109O Entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC): Integrated analysis of ALKA-372-001, STARTRK-1 and STARTRK-2

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Background: Entrectinib is a potent ROS1 inhibitor (as well as TRKA/B/C), designed to effectively penetrate the central nervous system (CNS); brain metastases are common in patients (pts) with advanced ROS1 fusion-positive NSCLC. Entrectinib achieves therapeutic levels in the CNS with antitumour activity in multiple intracranial tumour models. We present updated integrated safety and efficacy data from three Phase 1/2 entrectinib studies (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]) in pts with locally advanced/metastatic ROS1 fusion-positive NSCLC.

Methods: The analysis included pts with ROS1 inhibitor-naïve NSCLC harbouring a ROS1 fusion identified via nucleic acid-based diagnostic platforms. The ROS1 safety-evaluable population included pts who received $\geq$1 dose of entrectinib; the integrated efficacy analysis included pts with at least 6 months of follow-up. Tumour assessments were done at wk 4 and then every 8 wks by blinded independent central review (BICR), using RECIST v1.1. Primary endpoints by BICR: overall response rate (ORR), duration of response (DOR). Key secondary endpoints: progression-free survival (PFS), safety. Additional endpoints: intracranial ORR (complete/partial response), DOR in pts with intracranial response, PFS in pts with or without baseline CNS disease.

Results: In the ROS1 safety-evaluable population (n = 134), at least one treatment-related AE (TRAE) of any grade was seen in 93% of pts. Pts with at least one TRAE by highest grade were: grade 1/2, 59%; grade 3, 31%; grade 4, 4%. There were no grade 5 TRAEs. TRAEs led to dose reduction or discontinuation in 34% and 5% of pts, respectively. Efficacy outcomes are summarised in the table.

Table: 109O

Baseline characteristics	Pts with treatment-naïve, ROS1-positive NSCLC (n = 53)
Median age range	53 years 27–73 years
Gender male female	36% 64%
Smoking status never smoked	59% 42%
former/current smoker	
Efficacy outcomes	
ORR (BICR)	77% (95% CI 64–88) 3 CR 38 PR
Median DOR (BICR)	25 months (95% CI 11–35)
Median PFS (BICR)[A] without CNS disease	26 months (95% CI 16–37)
(n = 30) with CNS disease (n = 23)	14 months (95% CI 5–NR)
Intracranial ORR (n = 20)[B]	55% (95% CI 32–77) 4 CR 7 PR
Median intracranial DOR (n = 11)[C]	13 months (95% CI 6–NR)

BICR, blinded independent central review; CNS, central nervous system; CR, complete response, DOR, duration of response; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PR, partial response
[A]Pts with measurable CNS disease at baseline per Investigator,
[B]Pts with measurable CNS disease at baseline per BICR,
[C]In pts with an intracranial response

Conclusions: Entrectinib is highly active in pts with ROS1 fusion-positive NSCLC, including pts with CNS disease. Entrectinib is well tolerated with a manageable safety profile.

Clinical trial identification: ALKA-372-001 = EudraCT 2012-000148-88 – start date: 2015, trials ongoing STARTRK-1= NCT02097810 – start date: 2014, active, not recruiting (last update 2018) STARTRK-2 = NCT02568267 – start date: 2015, recruiting (last update 2018).

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