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Intracranial efficacy of entrectinib in patients with NTRK fusion-positive solid tumours and baseline CNS metastases

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Background

NTRK gene fusions are clinically actionable oncogenic drivers in solid tumours. CNS metastases are diagnosed in 10–30% of solid tumours and associated with poor outcome. Entrectinib is a CNS-active TRK inhibitor that crosses the blood-brain barrier and has demonstrated systemic and intracranial (IC) efficacy in patients (pts) with *NTRK* fusion-positive (fp) solid tumours in three phase 1/2 clinical trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]). We report an updated integrated analysis of these entrectinib studies, focussing on IC activity (data cut-off: 31 Oct 2018).

Methods

Pts with *NTRK*-fp solid tumours and baseline CNS metastases (asymptomatic or pretreated and controlled; measurable or non-measurable) were included. IC tumour assessments, performed at the end of week 4 and every 8 weeks thereafter, were evaluated by blinded independent central review (BICR) using RECIST v1.1. Study endpoints were IC objective response rate (IC ORR), IC duration of response (IC DoR) and IC progression-free survival (IC PFS). Safety was evaluated in the integrated safety population, all pts who received ≥1 dose entrectinib (N=504).

Results

Full analysis set (FAS) comprised 16 pts with baseline CNS metastases per BICR (measurable or non-measurable), with 5 tumour types (8 NSCLC; 4 thyroid; 2 sarcoma; 1 salivary; 1 breast). Of these 16 pts, 8 had measurable CNS metastases (measurable set) and were evaluable for response. IC outcomes for FAS and measurable set are summarised (Table). IC ORRs were high in the FAS (50.0%) and measurable set (62.5%). IC efficacy was evident regardless of prior brain radiotherapy. In the safety population, neurotoxicity profile was similar in pts with (n=176) and without (n=328) baseline CNS metastases (per investigator), including cognitive disorders (6.3% and 6.4% respectively).

Conclusions

Entrectinib shows durable IC activity in pts with *NTRK*-fp solid tumours and baseline CNS metastases.Table: 3640

Intracranial outcomes	Pts with *NTRK*-fp solid tumours and baseline CNS metastases per BICR	
	Measurable set (n=8)	Full analysis set* (n=16)
IC ORR, n (%)	5 (62.5)	8 (50.0)
CR	1 (12.5)	4 (25.0)

Intracranial outcomes	Pts with *NTRK*-fp solid tumours and baseline CNS metastases per BICR	
	Measurable set (n=8)	Full analysis set* (n=16)
PR	4 (50.0)	4 (25.0)
SD, n (%)	1 (12.5)	1 (6.3)
PD, n (%)	1 (12.5)	1 (6.3)
Non-CR/non-PD, n (%)	0	5 (31.3)
Missing/unevaluable, n (%)	1 (12.5)	1 (6.3)
Median IC DoR in responders (95% CI)	NE (5.0–NE)	8.0 (6.7–NE)
Median IC PFS (95% CI)	10.1 (2.8–NE)†	8.9 (5.9–14.3)‡

IC, intracranial; NE, not estimable.*As per RECIST v1.1 non-measurable CNS disease could only be categorised as CR, non-CR/non-PD, or PD.†IC PFS events occurred in 4 pts (2 PD, 2 deaths).‡IC PFS events occurred in 10 pts (3 PD, 7 deaths).

Clinical trial identification

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

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