Abstract No: PD-021

Phase 1/2 study of the safety and efficacy of APL-101, a specific c-MET inhibitor

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Background

- The c-Met receptor tyrosine kinase is the cell surface receptor for hepatocyte growth factor (HGF) encoded by the MET protooncogene (Gherardi E et al., Nat Rev Cancer 12 (89) 2012).
- Dysregulation of the c-Met pathway is an established driver of oncogenesis. Three different types of genomic alteration can lead to clinically relevant oncogenesis: amplification, mutations and fusions (Guo R et al., Nature Rev 17 (569) 2020).
- APL-101 (PLB-1001; Bozitinib) is an oral, ATP-competitive, highly potent, specific type 1b c-Met inhibitor. c-Met enzymatic IC_{50} = 31 nM and IC_{50} = 0.52 nM with intracellular c-Met assay.
- Here we report the safety and preliminary efficacy of the Phase 1 portion of the SPARTA Study (NCT03175224).

Study Design and Objectives

SPARTA trial, primary objectives

Phase 1: Assess overall safety and tolerability, determine dose limiting toxicities (DLTs) and identify the recommended phase 2 dose (RP2D).
Phase 2: Assess efficacy by overall response rate and duration of response per RECIST v1.1.

Phase 1
Primary Endpoint: Safety and Phase 2 Dose

Eligibility
- ≥ 18 years of age
- ECOG PS 0 – 1
- Measurable disease
- NSCLC & solid tumors with c-Met dysregulation

N = (15 – 22)

100, 200, 300, 400 mg PO daily (divided twice daily) on Days 1 – 28 of a 28-day cycle

Phase 1 (100, 200 & 300 mg) c-Met Dysregulation Inclusion Criteria
- c-Met overexpression: immunohistochemistry 2+ with ≥ 50% tumor cells.
- c-Met amplification (c-Met/Cep 7 ratio ≥ 2.2 or GCN ≥ 6 copy).
- Mutation (EXON 14 skip mutation or other known mutations).
- MET fusions per protocol .

Phase 1 (400 mg) and Phase 2 RP2D c-Met Dysregulation Inclusion Criteria
- c-Met amplification (c-Met/Cep-7 ratio of ≥ 2.2 or GCN of ≥ 6 copy)

A minimum of 5 subjects of the high-level amplification (c-Met/Cep-7 ratio of ≥ 5 or GCN ≥ 10 gene copy) for the Stage 1 of the Simon 2 stage design.
- Mutation (EXON 14 skip mutation or other known c-MET mutations in Phase 1 400 mg Cohort).
- MET fusions per protocol.

Phase 2
Primary Endpoint: Response rate

Cohort A1
EXON 14 Skip NSCLC (c-Met Naïve) 1L
(Stage 1 = 15, Stage 2 = 31)

Cohort A2
EXON 14 Skip NSCLC (c-Met Naïve) 2L/3L
(Stage 1 = 15, Stage 2 = 31)

Cohort B
EXON 14 Skip NSCLC (c-Met experienced)
(Stage 1 = 10, Stage 2 = 19)

Cohort C
All tumor types with c-Met amplification (EXON 14 Skip NSCLC Excluded)
(Stage 1 = 10, Stage 2 = 19)

Cohort D
All tumor types with c-Met fusions
(Stage 1 = 10, Stage 2 = 19)

Tx Term & 30-day FU/OS

Results

Baseline Characteristics and Patient Disposition

- All data described relates to the Phase 1 portion of the trial.
- As of the data cut-off on 28 April 2020, 17 subjects were included in the safety analysis.
- Median time between diagnosis and study treatment onset was 34.9 months.
- Baseline characteristics, primary tumor origin and type of c-Met aberration are shown.

Baseline Characteristics	
Age; Mean, years (SD)	60.9 (14.3)
Median (Min – Max)	64.0 (34.0 – 84.0)
Sex; n (%)	
Female	6 (35.3%)
Male	11 (64.7%)
Race; n (%)	
White	17 (100%)
ECOG, n (%)	
0	4 (24%)
1	13 (76%)
Prior lines of systemic therapy Median (Range)	3.5 (1-10)

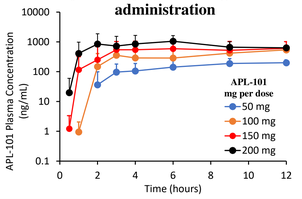
Tumor Types	
Breast cancer	1
Cancer of Unknown Primary	1
Cholangiocarcinoma	1
Colon / Rectal cancer	4
Gastric / GE junction cancer	1
Glioblastoma	3
Non-small cell lung cancer	3
Pancreatic cancer	2
Schwannoma	1

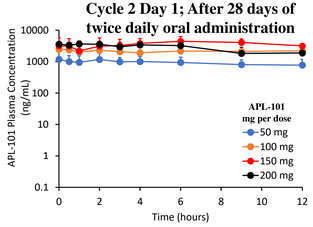
MET dysregulation	
Amplification	8
Overexpression	7
Mutation	2*

* Exon 14 skipping mutation (n = 1, Breast Cancer), missense in kinase domain (H1094Y) mutation (n = 1, NSCLC)

Plasma Pharmacokinetics

- C_{max} and AUC_{0-12} values increased proportionally with increasing APL-101 doses with mean $T_{1/2}$ ranging from 16 to 38 hours.
- The plasma exposure achieved after multiple day dosing at both 300 mg and 400 mg dose levels is higher than the plasma exposure associated with a 90% effective dose in c-Met dependent tumor xenograft models.





Results

Plasma Pharmacokinetics

Dose level	50 mg QD* (n=3)	100 mg QD* (n=4)	150 mg QD* (n=3)	200 mg QD* (n=5)	50 mg BID^ (n=3)	100 mg BID^ (n=4)	150 mg BID^ (n=2)	200 mg BID^ (n=4)
C_{max} (ng/mL) Mean (SD)	235 (42.5)	581 (206)	833 (326)	1218 (721)	1375 (739.5)	2950 (735.3)	4650 (nc)	5380 (1658)
T_{max} (hr) Median (Min,Max)	12 (9, 48)	7.5 (3, 48)	6.0 (2, 36)	2.0 (0, 9)	2.0 (0, 3)	4.0 (0, 12)	7.5 (6, 9)	1.0 (0, 2)
$AUC_{(0-12)}$ (ng•hr/mL) Mean (SD)	1512 (820)	3824 (2323)	5661 (4837)	10611 (nc)	11115 (5208.4)	23910 (4864)	44670 (nc)	31095 (nc) (n=1)
$T_{1/2}$ (hr) Mean (SD)	24.0 (11.5)	16.0 (5.0)	16.2 (3.6)	38.0 (5.0)				

*Cycle 1 Day 1, after single oral administration
^ Cycle 2 Day 1, after 28 days of twice daily oral administration; nc, not calculated

Treatment Related Adverse Events (AEs ≥ 10% of patients)

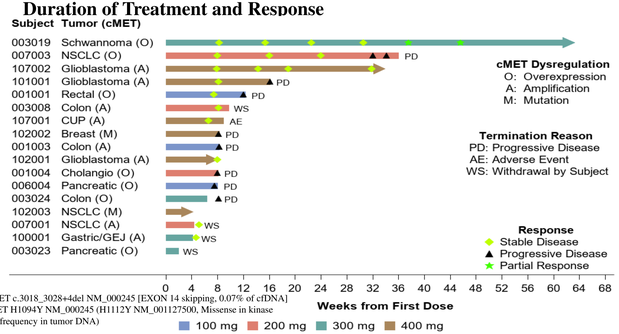
- All treatment related adverse events observed were either Grade 1 or Grade 2.
- No DLTs were observed at any of the dose levels.
- Recommended Phase 2 dose = 400 mg (i.e. 200 mg twice daily).
- No serious treatment-related or Grade ≥ 3 treatment-related AEs.
- No permanent discontinuation due to treatment related AEs.

Adverse Event \ Dose level	100 mg (n=3)	200 mg (n=4)	300 mg (n=4)	400 mg (n=6)	All (N=17)
Any	**2 (67)**	**2 (50)**	**3 (75)**	**6 (100)**	**13 (76)**
Fatigue	1 (33)	1 (25)	2 (50)	2 (33)	**6 (35)**
Hypoalbuminemia	0	0	2 (50)	3 (50)	**5 (29)**
Diarrhea	1 (33)	0	1 (25)	2 (33)	**4 (24)**
Peripheral Edema	0	2 (50)	1 (25)	1 (17)	**4 (24)**
Hypocalcemia	0	0	0	3 (50)	**3 (18)**
Anemia	0	0	0	2 (33)	**2 (12)**
Dyspnea	0	1 (25)	1 (25)	0	**2 (12)**
Hyponatremia	0	1 (25)	1 (25)	0	**2 (12)**
Nausea	0	1 (25)	0	1 (17)	**2 (12)**
Rash	0	0	0	2 (33)	**2 (12)**

Duration of Treatment and Response

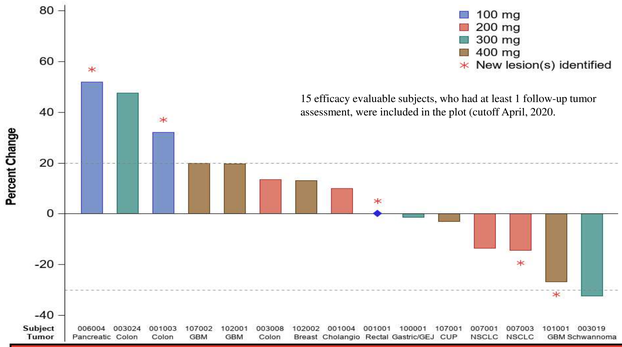
		N (%)		Median, days
Best Overall Response	Partial Response	1 (7%)	Duration of Exposure	58 (Range: 13 - 443)
	Stable Disease	9 (60%)	Progression-Free Survival	84 (95% CI: 57, 224)
	Progressive Disease	5 (33%)		
Clinical Benefit Rate (CR + PR + [SD ≥ 4 cycles])		3 (20%)		

Duration of Treatment and Response



Subject 102002 : MET c.3018_3028+4del NM_000245 [EXON 14 skipping, 0.07% of cfDNA]
Subject 102003: MET H1094Y NM_000245 (H1112Y NM_001127500, Missense in kinase domain, 72% allele frequency in tumor DNA)

Best Change from Baseline in Sum of Target Lesions



15 efficacy evaluable subjects, who had at least 1 follow-up tumor assessment, were included in the plot (cutoff April, 2020.

Summary

- Phase 1 of this study is complete; RP2D 400 mg total daily dose.
- APL-101 shows a favorable and well tolerated safety profile; No DLTs and no permanent discontinuation of study treatment due to treatment-related AEs.
- Among 15 subjects in the efficacy-evaluable population, one subject had a confirmed partial response (schwannoma) and 9 (60%) had a best response of stable disease.
- Clinical Benefit Rate (CR + PR + [SD ≥ 4 cycles]) was 20%.

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We thank patients, their families and caregivers for participating in this clinical trial. We also thank the research staff and study teams at each participating site

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