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43P MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

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polyploidy. A potent and potentially broad single agent activity was observed in models of human cancer.

Methods: Radiometric kinase assays, target residency surface plasmon resonance and crystal violet/YO-PRO proliferation assays were used. Phospho-TTK was measured by immunoblotting, SAC integrity by immuno-precipitation/-fluorescence and mitotic progression by flow cytometry. Nude mice bearing triple-negative breast cancer (TNBC) xenografts were treated with IV BAL0891 weekly/twice-weekly; drug levels and TTK target occupancy were evaluated using LC-MS/MS.

Results: In vitro, BAL0891 showed dual activity on TTK and PLK1 with prolonged TTK and transient PLK1 target residency; the former was also observed in tumor cells. Consistent with a dominant TTK-targeting activity, BAL0891 treatment potentiated aberrant mitotic exit and increased ploidy in HT29 tumor cells. Evaluation of effects on SAC formation and accumulation at the KT, including comparison with TTK- and PLK1-specific inhibitors at GI50 concentrations, suggested that both BAL0891 targets contribute to rapid SAC deregulation. An in vitro anti-proliferative screen indicated a broad anti-cancer potential (low nM GI50s) with >5uM GI50s on non-immortalized cells. Intermittent IV BAL0891 dosing was well-tolerated with potent anti-tumor activity in TNBC models, and regressions and pathological cures in some. Tumor TTK drug occupancy for up to one week was consistent with the efficacy of intermittent dosing schedules.

Conclusions: BAL0891 is a novel, dual TTK/PLK1 mitotic checkpoint inhibitor. In tumor cells, a prolonged effect on TTK combined with a transient effect on PLK1 contributes to rapid SAC disruption and aberrant mitotic exit, associated with potent single agent activity in mouse models of human cancer.

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43P MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

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Background: Therapy with CPI has improved OS in a subset of pts with NSCLC. Mechanisms of CPI resistance, however, have been described, including an immunosuppressive tumor microenvironment (TME), which may recruit immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarized macrophages in the TME. Sitra, a spectrum-selective TKI targeting TAM (Tyro3/Axl/MerTK) receptors and VEGFR2, reduces the number of MDSCs and Tregs and increases the M1/M2-polarized macrophage ratio. It is hypothesized to overcome an immunosuppressive TME and augment antitumor immune responses.

Methods: MRTX-500 (NCT02954991) is a phase II study evaluating sitra (120 mg QD) + nivo (Q2W or Q4W) in pts with NSQ NSCLC who have progressed on or after treatment, with a CPI-based regimen (anti-PD1/PD-L1) and/or platinum doublet chemotherapy. The primary endpoint is ORR per RECIST 1.1. Secondary endpoints include OS, PFS, and safety. We report updated efficacy data for pts with NSCLC with PCB (prior clinical benefit; CR, PR, or SD ≥12 weeks) from a CPI who were treated with sitra + nivo as either 2L or 3L therapy.

Results: As of 17 October 2020, 68 pts with PCB (57% female; median age, 66 years; ECOG PS 0/1/2, 27%/66%/7%) were treated. Median follow-up was 28 months, median OS was 15 months (95% CI 9.3, 21.1),1- and 2-year OS rates were 56% and 32%, respectively. Median PFS was 6 months, and ORR was 16% (11/68), including 2 CRs. Median duration of response was 13 months. In all CPI-experienced pts evaluable for safety (n=124), treatment related adverse events (TRAEs) occurred in 91% of pts, with Gr 3/4 TRAEs occurring in 60% of pts. The most common (≥10%) Gr 3/4 TRAEs were hypertension and diarrhea. There were no Gr 5 TRAEs. Discontinuation rates for sitra and nivo due to any AE were 30% and 27%, respectively.

Conclusions: Sitra + nivo demonstrated antitumor activity and encouraging OS compared to historical controls and no new safety signals were observed in pts with NSQ NSCLC who progressed on prior CPI. This combination is being evaluated in the phase III SAPPHIRE study. Previously presented at ESMO 2021, FPN (Final Publication Number): 1191O, Ticiana Leal et al. - Reused with permission.

Clinical trial identification: NCT02954991.

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44P A first-in-human, open-label, dose-escalation study to investigate the safety and tolerability of CHC2014, a tropomyosin receptor kinase (TRK) inhibitor, in adult patients with advanced solid tumors

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Background: TRK inhibitors are used to treat adult and pediatric patients with solid tumors based on the presence of a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. CHC2014, a highly selective pan-TRK inhibitor, shows anti-tumor activity against tumors harboring wild-type or solvent front mutated NTRK fusions in non-clinical studies. This is the first-in-human dose-escalation study of oral pan-TRK inhibitor, CHC2014, in subjects with advanced solid tumors.

Methods: This phase I, open-label, multi-center, dose-escalation study at 4 centers in Korea (NCT04014257) enrolled 17 subjects into 5 dose-escalation cohorts; doses ranged from 50 to 300 mg given once a day (QD). The primary objective was to determine the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD). The secondary objectives were to determine the pharmacokinetic (PK) characteristics and assess safety and tolerability.

Results: 10 male and 7 female subjects aged between 28-73 years received treatment with CHC2014 (6 non-small cell lung cancers, 4 head and neck cancers, 2 uterine cancers, and 1 each of glioblastoma, pancreatic, bile duct, prostate, and ovarian cancer). There were no dose-limiting toxicities at 5 dose levels and MTD was not reached. The systemic exposure was dose-proportional from 50 to 300 mg with once-daily multiple administrations. The most frequently reported treatment-related treatment-emergent adverse events (TEAEs) were fatigue (23.5%), dysgeusia, constipation, and dyspepsia (each 17.6%), which were mostly Grade 1 or 2. Only 1 case of Grade 3 anemia was reported in the 300 mg QD cohort. There was no subject with treatment-related serious TEAE. Six subjects had stable disease based on RECIST 1.1 and RANO criteria.

Conclusions: CHC2014 was safe and well-tolerated at dose levels of 50 to 300 mg QD. Doses of 200 and 300 mg QD were defined as RP2D based on PK profile and safety results. A multi-national phase 2 study will be conducted to assess the efficacy and safety in patients with NTRK fusions.

Clinical trial identification: NCT04014257.

Legal entity responsible for the study: Handok Inc.

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45P Alofanib in subsequent therapy of advanced gastric cancer: Final results from the phase Ib clinical trial

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Background: Alofanib (RPT835) is a first-in-class allosteric inhibitor that induces conformational changes in the extracellular domain of FGFR2. Here, we present the final results of the phase Ib clinical study (RPT835GC1B) of alofanib.

Methods: Patients with metastatic gastric adenocarcinoma resistant to standard therapy with measurable disease were eligible. The dose finding part used a 3+3 design, starting with a dose level of 50 mg/m2, intravenously, 5 days on, 2 days off. Five dose levels were foreseen. Primary endpoint was maximum tolerated dose (MTD). Secondary endpoints included toxicity, PK, objective response rate (ORR), overall survival (OS), and progression-free survival (PFS).

Results: 21 patients were enrolled. 4 (19%), 14 (67%), 9 (43%)/3 (14%), and 12 (57%) patients had ECOG PS 2, ≥2 metastatic sites, liver/bone metastases, and 3-6 lines previous therapy, respectively. The MTD has not been reached and dose of 350 mg/m2 has been declared as RP2D. With median follow-up of 13 months 15 (71.4%) patients had any grade treatment related adverse events (TRAE). Grade 3-4 TRAE occurred in 6 (28.6%) patients. Two (9.5%) patients discontinued treatment due to grade 3 diarrhea and grade 4 reactions immediately after injections. One partial response (5.3%) with a duration of 18.5 months was identified. Disease control rate (DCR) was 68.4% and median duration of stable disease was 4.91 months. Median PFS was 3.63 (95% CI 1.6 — 5.7) months. Median OS was 7.0 (3.8 — 10.2) months. 6-month OS rate was 57%. OS was almost 2 times better in patients with DCR (median 10,1 vs. 5.9 months) and without bone metastases (8.6 vs. 3.1). Only 1 patient (4.8%) had FGFR2 amplification (time to death was 7 months). PK parameters linearly changed depending on the dose level, but no correlation with efficacy was found. Table summarizes rate of TRAE and DCR in dose cohorts.

Table: 45P

	Dose level				
	1 50 mg/m2	2 100 mg/m2	3 165 mg/m2	4 250 mg/m2	5 350 mg/m2
N	3	3	3	3	9
Any TRAE, N (%)	2 (66.7)	2 (66.7)	3 (100)	2 (66.7)	6 (66.7)
Grade 3-4 TRAE, N (%)	2 (66.7)	0	2 (66.7)	0	2 (22.2)
DCR, N (%)	3 of 3 (100), including partial response	2 of 3 (66.7)	2 of 3 (66.7)	2 of 3 (66.7)	4 of 7 (57.1)

Conclusions: Alofanib was feasible and showed early signals of efficacy in heavily-pretreated patients with metastatic gastric cancer.

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