGFR+ NSCLC in combo with osimertinib

LD1-0025-361336: EGFR+ NSCLC PDX, partially resistant to EGFRi with *MET* amplification

Cancer	Model	Genetic background	EGFRi outcome	*MET* amplified	*MET* RNA (FPKM)	HGF RNA (FPKM)
NSCLC	PDX	*EGFR* ex19del	Partial resistance	Yes (GCN=18)	244.5 (Medium)	0 (Low)



PD effect:
The strongest anti-tumor activity was associated with MET protein degradation

Figure 2. APL-101 and savolitinib showed comparable anti-tumor activity against type 2 EGFR+ NSCLC PDX, where tumor growth was partially inhibited by the two METi but was completely inhibited by combo of METi with osimertinib.

Upfront combination of APL-101 with osimertinib may prevent MET-dependent resistance in Type 3 EGFR+ NSCLC

LU1868: EGFR+ NSCLC PDX, sensitive to EGFRi and *MET* not amplified

Cancer	Model	Genetic background	EGFRi outcome	MET amplified	MET RNA (FPKM)	HGFRNA (FPKM)
NSCLC	PDX	*EGFR* T790M	Sensitive	No	17.1 (Low)	0.3 (Low)

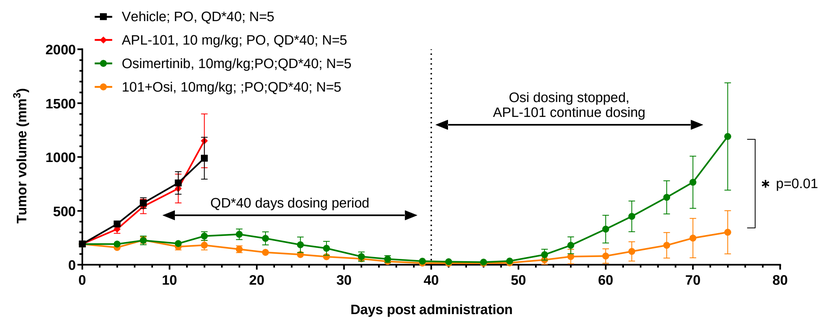


Figure 3. APL-101 suppresses tumor re-growth in an EGFRi-sensitivie EGFR+ NSCLC PDX (LU1868) after osimertinib dosing stop even though *MET* is not amplified and *MET* RNA expression level is low in this tumor, suggesting that MET may be a general mechanism to prevent resistance to EGFR therapies during EGFR therapy treatment response window.