1286P Activity of tepotinib in brain metastases (BM): Preclinical models and clinical data from patients (pts) with MET exon 14 (METex14) skipping NSCLC

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Background: BM occur in 20–40% of NSCLC harboring *MET*ex14 skipping. We investigated the activity of the MET inhibitor tepotinib in BM in preclinical models and in pts from the VISION study (NCT02864992).

Methods: Penetration of the blood–brain barrier was assessed in Wistar rats (n=3) at 3.66 mg/kg/h iv tepotinib by determining the unbound brain ($f_{u\ br}$)-to-plasma ($f_{u\ pl}$) concentration or exposure ratio ($K_{p\ u,u}$). Efficacy was assessed in two lung cancer patient-derived xenografts (PDX) from BM harboring high *MET* amplification (*MET* gain in copy number: LU5349 = 11, LU5406 = 24) grown in NOD-SCID mice. Subcutaneous PDX (n=5/group) or PDX orthotopically implanted into the brain (n=10/group) were treated with tepotinib 125 mg/kg or vehicle control orally once daily. Intracranial tumor growth was monitored by gadolinium-based MRI. In VISION Cohort A, pts with *MET*ex14 skipping NSCLC received tepotinib 500 mg once daily. Systemic objective response, as assessed per RECIST v1.1 by independent review committee (IRC) was a preplanned analysis in pts with baseline brain lesions identified by IRC (BM-IRC) or investigator assessment (BM-INV).

Results: Preclinical data indicated high binding of tepotinib in the brain, with unbound tepotinib in brain tissue lower than in plasma ($f_{u\ br}$ = 0.4%, $f_{u\ pl}$ = 4%). Concentrations of unbound tepotinib in the brain were 25% of plasma ($K_{p\ u,u}$ = 0.25).Tepotinib treatment resulted in tumor regression in both PDX models (mean % tumor volume: −84% in LU5349, −63% in LU5406). As of 1 Jan 2020, 22/152 pts enrolled in Cohort A had baseline BM, with similar baseline pt characteristics and comparable systemic response data (Table) as the overall population.

Table: 1286P

	BM-IRC	BM-INV
Number of patients with BM; n		
Non-target lesions	14	12
Target lesions	0	1
Objective response rate, % (95% CI)	57.1% (28.9, 82.3)	53.8% (25.1, 80.8)
Best overall response; n		
Partial response	8	7
Stable disease	3	3

Conclusions: Tepotinib administration resulted in tumor regression in MET-driven lung cancer BM PDX models. Clinical activity in pts with NSCLC harboring *MET*ex14 skipping with baseline BM was consistent with the overall population in VISION. Cohort C aims to assess intracranial response.

Clinical trial identification: NCT02864992.

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1287P Efficacy and safety of entrectinib in locally advanced/metastatic *ROS1* fusion-positive NSCLC: An updated integrated analysis

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Background: Entrectinib is a potent, selective, CNS active, ROS1 tyrosine kinase inhibitor (TKI). In a preliminary analysis (data cut-off: 31 May 2018) of pts with *ROS1* fusion-positive (*ROS1*-fp) NSCLC enrolled in phase 1/2 studies (ALKA-372-001, STARTRK-1, STARTRK-2; EudraCT 2012-000148-88, NCT02097810, NCT02568267), treatment with entrectinib produced clinically meaningful and durable systemic responses with a manageable safety profile. We report on an updated integrated analysis in a larger patient population with longer follow-up (data cut-off: 1 May 2019).

Methods: Enrolled pts were ROS1 TKI naïve with measurable disease; most received entrectinib 600mg once daily. Tumours were assessed by blinded independent central review using RECIST v1.1, after 4 wks and every 8 wks thereafter. Primary endpoints were objective response rate (ORR) and duration of response (DoR). Progression-free survival (PFS), overall survival (OS), efficacy in pts with/without baseline CNS metastases, and safety were also assessed.

Results: The efficacy-evaluable population comprised 161 pts with *ROS1*-fp NSCLC; baseline characteristics are shown (Table). Median follow-up: 15.8 months (range 0.1–43.2). ORR, 67.1% (95% CI 59.3–74.3); 14 pts (8.7%) achieved complete

response, 94 (58.4%) partial response, 14 (8.7%) stable disease, 15 (9.3%) disease progression. Median DoR, 15.7 months (95% CI 13.9—28.6); median PFS, 15.7 months (95% CI 11.0—21.1); median OS, not estimable (NE) (95% CI 28.3—NE). In the subgroup with prior immunotherapy (n=24), ORR, 70.8% (95% CI 48.9—87.4). In pts with investigator-assessed CNS metastases at baseline, ORR, 62.5% (95% CI 48.6—75.1). The safety profile was similar to that previously reported.

Table: 1287P

Baseline characteristic, n (%)	*ROS1*-fp NSCLC (N = 161)
Male,	57 (35.4)
Age (years), mean (SD)	54.7 (12.5)
Race*	
White	71 (44.1)
Asian	73 (45.3)
Other	9 (5.6)
Current/former smoker	60 (37.3)
ECOG PS	
0	66 (41.0)
1	79 (49.1)
2	16 (9.9)
CNS metastases at baseline[†]	56 (34.8)
Measurable	12 (7.5)
Histology	
Adenocarcinoma	156 (96.9)
Adenosquamous carcinoma	1 (0.6)
Bronchioloalveolar carcinoma	1 (0.6)
NSCLC — NOS	3 (1.9)
Prior therapy	
Chemotherapy	110 (68.3)
Immunotherapy	24 (14.9)
Targeted therapy[‡]	14 (8.7)
Hormonal therapy	1 (0.6)
Radiotherapy	57 (35.4)
Surgery	83 (51.6)

*Race not reported for 8 patients. [†]CNS metastases at baseline per investigator; [‡]Included tyrosine kinase inhibitors. Two pts from STARTRK-2 received previous crizotinib

Conclusions: This updated analysis, using a larger dataset with longer follow-up, shows that entrectinib induces clinically meaningful responses in pts with *ROS1*-fp NSCLC, including pts with CNS metastases at baseline.

Clinical trial identification: ALKA-372-001 (EudraCT 2012-000148-88); STARTRK-1 (NCT02097810); STARTRK-2 (NCT02568267).

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1288P Efficacy of entrectinib in patients with *NTRK* or *ROS1* fusion-positive NSCLC with CNS metastases at baseline

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Background: CNS metastases are particularly common in NSCLC; effective targeted therapy requires potent intracranial activity. Entrectinib crosses the blood-brain barrier and has shown robust systemic and intracranial efficacy in pts with *NTRK* and *ROS1* fusion-positive (*NTRK*-fp and *ROS1*-fp, respectively) solid tumours based on an integrated analysis of three phase 1/2 clinical trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]). We report an updated analysis of these studies with longer follow-up, focusing on pts with CNS metastases at baseline.

Methods: Pts with *NTRK*-fp or *ROS1*-fp (data cut-off: 31 October 2018 and 1 May 2019, respectively) locally advanced/metastatic NSCLC with CNS metastases at baseline (asymptomatic or pretreated and controlled) as judged by blinded independent central review (BICR) were included. Responses were evaluated by BICR (RECIST v1.1) after wk 4, then every 8 wks. Intracranial objective response rate (ORR), intracranial duration of response (DoR) and intracranial progression-free survival (PFS) were assessed.

Results: Among 13 evaluable pts with NTRK-fp NSCLC, median age was 60 years, 53.8% were female, and 69.2% had adenocarcinoma; eight pts (61.5%) had CNS lesions at baseline. Five pts (38.5%) had received prior radiotherapy (RT) of the brain, with three completing RT $\geq$2 months prior to entrectinib. Among 161 evaluable pts with ROS1-fp NSCLC, median age was 54 years, 64.6% were female and 96.9% had adenocarcinoma; 46 pts (28.6%) had baseline CNS lesions. Twenty-seven pts (16.8%) had received prior RT of the brain, with 10 completing RT $\geq$2 months prior to entrectinib. Intracranial ORR, median intracranial DoR and median intracranial PFS for these two cohorts are shown in the table. The safety profile was consistent with that reported previously.

Table: 1288P

Efficacy (BICR assessed)	*NTRK*-fp NSCLC with baseline CNS metastases* (n=8)	*ROS1*-fp NSCLC with baseline CNS metastases* (n=46)
Intracranial response		
ORR,† n (%)	5 (62.5)	24 (52.2)
Complete response, n (%)	3 (37.5)	8 (17.4)
Partial response, n (%)	2 (25.0)	16 (34.8)
Intracranial DoR		
Responders with event, n (% of responders)	2 (40.0)	13 (54.2)
Median, months (95% CI)	NE (5—NE)	12.9 (7.1—22.1)
Intracranial PFS		
Pts with event, n (%)	4 (50.0)	31 (67.4)
Median, months (95% CI)	8.9 (5.6—NE)	8.3 (6.4—15.7)

Confidence intervals (CI) calculated using the Clopper-Pearson method
*CNS metastases at baseline judged by BICR
†Proportion of pts achieving a complete or partial intracranial response
NE, not estimable

Conclusions: Entrectinib induced clinically meaningful intracranial responses in pts with *NTRK*-fp or *ROS1*-fp NSCLC with CNS metastases at baseline.

Clinical trial identification: ALKA-372-001 (EudraCT 2012-000148-88); STARTRK-1 (NCT02097810); STARTRK-2 (NCT02568267).

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