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Efficacy and safety of entrectinib in patients with locally advanced/metastatic *NTRK* fusion-positive solid tumours

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BACKGROUND

- *NTRK* gene fusions lead to transcription of chimeric TRK proteins with constitutively active kinase function that are potential oncogenic drivers across tumour types.[1,2]
- Entrectinib is a potent inhibitor of TRKA/B/C that was designed to cross the blood-brain barrier and remain in the CNS.[3,4]
- In an integrated analysis of three phase 1/2 studies (ALKA-372-001: EudraCT 2012-000148-88; STARTRK-1: NCT02097810; and STARTRK-2: NCT02568267), entrectinib demonstrated systemic and intracranial efficacy in patients with *NTRK* fusion-positive solid tumours[5,6]
  - At the primary data cut-off (31 May 2018): objective response rate (ORR) was 57.4%, median duration of response (DoR) was 10.4 months and median progression-free survival (PFS) was 11.2 months[5]
  - Intracranial responses were also demonstrated in 6 out of 11 patients with baseline CNS metastases.[5]
- We present updated data in a larger population with longer follow-up **(data cut-off 31 August 2020)**.

METHODS

- This analysis included patients ≥18 years with *NTRK* fusion-positive solid tumours.
- Patients received oral entrectinib 600 mg once daily; the efficacy analysis included patients enrolled prior to 31 July 2019 (≥12 months from first scheduled tumour assessment).
- Tumours were assessed by blinded independent central review (BICR) using RECIST v1.1, after 4 weeks and every 8 weeks thereafter.
- Primary endpoints were ORR and DoR. Key secondary endpoints included PFS, overall survival (OS), efficacy in patients with and without baseline CNS metastases and safety.

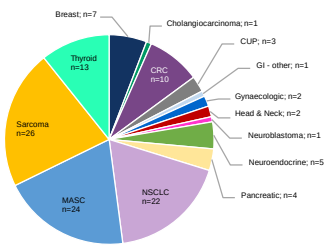
RESULTS

Summary Video

Study populations

- At data cut-off, the overall safety population (N=626) comprised all adult and paediatric patients who had received ≥1 dose of entrectinib, including 193 patients with *NTRK* fusion-positive solid tumours.
- The efficacy population included 121 patients with 14 different tumour types, who received ≥1 dose of entrectinib and had measurable disease at baseline (Table 1; Figure 1).
- Median survival follow-up was **25.8 months**.

Figure 1. Study population by tumour type



CRC, colorectal carcinoma; CUP, cancer of unknown primary; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer.

Table 1: Patient demographics and baseline characteristics

Characteristic	*NTRK* fusion-positive (N=121)
Median age, years (range)	57.0 (21–88)
Female, n (%)	62 (51.2)
Race, n (%)	
White / Asian / Black or African American / Other / Not reported	73 (60.3) / 29 (24.0) / 3 (2.5) / 1 (0.8) / 15 (12.4)
ECOG performance status, n (%)	
0 / 1 / 2	53 (43.8) / 57 (47.1) / 11 (9.1)
Prior lines of systemic therapy in the metastatic setting, n (%)	
0 / 1 / 2 / ≥3	37 (30.6) / 35 (28.9) / 26 (21.5) / 23 (19.0)
Any previous therapy, n (%)	
Chemotherapy / targeted therapy / immunotherapy / hormonal therapy	88 (72.7) / 24 (19.8) / 13 (10.7) / 10 (8.3)
CNS metastases at baseline per INV / per BICR, n (%)	
Present	26 (21.5) / 19 (15.7)
Measurable	*6 (5.0) / 11 (9.1)*
Absent	95 (78.5) / 102 (84.3)
Prior RT of the brain*, n (%)	17 (65.4)
Time from end of brain RT to first dose†, n (%)	
<2 months / 2 months–<6 months / ≥6 months	7 (41.2) / 5 (29.4) / 5 (29.4)

*Patients with baseline CNS metastases per investigator. †Patients with baseline CNS metastases per investigator and prior brain RT.
BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; INV, investigator; RT, radiotherapy.

Overall efficacy

- Confirmed ORR was **61.2%** (19 complete responses; 55 partial responses) and median DoR was **20.0 months** (Table 2). The ORR was similar in patients with and without CNS metastases at baseline.
- Median PFS was **13.8 months**, and median OS was **33.8 months** (Table 2).
- Responses were observed across tumour types (Table 3; Figure 2).

Intracranial efficacy and time to CNS progression

- Entrectinib was associated with **deep and durable intracranial responses** in patients with baseline CNS metastases by BICR (Table 4).
- Time to CNS progression (only confirmed CNS progression counted as an event; death was censored) in the overall *NTRK* fusion-positive population and the subpopulations of patients with and without CNS metastases at baseline (per investigator assessment) is shown in Figure 3.
- Of the 26 patients with baseline CNS involvement, 6 (23.1%) had an event (12-month event-free rate: 81%).
- None of the patients without baseline CNS metastases had symptomatic, scan-confirmed CNS progression at cut-off (12-month event-free rate: **100%**)
  - Regular CNS scans of patients without baseline CNS disease were not mandated by the protocol but only required if clinically indicated.

Table 2: Overall efficacy

Parameter	Efficacy population (N=121)	Baseline CNS metastases‡ (n=26)	No baseline CNS metastases‡ (n=95)
ORR*, n (%) 95% CI	74 (61.2) 51.9–69.9	15 (57.7) 36.9–76.7	59 (62.1) 51.6–71.9
Complete response, n (%)	19 (15.7)	2 (7.7)	17 (17.9)
Partial response, n (%)	55 (45.5)	13 (50.0)	42 (44.2)
Stable disease, n (%)	13 (10.7)	4 (15.4)	9 (9.5)
Progressive disease, n (%)	13 (10.7)	2 (7.7)	11 (11.6)
Non-CR/PD, n (%)	6 (5.0)	0	6 (6.3)
Missing or unevaluable†, n (%)	15 (12.4)	5 (19.2)	10 (10.5)
Median time to response*, months (95% CI)	1.0 (0.9–1.0)	1.7 (0.9–2.8)	1.0 (0.9–1.0)
Median DoR*, months (95% CI)	20.0 (13.0–38.2)	17.2 (6.0–29.4)	29.0 (12.9–NE)
Median PFS*, months (95% CI)	13.8 (10.1–19.9)	11.7 (4.7–30.2)	13.8 (10.2–20.8)
Median OS, months (95% CI)	33.8 (23.4–46.4)	19.9 (7.9–NE)	37.1 (23.9–NE)

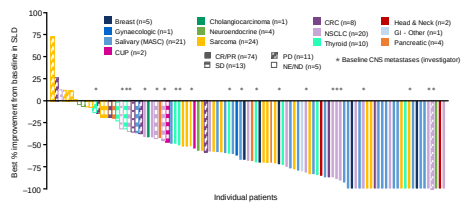
*BICR assessed, RECIST v1.1. †Includes patients with unevaluable on-study scans or those who discontinued prior to obtaining adequate scans to evaluate or confirm response. ‡CNS metastases status determined by investigator. BICR, blinded independent central review; CNS, central nervous system; CR, complete response; NE, not estimable; PD, progressive disease.

Table 3: Efficacy by tumour type

Tumour types (n≥4)*	n	ORR, % (95% CI)	DoR, months (95% CI)
Sarcoma	26	57.7 (36.9–76.7)	15.0 (4.6–NE)
Salivary (MASC)	24	83.3 (62.6–95.3)	NE (NE)
NSCLC	22	63.6 (40.7–82.8)	19.9 (10.4–29.4)
Thyroid cancer	13	53.8 (25.1–80.8)	13.2 (7.9–NE)
Colorectal carcinoma	10	20.0 (2.5–55.6)	17.6 (15.1–20.0)
Breast cancer	7	71.4 (29.0–96.3)	12.9 (4.2–NE)
Neuroendocrine tumours	5	40.0 (5.3–85.3)	NE (11.1–NE)
Pancreatic cancer	4	75.0 (19.4–99.4)	12.9 (7.1–12.9)

*Other tumour types in the efficacy-evaluable population were: carcinoma of unknown primary (n=3); gynaecologic and head & neck cancers (n=2 each); neuroblastoma, gastrointestinal tract carcinoma, cholangiocarcinoma (n=1 each). One patient with neuroblastoma died 3 days after starting therapy due to a non-related AE. AE, adverse event; MASC, mammary analogue secretory carcinoma; NE, not estimable; NSCLC, non-small cell lung cancer.

Figure 2. Best percent change from baseline in tumour sum (BICR assessment)



CNS, central nervous system; CR, complete response; CRC, colorectal carcinoma; CUP, cancer of unknown primary; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; ND, not determined; NE, not estimable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

Safety

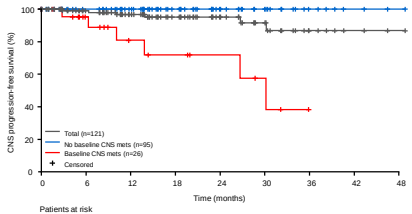
- Entrectinib had a safety profile in line with that previously reported, with most treatment-related adverse events (TRAEs; Table 5) reversible and resolved via dose reductions or modifications.
- The median dose intensity was 91.3% (interquartile range [IQR] 65.9–99.6) in the *NTRK* fusion-positive safety population and 94.2% (IQR 67.8–100.0) in the overall safety population.

Table 4: Intracranial efficacy (per BICR)

Parameter	Baseline CNS metastases (BICR) (N=19)	Measurable baseline CNS metastases (BICR) (N=11)
Intracranial ORR, n (%) (95% CI)	10 (52.6) (28.9–75.6)	7 (63.6) (30.8–89.1)
Complete response, %	6 (31.6)	3 (27.3)
Partial response, %	4 (21.1)	4 (36.4)
Median intracranial DoR, months (95% CI)	17.2 (7.4–NE)	22.1 (7.4–NE)
Median intracranial PFS, months (95% CI)	10.1 (6.3–26.7)	19.9 (5.9–NE)

BICR, blinded independent central review; CNS, central nervous system; NE, not estimable.

Figure 3. Time to CNS progression (deaths censored)



Patients at risk

Total	121	101	91	82	71	55	47	37	31	24	20	13	7	5	3	2	1
No CNS mets	95	81	76	71	62	48	40	32	26	20	17	12	7	5	3	2	1
CNS mets	26	20	15	11	9	7	7	5	5	4	3	1					

CNS, central nervous system.

Table 5: Safety summary

TRAEs reported in ≥10% of patients Patients, %	*NTRK* fusion-positive safety population (n=193)	Overall safety population (N=626)
Dysgeusia	35.2	35.9
Diarrhoea	31.1	25.9
Fatigue	27.5	28.8
Weight increase	27.5	27.3
Constipation	25.9	25.1
Blood creatinine increase	25.9	21.2
Dizziness	24.9	26.8
Oedema peripheral	18.1	16.1
Anaemia	17.1	15.7
Nausea	16.6	20.3
AST increase	16.6	13.1
ALT increase	15.5	12.5
Paraesthesia	11.9	15.8
Myalgia	10.9	14.4
Vomiting	10.9	13.6
Arthralgia	5.2	10.2

NTRK-fp, *NTRK* fusion-positive; TRAEs, treatment-related adverse events.

CONCLUSIONS

- With additional clinical experience, entrectinib continues to demonstrate durable overall and intracranial responses, regardless of CNS status at baseline:
  - In patients without baseline CNS metastases, ORR was **62.1%** (17 CR) and median DoR was **29.0 months**
  - In patients with baseline CNS metastases, ORR was **57.7%** and median DoR was **17.2 months**.
- Entrectinib can address the unmet need of a **CNS-active treatment** in patients with *NTRK* fusion-positive solid tumours.

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Disclosures

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