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 [ex14]) 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), ex14 (n = 7) and fusions (n = 2). Median age was 63 (44–84). Median number of prior therapies was 3 (1–8). 71.8% (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 fatigue (33%), and nausea (33%). No events of interstitial lung disease/pneumonitis, grade 3 edema, or fatigue (33%), and nausea (33%). No events of interstitial lung disease/pneumonitis, grade 3 edema, or

Conclusions: TPX-0022 is a novel MET/SRC/CSF1R inhibitor. TPX-0022 was generally well-tolerated. Responses were observed in ≥ex14 NSCLC and MET fusion CRC. TPX-0022 exposure increased in a dose-dependent manner and steady state trough concentrations were above the IC50 for inhibition of MET phosphorylation. Phase 2 studies are planned in pts with cancers harboring MET alterations.

Conflict of interest: Ownership: Eurocure Insights, Acuta, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Boehringer Ingelheim, CStonePharma, CStone Pharma, Genentech, Glaxo, Group H, Guoidepoint, H.C. Wainwright, Infinity, Janssen, Merrimack, Mediscapel, NTRK Connect, Numab, Pfizer, Prime Oncology, Seattle Genetics, SlingShot, Takeda, Trieza Therapeutics, WebMD.

Board of Directors: Galen, Genencur Inc, Intercap Bio Conversion Corp. Corporate-sponsored Research: David Hong: AbbVie, Adaptimmune, Aldi-Norte, Amgen, Astra-Zeneca, Bayer, BMS, Dalichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, Medimmune, Mirati, mRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Numab, Pfizer, Seattle Genetics, Takeda, Turning Point Therapeutics, Verastem. Other Substantive Relationships: Hong, Travel, Accommodations, Expenses: Bayer, LOXO, mRNA, Genmab, AACR, ASCO, SITC.

Sunday, 25 October 2020
15:45–17:15
PLENARY SESSION 2
Late Breaking and Best Proffered Papers

3LBA
Late Breaking
KRYS1:1– 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