Session title: New Therapeutics in Phase I and II studies
Session type: Poster Discussion Session
Track: LIVE - pre-rec and live Q&A
Catalog number: 21
Presentation number: PD-021

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

Biography
Sani H. Kizilbash, M.B.B.S, M.P.H. is an Assistant Professor of Oncology at Mayo Clinic (Rochester, Minnesota, USA) with a focus on experimental therapeutics and central nervous system malignancies. He joined the medical oncology staff at Mayo Clinic Rochester in 2016 and is actively engaged in the clinical and research programs of the Neuro-Oncology and Early Cancer Therapeutics disease groups. His previous laboratory research involved the use of patient-derived xenograft glioblastoma mouse models to evaluate the pharmacodynamics and efficacy of novel therapeutics (e.g. PARP inhibitors, EGFR inhibitors, etc.), and knockout mouse models to interrogate brain-drug pharmacokinetics in the presence and absence of efflux transporters. His current research efforts have predominantly focused on clinical trial development. He is actively involved in the leadership and/or conduct of most of the early phase clinical trials in patients with central nervous system malignancies at Mayo Clinic Rochester (either investigator-initiated or industry initiated). Significantly, he recently designed and is the principal investigator for a national phase Ib clinical trial investigating the addition of telaglenastat to radiation/temozolomide in patients with IDH mutant glioma (NCT03528642). This trial is currently active across the NCI Early Therapeutics Clinical Trials Network. He also designed and is the principal investigator for a Mayo Clinic only phase I trial investigating WSD-0922, a brain penetrant EGFR inhibitor (NCT04197934). Additional significant clinical trial involvement includes his role as co-chair of an Alliance for Clinical Trials in Oncology phase II/III trial investigating veliparib in patients with newly diagnosed glioblastoma (NCT02152982).

1Mayo Clinic, Medical Oncology, Rochester, USA.
2University of Southern California- Norris Comprehensive Cancer Center, Medical Oncology, Los Angeles, USA.
3Park Nicollet Clinic, Hematology and Oncology, Saint Louis Park, USA.
4Penn State Cancer Institute – Penn State Health Milton S. Hershey Medical Center, Medical Oncology, Hershey, USA.
5West Virginia University – West Virginia Cancer Institute, Medical Oncology, Morgantown, USA.
6Mayo Clinic, Hematology and Oncology, Jacksonville, USA.
7University of Wisconsin – Carbone Cancer Center, Hematology and Oncology, Madison, USA.
8Helen F. Graham Cancer Center at Christiana Care Health System, Medical Oncology, Wilmington, USA.
9Apollomics Inc., Clinical Development, Foster City, USA.
10University of North Carolina- Lineberger Comprehensive Cancer Center, Medical Oncology, Chapel Hill, USA.
Background: APL-101 is an oral, ATP-competitive, selective type 1b c-MET inhibitor. Herein, we report results of a Phase 1 dose-escalation study in subjects with advanced c-MET-dysregulated solid tumors. This study assessed the safety and tolerability of APL-101 and determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D).

Methods: Subjects with locally advanced or metastatic incurable refractory solid tumors with c-MET dysregulation were enrolled (NCT03175224). c-MET dysregulation was quantified by fluorescence in situ hybridization or next generation sequencing (NGS) for c-MET amplification (c-Met/Cep 7 ≥ 2.2; GCN ≥ 6 copy), NGS for c-MET EXON 14 skipping, and immunohistochemistry for c-MET overexpression (≥ 50% tumor cells). Subjects were enrolled in a standard 3 + 3 dose escalation based on a modified Fibonacci sequence. APL-101 was orally administered at daily doses of 100 to 400 mg in two divided doses. Toxicities were graded according to the CTCAE 4.03, and preliminary efficacy was based on RECIST 1.1.

Results: A total of 17 subjects were enrolled and treated in 4 dose cohorts. The mean age was 60.9 years (SD, 14.3) and 76.5% of subjects (n=13) had an Eastern Cooperative Oncology Group performance status of 1. The median number of prior lines of therapy was 3.5 (range, 1-10). Median time since diagnosis was 34.9 months (range, 4.0-168.6). Eight subjects had c-MET amplification, 7 had c-MET overexpression, 1 had non-lung cancer c-MET EXON 14 skipping mutation and one had a c-MET kinase domain mutation (H1094Y). APL-101 demonstrated linear pharmacokinetics. Following single oral administration of enteric-coated capsules of APL-101 at 50, 100, 150, and 200 mg, the average T ranged from 16 to 38 hours. No DLTs were observed. The most common (>10%) treatment-related adverse events (AEs) included, fatigue (35.3%), hypoalbuminemia (29.4%), diarrhea (23.5%), peripheral edema (23.5%), hypocalcemia (17.6%), anemia (11.8%), dyspnea (11.8%), hyponatremia (11.8%), nausea (11.8%), and rash (11.8%). No Grade 3 or above related Serious AEs were observed in any dose cohort. Among the 15 subjects in the efficacy-evaluable population, 1 subject with Schwannoma had a partial response and 9 had best response as stable disease (60%). The clinical benefit rate (SD≥4 cycles) was 20.0%. Median progression-free survival (PFS) was 84 days (95% CL: 57, 224). The median duration of exposure was 58 days (range 13-443 days). The RP2D is 400 mg total daily dose.

Conclusions: APL-101 was generally well tolerated in advanced solid tumors with c-MET dysregulations. No DLTs were observed and the RP2D was determined to be 400 mg. Enrollment in the global Phase 2 basket-type trial focusing on lung cancer with Exon 14 skipping and solid tumors with c-MET gene amplification or fusions is underway.

Conflict of interest:

Ownership:
Apollomics Inc Stock Ownership: G. Choy, L. Espiritu, X. Zhang, A. Luria, F. Benedetti

Advisory Board:
P. Ma - Apollomics Advisory Board
M. Burkard - Medical Advisory Board of Strata Oncology

Other Substantive Relationships:
S.H. Kizilbash - No personal funds received from any entity.
P. Ma - Speakers Bureau - Merck, AstraZeneca, Bayer, Takeda
K. Mody - NIH Grant # P50 CA21064, Consulting with Astra Zeneca Pharmaceuticals, Agios, Senwha Biosciences, Basilea Pharmaceuticals, Genentech, Incyte, Puma Biotechnology, Eisai, Exelixis, Ipsen
M. Burkard - Research funding from Abbvie, Genentech, Puma, Arcus, Apollomics, and Loxo Oncology.
N. Sankar - Consultant for Apollomics Inc.