Vebreltinib: A novel brain-penetrating MET kinase inhibitor demonstrates the mechanism of action and pharmacological anti-tumor activity in diverse patient-derived MET-dysregulated tumor models at clinically relevant drug levels

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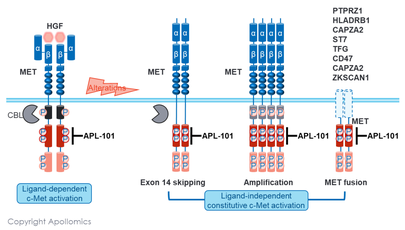
Introduction

Dysregulation of the MET signaling pathway drives oncogenesis in many human cancers, the majority of which have not been addressed by a MET targeted therapy albeit the emerging therapies for *MET* exon 14 skipping (*MET* ex14) NSCLC. We have developed a novel highly selective MET kinase inhibitor vebreltinib (APL-101, PLB1001, bozitinib) to address unmet medical need.

Vebreltinib is being jointly investigated in ongoing pivotal Phase 2 and 2/3 studies in MET-dysregulated NSCLC, primary CNS cancers and basket solid tumors globally ex-China (as APL-101) and in China (as PLB-1001). The Phase 1 portion of both studies have reached the same RP2D (200 mg BID by oral administration) for treatment of NSCLC with MET dysregulations (1-2). Vebreltinib demonstrated blood-brain barrier permeability in Phase 1 glioblastoma study (3). Clinical response has been observed in NSCLC with *MET*ex14, and in a number of other solid tumors (i.e. glioma, glioblastoma, pancreatic cancer, cholangiocarcinoma, esophageal carcinoma, sarcoma, and metastatic schwannoma) with MET alterations to include *MET*ex14,*MET* amplification, *MET* fusions, MET and HGF overexpression (3-4).

Vebreltinib was recently granted conditional approval in China for treatment of patients with locally advanced or metastatic *MET* exon 14 skipping NSCLC based on ORR of 75% (95% CI, 61.1%-86.0%, n=52).

MET alterations and oncogenic addiction



Summary

- APL-101 is an ATP-competitive inhibitor with Ki of approximately 2.2 nM.
- Exquisite kinome selectivity and nanomolar cellular potency on growth inhibition of MET-dependent tumor cells.
- ED90 of 6 mg/kg PO/QD in MET-amplified MKN45 gastric tumor xenograft model with plasma EC50 of 886 ng/ml on phospho-MET inhibition.
- Anti-tumor activity in diverse PDXs carrying *MET* ex14, *MET* fusions, and *MET* amplification at clinically relevant drug levels.

Conclusion

Vebreltinib is a novel potent MET kinase inhibitor showing promising preclinical activity against PDXs from diverse organs sites and genomic alterations such as *MET* ex14, *MET* fusion, *MET* amplification, or HGF over-expression at clinically relevant drug levels, providing proof-of-concepts for continued clinical development.

Reference

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2. Yang J, Zhou Q, Chen H, Wu L, Zhao J, Guo R, et al. A phase I study of cMET inhibitor bozitinib in patients with advanced NSCLC harboring cMET alterations. Cancer Res. 2020; 80 (16_Supplement): CT127.
3. Hu H, Mu Q, Bao Z, Chen Y, Liu Y, Chen J, *et al.* Mutational Landscape of Secondary Glioblastoma Guides MET-Targeted Trial in Brain Tumor. Cell. 2018;175(6):1665.
4. Li JJ, Zhang X, Sankar N, Espiritu L, Redkar S, Yu GL, Kizilbash SH. MET/HGF Coexpression as a Novel Predictive Biomarker for Response to MET Inhibitor Therapy in a Case of Psammomatous Melanotic Schwannoma. JCO Precis Oncol. 2022;6:e2200096.

APL-101 is a potent and selective MET TKI

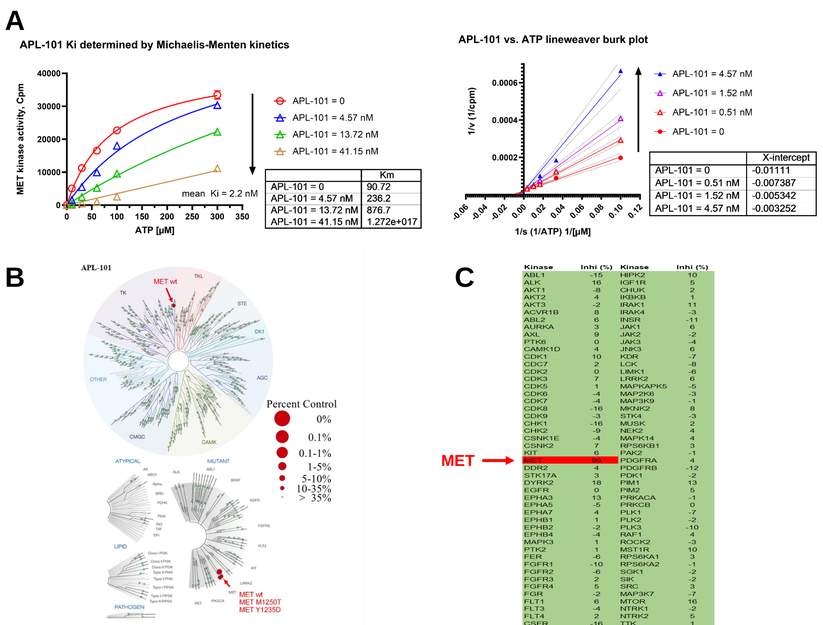

Figure 1. A. APL-101 kinetic study using Eurofins c-Met Kinase Direct-Substrate Measurement Assay, showing Ki of 2.2 nM**. B.** Kinase competitive binding screening using KINOMEscan selectivity panel at 1 μM APL-101 on 468 kinases: 409 wild type, 3 pathogen, 8 atypical, 13 lipid, and 59 mutant kinases. **C.** Selectivity screening of 100 protein serine/threonine and tyrosine kinases known to function in cell signaling, including MET. Inhibition of kinase catalytic activities was screened at 2 μM APL-101.

Cellular potency on growth inhibition of MET-dependent tumor cells

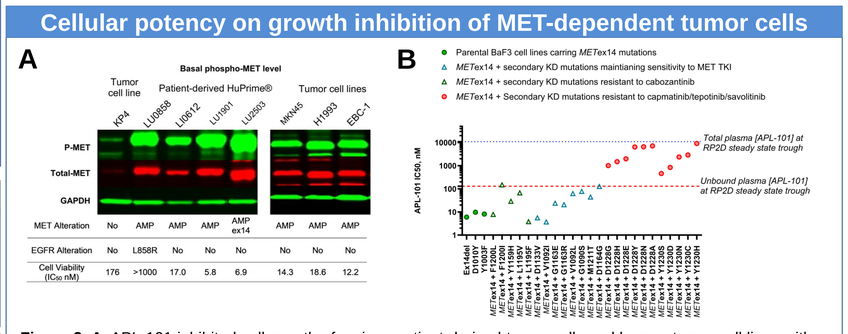

Figure 2. A. APL-101 inhibited cell growth of various patient-derived tumor cells and human tumor cell lines with MET driver alteration and high basal level of phosphorylated MET (P-MET, Y1234/Y1235), except for LU0858 carrying both MET and EGFR driver alterations. LU0858, LU1901, LI0612: patient-derived lung cancer cells of the HuPrime® origin. **B.** APL-101 anti-proliferation effects on IL-3 dependent murine pro-B Ba/F3 cell lines carrying stable exogenous MET exon 14 mutations and secondary kinase domain mutations resistant to type I MET TKIs (capmatinib, tepotinib, savolitinib, crizotinib) and type II MET TKI cabozantinib. Clinically relevant levels of APL-101, plasma trough concentration at RP2D, are indicated by the dash line intersecting with the Y-axis (APL-101 IC50), Red indicates unbound plasma APL-101, Blue indicates total plasma APL-101.

APL-101 demonstrated desired *in vivo* PD-PK-Efficacy relationship

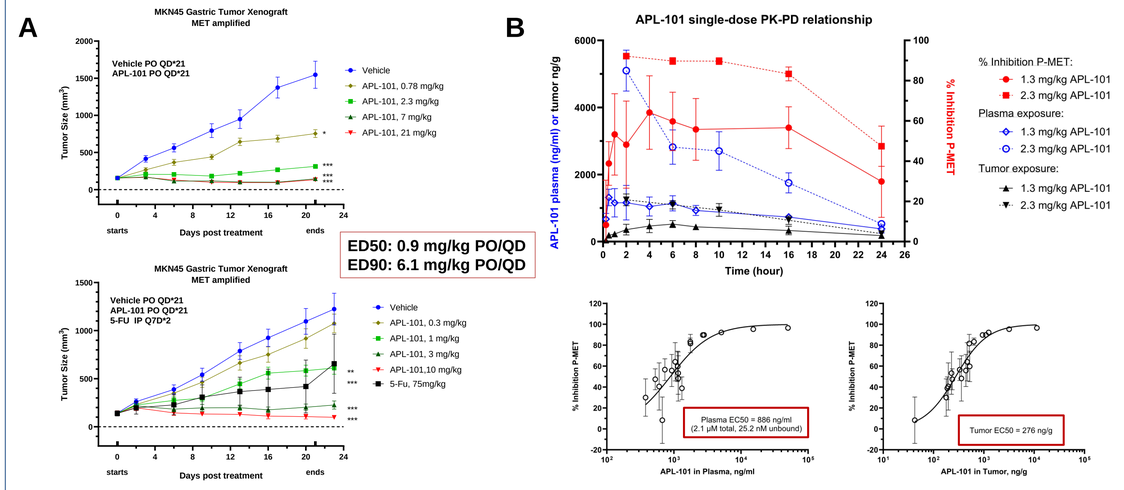

Figure 3. A. *In vivo* anti-tumor effect of APL-101 in MET amplified MKN45 gastric tumor xenografts in two independent experiments with ED50 of 0.9 mg/kg and ED90 of 6.1 mg/kg PO/QD. **B**. APL-101 pharmacokinetics (PK) and pharmacodynamics (PD), efficacy relationship in MKN45 tumor model. Shown in graph are Phospho (P)-MET inhibition (PD), plasma and tumor APL-101 exposure with single oral administration of APL-101 at 1.3 (Solid lines) and 2.3 mg/kg (Dash lines). Percent inhibition of P-MET, plasma and tumor exposures are indicated in read circle/square, blue diamonds/circle, and black triangles respectively. The two doses were associated with EC50 of 886 ng/ml (2.1 μM total, 25.2 nM unbound) plasma APL-101, ≥50% Inhibition of MET phosphorylation for a period of at least 16 hours. * p<0.05; ** P<0.01; *** P<0.001.

Anti-tumor activity in diverse *MET* altered PDXs at clinically relevant drug levels

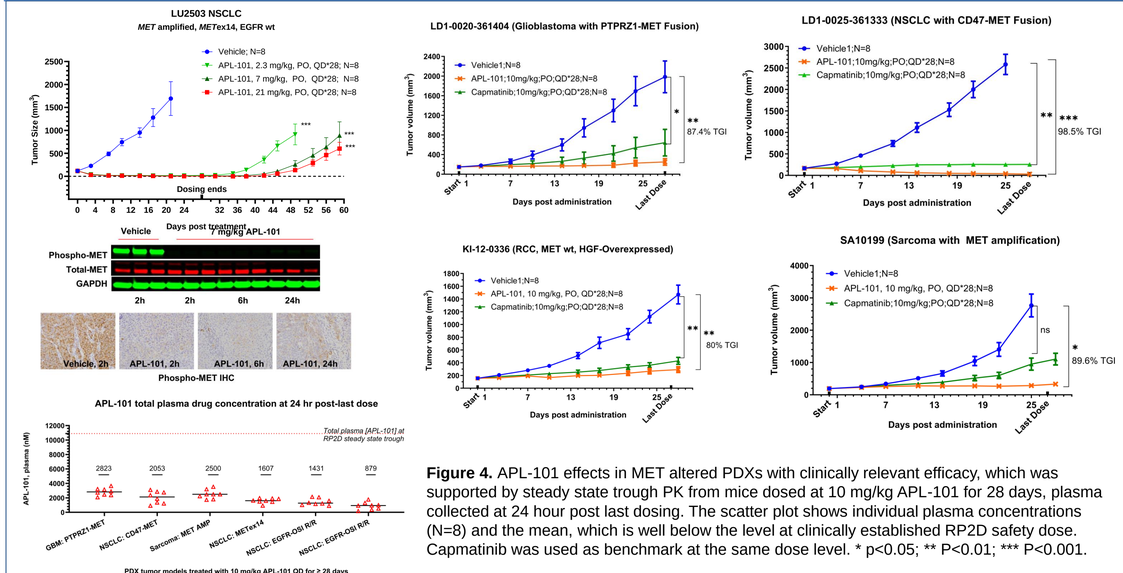

Figure 4. APL-101 effects in MET altered PDXs with clinically relevant efficacy, which was supported by steady state trough PK from mice dosed at 10 mg/kg APL-101 for 28 days, plasma collected at 24 hour post last dosing. The scatter plot shows individual plasma concentrations (N=8) and the mean, which is well below the level at clinically established RP2D safety dose. Capmatinib was used as benchmark at the same dose level. * p<0.05; ** P<0.01; *** P<0.001.