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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.

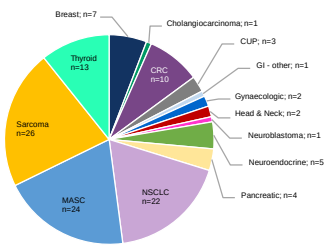
## RESULTS

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) |

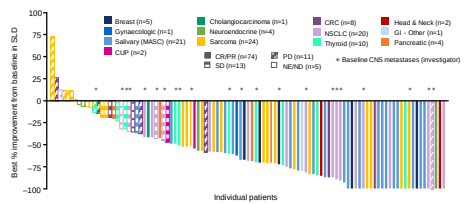
*BICR assessed, RECIST v1.1. †Includes patients with unevaluable on-study scans or those who discontinued prior to obtaining adequate scans to evaluate or confirm response. ‡CNS metastases status determined by investigator. BICR, blinded independent central review; CNS, central nervous system; CR, complete 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

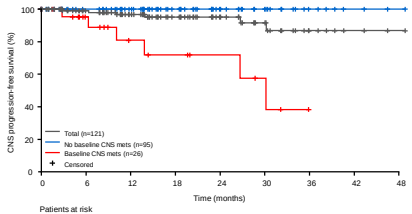
- Entrectinib had a safety profile in line with that previously reported, with most treatment-related adverse events (TRAEs; Table 5) reversible and resolved via dose reductions or modifications.
- The median dose intensity was 91.3% (interquartile range [IQR] 65.9–99.6) in the *NTRK* fusion-positive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

**L.B.** reports: advisory/consultancy for Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Janssen, Merck Sharp & Dohme and Regeneron; research grant/funding (institutional) from BeyondSpring Pharma; shareholder/stockholder/stock options from Epic Sciences. For co-author disclosures please refer to the abstract: https://oncologypro.esmo.org/

**Acknowledgements**

We would like to thank the patients, their families, and participating study centres. This study was funded by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Laura Vergoz, PhD of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

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