Updated efficacy and safety data of entrectinib in patients with locally advanced/metastatic *NTRK* fusion-positive (fp) solid tumours

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BACKGROUND

- *NTRK* gene fusions encode chimeric tropomyosin receptor kinase proteins, resulting in constitutively active kinases that are **oncogenic drivers** of various solid tumour types.[1,2]
- Entrectinib is a potent, CNS-active, *TRK* and *ROS1* inhibitor.[3]
- In a previous analysis of three phase I/II trials (ALKA-372-001: EudraCT 2012-000148-88; STARTRK-1: NCT02097810; STARTRK-2: NCT02568267), **entrectinib demonstrated deep systemic and intracranial (IC) efficacy** in patients with *NTRK*-fp solid tumours (data cut-off: 02 August 2021):[4]
  - Objective response rate (ORR): **61.3%** (95% CI: 53.1–69.2); median duration of response (DoR): **20.0 months** (95% CI: 13.2–31.1)
  - Median progression-free survival (PFS): **13.8 months** (95% CI: 10.1–20.0); median overall survival (OS): **37.1 months** (95% CI: 27.2–not estimable [NE])
  - IC-ORR: **69.2%** (95% CI: 38.6–90.9).
- We present updated data from a larger population with approximately 30% more patients and 12 months of further follow-up (**data cut-off: 02 August 2022**)
  - This analysis also includes patients from TAPISTRY (NCT04589845), a phase II, open-label, multi-cohort study evaluating the efficacy and safety of targeted therapies or immunotherapy in patients with advanced solid tumours.[5]

METHODS

- Adult patients (≥18 years old) with locally advanced or metastatic *NTRK*-fp solid tumours from ALKA-372-001, STARTRK-1, STARTRK-2 and TAPISTRY (**enrolment cut-off: 02 July 2021**) were included in this analysis:
  - Patients with measurable disease who had received ≥1 dose of oral entrectinib (600 mg once daily) and had ≥13 months of follow-up from enrolment were included in the efficacy-evaluable population
  - The safety population comprised all patients who had ≥1 dose of entrectinib.
- Tumour responses were assessed by blinded independent central review (BICR) per RECIST v1.1 at Week 4 and every 8 weeks thereafter.
- Primary endpoints were BICR-assessed ORR and DoR; key secondary endpoints included BICR-assessed PFS, IC efficacy, investigator-assessed time to CNS progression, and OS.

RESULTS

- At the data cut-off, the efficacy-evaluable population comprised **194 patients** with 17 different types of solid tumours; baseline characteristics are shown in **Table 1**.
- Median survival follow-up was **38.7 months** (range: 0–72).

Table 1. Patient demographics and baseline characteristics

Characteristic	*NTRK*-fp efficacy population (N=194)
Median age, years (range)	58.0 (19–92)
Female, n (%)	100 (51.5)
Race, n (%)	
White	98 (50.5)
Asian	69 (35.6)
Black or African American	4 (2.1)
Other or not reported	23 (11.9)
ECOG PS, n (%)	
0	80 (41.2)
1	100 (51.5)
2	14 (7.2)
***NTRK* fusion**, n (%)	80 (41.2)
NTRK1	9 (4.6)
NTRK2	105 (54.1)
NTRK3	
Prior lines of systemic therapy, n (%)	
0	70 (36.1)
1	61 (31.4)
≥2	63 (32.5)
CNS metastases at baseline, n (%)	
Per investigator	36 (18.6)
Per blinded independent central review	28 (14.4)*

*Data for the three TAPISTRY patients are missing. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; fp, fusion positive

Overall efficacy

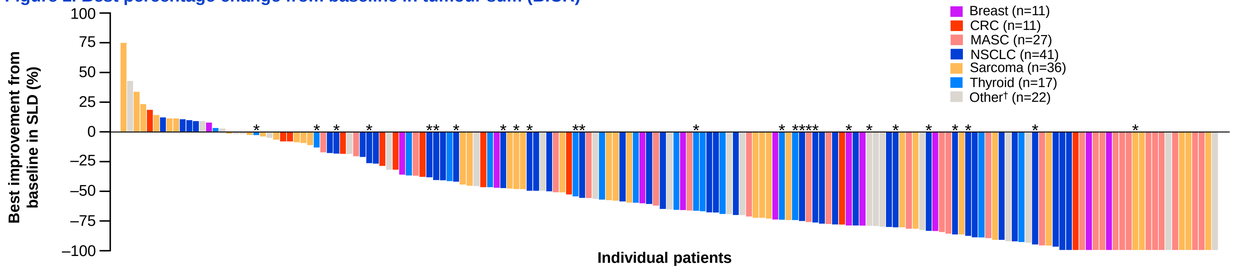
- The confirmed ORR per BICR was **62.4%** (**Table 2**); **16.5%** (n=32) of patients had a complete response (CR)
  - Responses were observed in patients with and without baseline CNS metastases, with ORRs of **61.1%** and **62.7%**, respectively (**Table 2**).
- A reduction in tumour size from baseline was observed in most patients and across different tumour types (**Figure 1**).
- Entrectinib was associated with durable systemic responses and long survival; median DoR was **29.4 months**, median PFS was **15.7 months,** and median OS was **38.2 months** (**Table 2**)
  - A benefit was observed regardless of the presence of CNS metastases at baseline.

Table 2. Overall efficacy

Parameter	Efficacy population (N=194)	Baseline CNS mets* (n=36)	No baseline CNS mets* (n=158)
ORR†, % (95% CI)	62.4 (55.2–69.2)	61.1 (43.5–76.9)	62.7 (54.6–70.2)
CR, n (%)	32 (16.5)	3 (8.3)	29 (18.4)
PR, n (%)	89 (45.9)	19 (52.8)	70 (44.3)
SD, n (%)	19 (9.8)	4 (11.1)	15 (9.5)
PD, n (%)	23 (11.9)	3 (8.3)	20 (12.7)
Non-CR/non-PD, n (%)	7 (3.6)	0 (0.0)	7 (4.4)
Missing/unevaluable‡, n (%)	24 (12.4)	7 (19.4)	17 (10.8)
Median DoR†, months (95% CI)	29.4 (17.2–36.8)	27.3 (13.0–33.3)	30.4 (16.9–NE)
Median PFS†, months (95% CI)	15.7 (13.7–22.9)	13.8 (5.1–30.3)	15.7 (13.7–28.0)
Median OS, months (95% CI)	38.2 (28.6–56.5)	28.3 (8.9–48.9)	40.5 (30.4–NE)

*CNS metastases status at baseline, per investigator; †Assessed by BICR per RECIST v1.1; ‡Includes patients with unevaluable on-study scans or those who discontinued treatment prior to obtaining adequate scans to evaluate or confirm response. BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; mets, metastases; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Figure 1. Best percentage change from baseline in tumour sum (BICR)



*Patients with investigator-assessed CNS metastases at baseline; †Other tumour types in the efficacy-evaluable population: neuroendocrine (n=7); head and neck (n=5); pancreatic (n=4); cancer of unknown primary (n=3); gynaecological (n=2); adrenal, cholangiocarcinoma, gastrointestinal, neuroblastoma, penile, prostate (n=1) each.
BICR; blinded independent central review; CNS, central nervous system; CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer; SLD, sum of longest diameters.

- Deep responses were observed in both treatment-naïve and previously treated patients, and in patients with different tumour types (**Table 3** and **Table 4**).
- Patients who had received prior therapy in the metastatic setting showed durable responses across many tumour types (**Table 3** and **Table 4**).

Table 3. Efficacy (BICR) by number of prior lines of systemic therapy

Parameter	Prior lines of systemic therapy*					
	0 (n=70)	1 (n=61)	2 (n=33)	3 (n=15)	4 (n=11)	>4 (n=4)
ORR, n (%) 95% CI	53 (75.7) 64.0–85.2	33 (54.1) 40.9–66.9	21 (63.6) 45.1–79.6	9 (60.0) 32.3–83.7	5 (45.5) 16.8–76.6	0 (0.0) 0.0–60.2
	0 (n=53)	1 (n=33)	2 (n=21)	3 (n=9)	4 (n=5)	>4 (n=0)
Median DoR, months 95% CI	NE 22.0–NE	29.5 15.1–47.8	16.9 9.3–29.4	NE 9.0–NE	NE 2.8–NE	–

*In the metastatic setting. BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, objective response rate.

Table 4. Efficacy (BICR) by tumour type

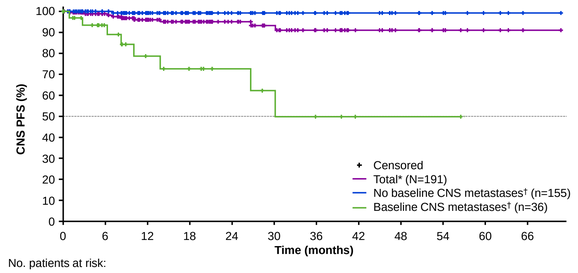
Tumour type*	ORR, n/N (%)	Median DoR, months (range)
NSCLC	32/51 (62.7)	27.3 (4–70†)
Sarcoma	23/38 (60.5)	15.0 (3–58†)
MASC	27/31 (87.1)	NE (3–62†)
Thyroid	14/21 (66.7)	17.2 (6–55†)
Colorectal	4/13 (30.8)	15.1 (6–20)
Breast	8/13 (61.5)	12.9 (4–64†)

*Other tumour types in the efficacy-evaluable population: neuroendocrine (n=7); head and neck (n=5); pancreatic (n=4); cancer of unknown primary (n=3); gynaecological (n=2); adrenal, cholangiocarcinoma, gastrointestinal, neuroblastoma, penile, prostate (n=1 each); †Censored. BICR, blinded independent central review; DoR, duration of response; MASC, mammary analogue secretory carcinoma; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate.

Intracranial efficacy and time to CNS progression

- CNS data by BICR for TAPISTRY were not available at the time of this analysis.
- In patients with measurable baseline CNS metastases per BICR (n=17):
  - IC-ORR was **70.6%** (95% CI: 44.0–89.7), including six IC-CRs (**35.3%**)
  - Median IC-PFS was **17.9 months** (95% CI: 5.9–26.7).
- Of the 36 patients with investigator-assessed baseline CNS metastases, eight (22%) had an event (12-month event-free rate: **78.7%**; **Figure 2**).
- Of the 158 patients without investigator-assessed baseline CNS metastases, only one patient had an event (12-month event-free rate: **99.2%**; **Figure 2**).

Figure 2. Time to CNS progression (deaths censored)



No. patients at risk:

191	163	147	131	109	94	81	68	58	49	42	34	29	26	19	18	13	11	9	6	4	3	1	1	NE
155	136	126	116	96	83	71	60	51	43	37	30	26	23	18	17	12	10	8	6	4	3	1	1	NE
36	27	21	15	13	11	10	8	7	6	5	4	3	3	1	1	1	1	1	NE					

*Data for the three TAPISTRY patients are missing; †Baseline CNS metastases by investigator.
CNS, central nervous system; NE, not estimable; PFS, progression-free survival.

Safety

- In the overall safety population (N=296), entrectinib demonstrated a manageable safety profile:
  - The median dose intensity was **94.1%** (range: 14.2–233.3)
  - Most treatment-related adverse events (TRAEs) were Grade 1/2; the four most frequent were **dysgeusia** (34.5%), **constipation** (29.1%), **diarrhoea**, and **weight increase** (both 28.7%)
  - TRAEs leading to dose reduction, interruption and discontinuation occurred in 24.0%, 34.1%, and 6.4% of patients, respectively.

CONCLUSIONS

In patients with *NTRK*-fp solid tumours, entrectinib has continued to induce deep and durable systemic and intracranial responses.

The safety profile of entrectinib was consistent with previous analyses and most TRAEs were manageable.

Overall ORR 62.4%

Median DoR 29.4 months

Median PFS 15.7 months

Median OS 38.2 months

Manageable safety profile

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Disclosures

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