Saturday, 24 October 2020 15:05–16:35

PLENARY SESSION 1

Late Breaking and Best Proffered Papers

1LBA Late Breaking

First-in-human safety, pharmacokinetics, and preliminary efficacy of TPX-0022, a novel inhibitor of MET/SRC/CSF1R in patients with advanced solid tumors harboring genetic alterations in MET

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Background: Oncogenic alterations in MET, including amplifications, fusions, and activating mutations (kinase domain [KD] or exon 14 [Δex14]), occur in many tumor types. TPX-0022 is a novel type I tyrosine kinase inhibitor (TKI) that targets MET, SRC, and CSF1R. SRC family kinases are key downstream nodes for MET signaling that regulate hepatocyte growth factor expression which may contribute to MET inhibitor resistance. Targeting CSF1R modulates tumor associated macrophages which may contribute to TPX-0022 activity. TPX-0022 has shown activity in multiple preclinical xenograft models. This phase I study (NCT03993873) is assessing the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and clinical activity of TPX-0022 in patients (pts) with advanced solid tumors harboring genetic MET alterations.

Patients and methods: Adults with advanced cancers harboring genetic MET alterations detected by tissue or liquid biopsy were enrolled in a 3+3 dose escalation trial. Expansion was allowed at doses where clinical activity was observed. Treatment with a prior MET inhibitor was allowed. TPX-0022 was given orally in continuous 28-day cycles.

Results: As of 17 September 2020, 18 pts have been enrolled across 4 doses (20–120 mg QD): non-small cell lung cancer (NSCLC; n = 11), colorectal cancer (CRC; N = 4) and gastric (GC; n = 3). MET alterations included amplification (N = 9), Δex14 (n = 7) and fusion (n = 2). Median age was 63 (44–84). Median number of prior therapies was 3 (1–6). 7/18 (39%) had received a prior MET inhibitor. The most common adverse events (AEs) were dizziness (61%), amylase increase (33%), lipase increase (33%), fatigue (33%), and nausea (33%). There were no grade ≥3 treatment-related AEs. No events of interstitial lung disease/pneumonitis, grade 3 edema, or grade 3/4 ALT/AST elevation were reported. MTD was not reached. One dose limiting toxicity of grade 2 dizziness occurred at 120 mg QD. Systemic exposure increased in a dose-dependent manner. The steady state trough concentrations were above the IC_{95} for inhibition of MET phosphorylation. Efficacy was assessed by RECIST 1.1 and eleven subjects were efficacy evaluable. One subject with Δex14 NSCLC achieved a PR. Two subjects with MET amplified GC achieved a PR and one subject with MET amplified CRC achieved a PR (unconfirmed).

Conclusions: TPX-0022 is a novel MET/SRC/CSF1R inhibitor. TPX-0022 was generally well-tolerated. Responses were observed in Δex14 NSCLC and MET amplified GC and CRC. TPX-0022 exposure increased in a dose-dependent manner and steady state trough concentrations were above the IC_{95} for inhibition of MET phosphorylation. Phase 2 studies are planned in pts with cancers harboring MET alterations.

Conflict of interest:
Ownership:
David Hong: Molecular Match (Advisor), OncoResponse (Founder), Presagia Inc (Advisor).
Advisory Board:
Hong: Alpha Insights, Acuta, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Boxer Capital, COG, ECOR1, Expert Connect, Genentech, GLG, Group H, Guidepoint, H.C. Wainwright, Infinity, Janssen, Merrimack, Medscape, NTRK Connect, Numab, Pfizer, Prime Oncology, Seattle Genetics, SlingShot, Takeda, Trieza Therapeutics, WebMD.
Board of Directors:
Cho: Gencurix Inc, Interpark Bio Convergence Corp.
Corporate-sponsored Research:
David Hong: AbbVie, Adaptimmune, Aldi-Norte, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, MedImmune, Mirati, miRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Numab, Pfizer, Seattle Genetics, Takeda, Turning Point Therapeutics, Verstatem.
Other Substantive Relationships:
Hong: Travel, Accommodations, Expenses: Bayer, LOXO, miRNA, Genmab, AACR, ASCO, SITC.

2LBA Late Breaking

Discovery of Covalently-bound, First-in-Class Allosteric Inhibitor of PRMT5

D. McKinney[1], M. Ranaghan[1], B. McMillan[2], M. Brousseau[1], M. O'Keefe[1], J. Moroco[1], R. Singh[1], B. Besnik[1], P. McCarren[1], K. Mulvaney[3], W. Sellers[3], A. Ianari[3]. *[1]The Broad Institute, CDoT, Cambridge, USA; [2]Tango Therapeutics, Biochemistry/Biophysics, Cambridge, USA; [3]The Broad Institute, Cancer Program, Cambridge, USA*

MTAP-deleted cancer cells are selectively dependent on the expression of both the methyltransferase PRMT5 and its substrate adaptor proteins (SAPs), pICln and Riok1. Inhibition of this interaction represents a possible therapeutic strategy for MTAP-deleted cancers. We recently elucidated the molecular basis for the PRMT5-adaptor interaction, which is mediated by a highly conserved binding motif across SAPs (PRMT5 Binding Motif – or PBM) and a surface exposed pocket on PRMT5 (PBM groove) (Mulvaney et al, 2020 BioRxiv). Based on these observations, we conducted a FP-based HTS against >800 K small molecules to identify compounds that inhibit the interaction between SAPs via the PBM-groove. This screen led to the identification of a class of compounds that target this mechanism with a covalent mode of action. Structure based drug design (x-ray co-crystal and cryo-EM) allowed for improvement in apparent potency with concomitant reduction of chemical reactivity. The resulting exemplar BRD0639 represents a first-in-class PRMT5 covalent allosteric inhibitor that targets this protein-protein interaction.

No conflict of interest.

Sunday, 25 October 2020 15:45–17:15

PLENARY SESSION 2

Late Breaking and Best Proffered Papers

3LBA Late Breaking

KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Advanced/Metastatic Non–Small-Cell Lung Cancer (NSCLC) Harboring KRAS G12C Mutation

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Background: KRAS is a key mediator of a signaling cascade that promotes cellular growth and proliferation and is the most frequently mutated oncogene in cancers, including lung adenocarcinoma. Adagrasib, an investigational