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Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

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See **Online** for appendix

Data sharing

Qualified researchers can request access to individual patient-level data through the clinical study data request platform. Further details on Roche's criteria for eligible studies are available online. Those interested in accessing study data should view Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents can also be found online.

For the **data request platform** see <https://www.clinicalstudydatarequest.com>

For **Roche's criteria** see <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>

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Summary

Background—Entrectinib is a potent inhibitor of tropomyosin receptor kinase (TRK) A, B, and C, which has been shown to have anti-tumour activity against *NTRK* gene fusion-positive solid tumours, including CNS activity due to its ability to penetrate the blood–brain barrier. We present an integrated efficacy and safety analysis of patients with metastatic or locally advanced solid tumours harbouring oncogenic *NTRK1*, *NTRK2*, and *NTRK3* gene fusions treated in three ongoing, early-phase trials.

Methods—An integrated database comprised the pivotal datasets of three, ongoing phase 1 or 2 clinical trials (ALKA-372–001, STARTRK-1, and STARTRK-2), which enrolled patients aged 18 years or older with metastatic or locally advanced *NTRK* fusion-positive solid tumours who received entrectinib orally at a dose of at least 600 mg once per day in a capsule. All patients had an Eastern Cooperative Oncology Group performance status of 0–2 and could have received previous anti-cancer therapy (except previous TRK inhibitors). The primary endpoints, the proportion of patients with an objective response and median duration of response, were evaluated by blinded independent central review in the efficacy-evaluable population (ie, patients with *NTRK* fusion-positive solid tumours who were TRK inhibitor-naïve and had received at least one dose of entrectinib). Overall safety evaluable population included patients from STARTRK-1, STARTRK-2, ALKA-372–001, and STARTRK-NG ([NCT02650401](#)); treating young adult and

paediatric patients [aged ≥ 21 years]), who received at least one dose of entrectinib, regardless of tumour type or gene rearrangement. *NTRK* fusion-positive safety evaluable population comprised all patients who have received at least one dose of entrectinib regardless of dose or follow-up. These ongoing studies are registered with [ClinicalTrials.gov](https://clinicaltrials.gov), [NCT02097810](https://clinicaltrials.gov/ct2/show/study/NCT02097810) (STARTRK-1) and [NCT02568267](https://clinicaltrials.gov/ct2/show/study/NCT02568267) (STARTRK-2), and EudraCT, 2012-000148-88 (ALKA-372-001).

Findings—Patients were enrolled in ALKA-372-001 from Oct 26, 2012, to March 27, 2018; in STARTRK-1 from Aug 7, 2014, to May 10, 2018; and in STARTRK-2 from Nov 19, 2015 (enrolment is ongoing). At the data cutoff date for this analysis (May 31, 2018) the efficacy-evaluable population comprised 54 adults with advanced or metastatic *NTRK* fusion-positive solid tumours comprising ten different tumour types and 19 different histologies. Median follow-up was 12.9 months (IQR 8.77–18.76). 31 (57%; 95% CI 43.2–70.8) of 54 patients had an objective response, of which four (7%) were complete responses and 27 (50%) partial responses. Median duration of response was 10 months (95% CI 7.1 to not estimable). The most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (seven [10%] of 68 patients in the *NTRK* fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anaemia (8 [12%] and 16 [5%]). The most common serious treatment-related adverse events were nervous system disorders (three [4%] of 68 patients and ten [3%] of 355 patients). No treatment-related deaths occurred.

Interpretation—Entrectinib induced durable and clinically meaningful responses in patients with *NTRK* fusion-positive solid tumours, and was well tolerated with a manageable safety profile. These results show that entrectinib is a safe and active treatment option for patients with *NTRK* fusion-positive solid tumours. These data highlight the need to routinely test for *NTRK* fusions to broaden the therapeutic options available for patients with *NTRK* fusion-positive solid tumours.

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Introduction

Fusions involving the *NTRK* gene family—*NTRK1*, *NTRK2*, and *NTRK3*—lead to the expression of chimeric rearrangements in tropomyosin receptor kinases (TRKs) A, B, and C, respectively, with constitutively active kinase function.¹ *NTRK* fusions act as oncogenic drivers and are potential therapeutic targets across a broad range of tumour types, including sarcomas, non-small-cell lung cancer (NSCLC), and mammary analogue secretory carcinoma.^{2,3} These gene fusions were originally identified in colorectal cancer^{4,5} and occur in approximately 0.3% of all solid tumours, although frequency varies widely by cancer type,^{1,6–8} as does that of corresponding aberrant expression of the TRK proteins.⁹

Novel compounds under development for the treatment of cancers with *NTRK* gene fusions include selective inhibitors of the TRK family of kinases. In November, 2018, the US Food and Drug Administration (FDA) granted accelerated approval of larotrectinib use in adults and children with solid tumours harbouring an *NTRK* gene fusion without a known acquired resistance mutation.^{10,11} However, only a few patients with CNS involvement have been reported to respond to larotrectinib, and its efficacy in such settings has not been well delineated.^{12,13} Additionally, intracranial objective response and duration of response have

not been reported for larotrectinib. Thus, an unmet medical need exists for effective treatments with CNS activity for patients with *NTRK* fusion-positive tumours.

Entrectinib is a potent inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK that is specifically designed to have systemic activity and cross the blood–brain barrier.^{14,15} In vitro, entrectinib potently inhibits TRKA, TRKB, and TRKC at low nanomolar concentrations, with an average median inhibitory concentration of 0.002 µM.¹⁵ Animal studies have reported substantial concentrations of entrectinib in the CNS, with blood-to-brain concentration ratios in dogs, rats, and mice ranging from 0.43 to 1.90.¹⁴

Three clinical trials have been done to assess the safety and activity of entrectinib in adult patients with advanced or metastatic cancer. Two phase 1 trials (ALKA-372–001 and STARTRK-1) showed that entrectinib was well tolerated with clinical activity in patients with *NTRK*, *ROS1*, or *ALK* fusion-positive tumours, including those with CNS involvement.¹⁶ Among those patients treated in the ALKA-372–001 and STARTRK-1 studies, four patients had *NTRK* fusion-positive tumours that responded to entrectinib, with dramatic intracranial activity observed in one patient with metastatic *NTRK* fusion-positive NSCLC.^{16,17} A phase 2 trial (STARTRK-2) subsequently focused on a cohort of patients with cancers harbouring fusions involving the *NTRK1*, *NTRK2*, and *NTRK3* genes (the other cohorts focused on *ROS1* fusion-positive cancers).

In this pooled analysis, we aimed to evaluate the activity of entrectinib in patients across these three phase 1–2 trials, representing a range of metastatic or locally advanced or unresectable *NTRK* fusion-positive solid tumours, including those with CNS disease, and to characterise its safety in the context of all available data in adult and paediatric populations.

Methods

Study design and participants

Patients (aged ≥ 18 years) with metastatic or locally advanced *NTRK* fusion-positive solid tumours were enrolled in one of two phase 1 studies (ALKA-372–001 or STARTRK-1) or a phase 2 global basket study (STARTRK-2). ALKA-372–001 was done at two cancer centres in Italy. STARTRK-1 was done at ten sites (one medical centre in Korea, one hospital in Spain, and one hospital and seven cancer centres in the USA). STARTRK-2 is ongoing at more than 150 sites (cancer and medical centres, research institutes, hospitals, and universities) in 15 countries (appendix pp 2–10). Patients with *ROS1* or *ALK* gene rearrangements were also enrolled in the three clinical trials, but were not included in this *NTRK* fusion-positive focused integrated analysis.

Patients were included in this prespecified integrated analysis if they had a solid tumour that harboured a fusion in any *NTRK* gene (*NTRK1*, *NTRK2*, or *NTRK3*), had measurable disease assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (regardless of line of therapy), had received no previous therapy with TRK-targeted treatments (although previous treatment with other cancer therapies was allowed), and had received at least one dose of entrectinib at or above the recommended phase 2 dose established as 600 mg once daily.

Patients were assessed for eligibility for the three trials using either local molecular profiling or central RNA-based next-generation sequencing (Trailblaze Pharos, Ignyta, San Diego, CA, USA) to test for the presence of *NTRK* fusions. Local testing could include fluorescence in-situ hybridisation tests, quantitative PCR, or DNA-based or RNA-based next-generation sequencing. In ALKA-372-001 and STARTRK-1, patients were enrolled based on local testing only. In STARTRK-2, patients enrolled by local testing were required to provide tumour tissue (unless a biopsy was medically contraindicated) for independent central next-generation sequencing testing after enrolment. Patients enrolled in the trials were TRK inhibitor naive, had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, a life expectancy of at least 3 months (ALKA-372-001 and STARTRK-1) or at least 4 weeks (STARTRK-2), and adequate organ function. Patients with brain metastases could be enrolled if they had previous treatment resulting in control of symptoms or were asymptomatic. Patients requiring steroids for their brain metastases were allowed to continue their steroids, but must have received stable or decreasing doses for at least 2 weeks before the start of entrectinib treatment.

Patients were excluded if they had any of the following comorbidities: history of other previous cancer or currently active second malignancy; prolonged QTc interval; active infections; gastrointestinal disease; interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis; or peripheral neuropathy grade 2 or worse (appendix pp 14–18).

All studies were done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Written, informed consent was obtained from all patients. The protocols for all studies were approved by relevant institutional review boards or ethics committees (the protocol is available in the appendix).

Procedures

Initial doses of entrectinib in capsule form were 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, or 1600 mg in ALKA-372-001; 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg in STARTRK-1; and 600 mg in STARTRK-2, and were administered as intermittent (ALKA-372-001) or continuous once daily dosing (ALKA-372-001, STARTRK-1, and STARTRK-2) schedules (depending on what schedule patients in ALKA-372-001 were on, they could receive intermittent or continuous dosing). Patients continued treatment until documented radiographic progression, unacceptable toxicity, or withdrawal of consent).^{15,16}

Tumour response was assessed using CT or MRI scans. Screening tumour assessments (including brain scans) were done within 30 days of first administration of entrectinib. On-treatment tumour assessments were scheduled at the end of cycle 1 (4 weeks) and at the end of alternate cycles thereafter (ie, every 8 weeks), or whenever a clinical deterioration was observed, and at end of treatment if not done in the previous 4 weeks. Brain scans were done at the same frequency as on-treatment tumour assessments in patients with CNS disease at baseline per RECIST (version 1.1), according to investigator assessment. For patients without baseline CNS lesions, brain scans were done as clinically indicated, in accordance with standard clinical practice. For patients with a complete response or partial response, radiographic confirmation of objective tumour response or disease progression was based on

RECIST (version 1.1) and assessed both locally (investigator assessment) and by blinded independent central review no later than 4 weeks from when response criteria were first met. Tumour response was re-assessed at time of study drug discontinuation, unless an assessment had been done within the previous 4 weeks. All imaging scans were submitted for blinded independent central review. Patients were followed up until radiographic progression was documented by blinded independent central review, unacceptable toxicity, or withdrawal of consent. A patient could discontinue from study treatment at any time if the patient, the investigator, or the sponsor felt that it was not in the patient's best interest to continue. The following are possible reasons for early discontinuation of study treatment: disease progression, an adverse event that could not be adequately managed with dose modifications or interruption (if needed, dose reductions due to toxicity or treatment-related adverse events could occur for a maximum of 28 days and no more than two dose reductions were allowed), protocol violation, non-compliance with study procedures, loss to follow-up, or withdrawal of consent.

Safety was assessed by physical examination, clinical laboratory tests, and monitoring of adverse events, which were coded using the Medical Dictionary for Regulatory Activities (version 21.0 or higher) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Information on adverse events and laboratory samples were collected at each patient contact (days 1 and 15 of cycles 1–3, and day 1 of cycle 4 and of every subsequent cycle thereafter).

Molecular characterisation and fusion detection in tumour tissue were done by local or central assay methods that varied between studies (appendix p 19).

Outcomes

The co-primary endpoints of this integrated analysis were objective response (defined as the proportion of patients with a complete response or partial response as assessed by RECIST version 1.1 and Response Assessment in Neuro-Oncology Brain Metastases) and duration of response (measured from the date of first objective response [either complete or partial response] to first documentation of radiographic disease progression or the date of death due to any cause, whichever occurred first) by blinded independent central review.

Key secondary endpoints included progression-free survival (defined as time from first dose of entrectinib to first documentation of radiographic disease progression or death due to any cause at the time of data cutoff) according to blinded independent central review, overall survival (defined as the time from the first dose of entrectinib to the date of death due to any cause), clinical benefit rate (defined as confirmed complete response or partial response, or stable disease for 6 months from the first dose of entrectinib), time to CNS progression (defined as months from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause), and safety (safety monitoring consisted of collection of adverse events, serious adverse events, laboratory tests, and physical observations and measurements, including vital signs, electrocardiograms, ECOG performance status, eye exams, chest x-rays, and neurological functions). Additional prespecified secondary endpoints, assessed in patients with CNS disease at baseline, were

intracranial response, intracranial duration of response, and intracranial progression-free survival by blinded independent central review according to RECIST 1.1.

Statistical analysis

The hypothesis of this integrated analysis was to show the activity of entrectinib in patients with any solid tumour that harbours an *NTRK1*, *NTRK2*, or *NTRK3* gene fusion. For the primary and secondary outcomes, the integrated efficacy-evaluable population included patients with *NTRK* fusion-positive solid tumours who were TRK-inhibitor naive and had received at least one dose of entrectinib, had measurable disease at baseline, and at least 6 months' follow-up from the onset of treatment; patients were not assessable if they did not have measurable disease at baseline. The *NTRK* fusion-positive safety-evaluable population included all patients with *NTRK* fusion-positive solid tumours from all three studies who had received at least one dose of entrectinib at a dose of at least 600 mg. The overall safety-evaluable population also included safety data from the paediatric phase 1 study STARTRK-NG¹⁸ in patients aged 4–9–20 years. STARTRK-NG enrolled patients with *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* gene fusions, with non-neuroblastoma extracranial solid tumours, neuroblastoma, or primary CNS tumours. Entrectinib dosing in STARTRK-NG was dependent on drug formulation (up to 600 mg once daily in patients aged <18 years, as 300 mg/m² capsules or sprinkled on food for patients unable to swallow capsules for the recommended phase 2 dose for children of 550 mg/m²).¹⁹

For the integrated analysis, with the assumption that the true proportion of patients achieving an objective response was 60%, a sample size of 56 patients would yield a two-sided 95% CI with precision of at least 14%, with the lower confidence bound exceeding 30%. A proportion of responding patients greater than 30% was considered clinically meaningful.

Demographics, baseline characteristics, and safety data were summarised with descriptive statistics. The Kaplan–Meier method was used to estimate the median for time-to-event endpoints (duration of response, progression-free survival, and overall survival), with corresponding 95% CIs calculated. For objective responses according to blinded independent central review, the number, proportion, and corresponding two-sided Clopper–Pearson exact 95% CIs were summarised. SAS (version 9.3 or higher) was used for all statistical analyses. No interim analyses were planned. Investigator assessments of the primary efficacy endpoints were used for sensitivity analyses, which are not reported here.

These studies are registered as follows: ALKA-372–001, with the European clinical trials database, EudraCT 2012–000148–88; STARTRK-1, with Clinicaltrials.gov, [NCT02097810](#); and STARTRK-2, with Clinicaltrials.gov, [NCT02568267](#).

Role of the funding source

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and corresponding (GDD) authors had full access to all the data in the studies and the final responsibility for the decision to submit for publication.

Results

Patients were enrolled in ALKA-372-001 from Oct 26, 2012, to March 27, 2018; in STARTRK-1 from Aug 7, 2014, to May 10, 2018 (both studies were closed on May 17, 2018); and in STARTRK-2 on Nov 19, 2015 (enrolment is ongoing). All studies were ongoing on May 31, 2018, which was the data cutoff date for this integrated analysis. The median duration of follow-up was 12.9 months (IQR 8.77–18.76).

54 adult patients with advanced or metastatic *NTRK* fusion-positive solid tumours from STARTRK-2 (51 [94%] patients), STARTRK-1 (two [4%]), and ALKA-372-001 (one [2%]) were included in the integrated efficacy-evaluable population (table 1). Three patients in the two phase 1 studies received more than 600 mg entrectinib.

Most patients had a *NTRK1* or *NTRK3* fusion; the most frequently represented gene fusion was *ETV6-NTRK3*, which was identified in 25 (46%) patients (appendix pp 20–21). Two other frequent gene fusions, *TPM3-NTRK1* (in four [7%] patients) and *TPR-NTRK1* (four [7%]), were reported. Ten tumour types were treated, with at least 19 distinct histologies represented; the predominant tumour types were sarcoma (in 13 [24%] patients), NSCLC (ten [19%]), and mammary analogue secretory carcinoma of the salivary gland (seven [13%]; table 1).

Among the 54 patients who comprised the efficacy-evaluable population, 31 (57%; 95% CI 43.2–70.8) had an objective response: four (7%) had a complete response and 27 (50%) had a partial response. Nine patients (17%) had stable disease as their best overall response to entrectinib (table 2).

54 patients had a best overall response recorded at any single time point from the start of treatment until disease progression, which was also based on RECIST (version 1.1) of which 48 patients are included in the waterfall plot (excludes six patients without matched pre-therapy or post-therapy scans; figure 1A).

The proportion of patients achieving a response was similar in patients with *NTRK1* fusions (13 [59%; 95% CI 36.4–79.3] of 22) and *NTRK3* fusions (18 [58%; 39.1–75.5] of 31; appendix p 12). Only one (2%) patient had an *NTRK2* fusion; this patient did not have a response to entrectinib, with a change from baseline in the sum of the longest diameter of target lesions of –2% (appendix p 12).

Responses were recorded in all tumour types included in the analysis: six (86%; 95% CI 42–100) of seven patients with mammary analogue secretory carcinoma, five (83%; 36–100) of six patients with breast cancer, seven (70%; 35–93) of ten with NSCLC, two (67%; 9–99) of three with pancreatic cancer, six (46%; 19–75) of 13 with sarcoma, one (25%; 1–81) of four with colorectal cancer, and one (20%; 1–72) of five with thyroid cancer (figure 1A). Response to entrectinib did not seem to be related to the fusion partner (appendix p 13).

Median duration of response by blinded independent central review was 10 months (95% CI 7.1 to not estimable; figure 1B, 1C). At data cutoff, 29 patients had disease progression or had died, and median progression-free survival was 11 months (95% CI 8.0–1; figure 2A). At data cutoff, 16 (30%) of 54 patients had died, and the estimated median overall survival was 21 months (95% CI 14.9 to not estimable; figure 2B).

In the 12 (22%) of 54 patients with baseline CNS disease, as assessed by investigator, six (50%) had a partial response per blinded independent central review and four (33%) had stable disease (figure 3A, table 2). These results, which represent both intracranial and extracranial lesions, are similar to the responses recorded in the 42 (78%) patients without CNS metastatic disease at baseline (of whom 25 [60%; 95% CI 43.28–74.37] patients had an objective response per blinded independent central review, with 4 [10%] complete responses, and 21 [50%] partial responses). 17 patients in the whole efficacy-evaluable population of 54 patients had a CNS progression event. Median time to CNS progression was 17 months (95% CI 14.3 to not estimable).

According to blinded independent central review assessment, 11 (20%) of 54 patients had brain metastases at baseline and, in this population, six patients (55%; 95% CI 23.4–83.3) had an intracranial response according to blinded independent review (figure 3B). Seven (64%) of these 11 patients had previously received radiotherapy to the brain.

Median intracranial duration of response according to blinded independent central review was not estimable (95% CI 5.0 to not estimable). At data cutoff, five patients with intracranial disease at baseline had an intracranial progression-free survival event, and median intracranial progression-free survival according to blinded independent central review assessment was 14 months (95% CI 5.1 to not estimable).

The safety analysis included two safety populations: the *NTRK* fusion-positive safety-evaluable population (68 patients from STARTRK-1, STARTRK-2, and ALKA-372–001 who received at least one dose of entrectinib) and the overall safety-evaluable population (355 patients), which included patients from the phase 1 STARTRK-NG study with any tumour type and gene rearrangement who received at least one dose of entrectinib, and was divided into four groups: patients with *NTRK* fusion-positive tumours (68 [19%]), those with *ROS1* fusion-positive NSCLC (134 [38%]), paediatric patients (16 [6%]), and other (*ROS1* fusion-positive non-NSCLC, *ALK* fusion-positive, or patients with no gene fusion; 137 [39%]; appendix p 11). Safety data from both populations are presented to provide a broad safety summary gained from the 355 patients who have received entrectinib across four clinical trials, as well as providing the specific safety information for those patients with *NTRK* fusion-positive solid tumours. At data cutoff, the median treatment duration in the *NTRK* fusion-positive safety-evaluable population was 7.85 months (IQR 3.68–12.71) and in the overall safety populations was 5.8 months (1.50–11.60). The median number of entrectinib cycles received was 9.5 (IQR 5–16) for the *NTRK* fusion-positive safety-evaluable population and 8 (2–15) for the overall safety population. The number of reported safety events in the *NTRK* fusion-positive population treated with 600 mg entrectinib was consistent with the overall safety-evaluable population (data not shown).

In the *NTRK* fusion-positive safety-evaluable population (n=68), most adverse events regardless of causality were grade 1–2 and non-serious (appendix pp 22–25). In the overall safety population (n=355), the most frequently reported all-causality grade 3–4 adverse events (in 2% of patients) were anaemia (in 38 [11%] patients), increased weight (23 [7%]), dyspnoea (22 [6%]), and fatigue (15 [4%]; data not shown).

In both safety populations, most treatment-related adverse events were grade 1–2 and reversible (table 3). The most commonly reported serious treatment-related event was cognitive disorder in the overall safety population. In the *NTRK* fusion-positive population, there were three serious treatment-related events reported (one cognitive disorder, one cerebellar ataxia, and one dizziness). The most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (seven [10%] of 68 patients in the *NTRK* fusion-positive safety population and 18 [5%] of 355 patients in the overall safety-evaluable population) and anaemia (8 [12%] and 16 [5%]). Serious treatment-related adverse events were reported in seven (10%) patients in the *NTRK* fusion-positive and in 30 patients (9%) in the overall safety population. The most frequent in both populations were nervous system disorders (three [4%] vs ten [3%]). Three (4%) of 68 patients in the *NTRK* fusion-positive population and 14 (4%) of 355 patients in the overall safety population discontinued entrectinib due to treatment-related adverse events; 21 (31%) and 90 (25%) had dose interruption due to a treatment-related adverse event; and 27 (40%) versus 97 (27%) had a dose reduction due to a treatment-related adverse event. The most common adverse events leading to dose reductions were anaemia (5 [7%] patients), increased blood creatinine levels (4 [6%]), and fatigue (4 [6%]). At data cutoff, six (9%) deaths had occurred in the *NTRK* fusion-positive safety population (two acute respiratory failure, two cardio-respiratory arrest, one pneumonia, and one sepsis), and 20 (6%) deaths had occurred in the overall safety population (two acute respiratory failure, two cardio-respiratory arrest, two dyspnoea, two metastases to meninges, two pneumonia, two sepsis, one cardiogenic shock, one cerebral infarction, one suicide, one large intestine perforation, one pulmonary embolism, one respiratory failure, one septic shock, and one tumour lysis syndrome). All of these deaths were deemed unrelated to treatment.

Discussion

In this integrated analysis of patients with a wide variety of advanced cancers harbouring *NTRK1*, *NTRK2*, or *NTRK3* fusions, we show that entrectinib is active in multiple tumour types, showing both systemic anti-tumour activity and activity in CNS metastases. The proportion of patients achieving an objective response was 57%, with a similar proportion (55%) achieving an intracranial response. Anti-tumour activity was similar in both *NTRK1* and *NTRK3* gene fusion-positive cancers. Disease control was durable, with a median progression-free survival of 11 months and a median duration of response of 10 months. These results are especially encouraging for patients with tumour types with few treatment options, such as sarcomas.²⁰ On the basis of these and other data, entrectinib was granted accelerated approval by the US FDA in August, 2019 for the treatment of adults and children with solid tumours that have a *NTRK* gene fusion.

Previous reports initially documented case studies with substantial antitumour activity of entrectinib in patients with *NTRK* fusions.^{17,21} Importantly, other than a small number of patients with neuroblastoma harbouring *ALK* point mutations, there is no evidence of activity of entrectinib in tumours with any genomic aberrancies other than gene fusions, such as single nucleotide variants or copy number gain.^{16,22} Entrectinib administration induced a response and durable antitumour activity against intracranial metastases in a high proportion of patients with CNS involvement in this study. The inclusion of patients with *ROS1*-positive NSCLC and CNS disease in this integrated analysis has provided important CNS data that support the ability of entrectinib to cross the blood–brain barrier and to maintain intracranial therapeutic levels, highlighting its value as a CNS-active therapy in patients with existing brain metastases or in those who are at risk of developing brain metastases.

Several other TRK inhibitors are under investigation.^{11,23–25} Of these agents, larotrectinib has received accelerated approval by the US FDA for the treatment of adult and paediatric patients with *NTRK* fusion-positive solid tumours.^{11,26} In the pivotal integrated analysis of larotrectinib that comprised three trials (phase 1 adult, phase 2 adult and adolescent, and phase 1–2 paediatric) the proportion of patients achieving an objective response was higher than the response from this integrated analysis of entrectinib (75% vs 57%). However, direct comparisons between these separate trials of entrectinib and larotrectinib are challenging because of potentially confounding factors, including the fact that the differences in responses reported might be explained by the substantial differences in patient populations enrolled and study design. Additionally, potentially less responsive cancers such as colorectal and thyroid cancer were much less represented in the integrated analysis of larotrectinib than that of entrectinib¹¹ and the generally more responsive subtype of infantile fibrosarcoma was not represented in the entrectinib analysis. Moreover, patients in the entrectinib integrated analysis were older (adults only for the entrectinib analysis vs adults, children, and adolescents [22% of patients were aged < 14 years] for larotrectinib) and 22% of enrolled patients in the entrectinib analysis had CNS metastases at baseline compared with only 2% in the larotrectinib analysis.^{11,19} Several patients in the larotrectinib study underwent tumour resection on study, which suggests that these patients had non-advanced disease and thus a better prognosis. These factors might affect the overall results because paediatric patients with cancer have the potential for better outcomes than adults²⁷ and patients with CNS involvement are a poor-prognosis population with worse outcomes than those without CNS disease. Additionally, in the adult population, each trial included a wide variety of different tumour histologies, accounting for differing percentages of the overall patient population, further limiting study-to-study comparisons. Efficacy and safety testing of entrectinib in children with cancer is currently in progress (STARTRK-NG, [NCT02650401](#)).

NTRK1, *NTRK2*, and *NTRK3* gene fusions can be regarded as an oncogenic family because of their high homology in the kinase domain and ATP binding pocket.²⁸ These structural similarities might account for the almost identical responses seen in the entrectinib analysis in patients with *NTRK1* fusions and *NTRK3* fusions. The presence of large introns that are typically inadequately sequenced and difficult to analyse can make detection of *NTRK2* and

NTRK3 fusions more difficult, and only one patient with an *NTRK2* fusion was included in this dataset.

In cancers harbouring *NTRK* fusions, resistance to treatment can occur and cases of resistance to entrectinib and larotrectinib have been observed.²⁹ In one patient with entrectinib-resistant colorectal cancer, two resistance mutations (Gly595Arg and Gly667Cys) in the *NTRK1* kinase domain were found in the patient's circulating tumour DNA collected longitudinally during treatment.²⁸ Both mutations were detected in patient plasma obtained at progression, suggesting that both could be associated with acquired resistance to entrectinib in the clinical setting. Therefore, next-generation TRK inhibitors are now being tested in the clinic. Repotrectinib has shown preclinical evidence to overcome resistance due to acquired solvent-front mutations involving *ROS1* and *NTRK1*, *NTRK2*, and *NTRK3*.³⁰ BAY 2731954 (LOXO-195) has also shown the ability to overcome recurrent resistance mutations.^{15,30,31}

In this integrated analysis, entrectinib was well tolerated with a manageable safety profile. Most adverse events were transient and managed successfully with dose interruption or reduction and the number of discontinuations due to treatment-related adverse events was low. Overall, the safety profile of entrectinib in patients with *NTRK* fusion-positive cancer was consistent with that of the overall safety population and with that previously reported with other drugs of the same class such as larotrectinib and repotrectinib.^{11,15,16,32}

The limitations of this integrated analysis of entrectinib are based around the relatively small numbers of patients enrolled and the single-arm nature of these studies. The number of patients included in the analysis was slightly below the sample size requirement that was calculated a priori, although the lower bound of the 95% CI for response (43%) was sufficiently above the threshold of 30% that a high degree of confidence can be attached to the finding that entrectinib produces clinically meaningful responses in this patient population. Because of the rarity and variety of these tumour types, to do phase 3 studies or enrol large numbers of patients is difficult. Basket trials such as STARTRK-2 are designed to enable recruitment of such rare disease populations.

The results from this integrated analysis of entrectinib clinical trials indicate that entrectinib is an active treatment for patients with *NTRK* fusion-positive solid tumours either with or without malignant lesions in the CNS. The ongoing STARTRK-2 and STARTRK-NG trials will hopefully provide additional data to support the use of entrectinib as a targeted treatment for patients with *NTRK* fusion-positive tumours who have, or are at risk of developing, CNS metastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

RCD has received consulting fees from Ignyta, Genentech/Roche, Loxo Oncology, Bayer, Eli Lilly, AstraZeneca, Pfizer, and Rain Therapeutics; sponsored research agreements from Ignyta, Loxo, Mirati, Pfizer, Eli Lilly, and Strategia; royalties or licensing fees for intellectual property from Ignyta, Loxo, Abbott Molecular, Genentech/Roche, Chugai, Foundation Medicine, Black Diamond, and Rain Therapeutics; and has stock ownership in Rain Therapeutics. GDD has received grants from Novartis, Bayer, Ignyta, Roche, Epizyme, Pfizer, Loxo Oncology, AbbVie, Adaptimmune, GlaxoSmithKline, Janssen, PharmaMar, and Daiichi-Sankyo; personal fees from Novartis, Bayer, Polaris Pharmaceuticals, Ignyta, Roche, Epizyme, Mirati Therapeutics, Pfizer, Sanofi, EMD-Serono, Loxo Oncology, AbbVie, ZioPharm, WIRB Copernicus Group, MJ Hennessey/OncLive, Adaptimmune, Blueprint Medicines, G1 Therapeutics, CARIS Life Sciences, Janssen, CHAMPIONS Oncology, PharmaMar, and Daiichi-Sankyo; non-financial support from Novartis, Bayer, AbbVie, Roche, Epizyme, PharmaMar, and Daiichi-Sankyo; travel support to consulting meetings from Novartis, Bayer, Mirati Therapeutics, Roche, Loxo Oncology, Epizyme, Pfizer, EMD-Serono, WIRB Copernicus Group, MJ Hennessey/OncLive, Adaptimmune, Blueprint Medicines, CARIS Life Sciences, CHAMPIONS Oncology, PharmaMar, and Daiichi-Sankyo; minor equity from Blueprint Medicines, CARIS Life Sciences, Bessor Pharmaceuticals, ERASCA Pharmaceuticals, G1 Therapeutics, and Merrimack Pharmaceuticals; is a member of the Board of Directors for Blueprint Medicines and Merrimack Pharmaceuticals; and has a use patent on imatinib for GIST, licensed to Novartis with royalties paid to the Dana-Farber Cancer Institute. LB has received advisory board fees from Takeda, AstraZeneca, LOXO oncology, Abbvie, Bayer, and G1 therapeutics; received travel support from Mirati to travel to a scientific meeting; has research funding to the institution from Beyondspring pharma; and has stock in Epic sciences. BB reports sponsored research at Gustave Roussy Cancer Center from AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Ignyta, Ipsen, Merck KGaA, Merck Sharp & Dohme, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Pharma. CMB reports grants and non-financial support from Ignyta/Roche, Novartis, AstraZeneca, Mirati, Spectrum, and MedImmune; and has received personal fees from Revolution Medicines. DWB is on a data safety monitor board for BioMimix Pharmaceuticals. 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advisory boards for Boehringer-Ingelheim, Celgene, Eli Lilly, Novartis, Merck Serono, Roche, and Takeda; being part of speakers' bureaus for AbbVie, Bayer, Eisai, Eli Lilly, Guardant Health, and Novartis; has received travel support from Bayer, Merck Sharp & Dohme, Novartis, and Pfizer; and has received research funding from Merck Sharp & Dohme, Mundipharma, and Novartis. JN has received consulting fees from AstraZeneca, Bayer, Roche/Genentech, Takeda, Turnstone, and Western Oncolytics; sponsored research agreements from Merck; travel support from Caris; and has equity interest in Epic Sciences. TRO has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, and Roche/Genentech; sponsored research agreements from AstraZeneca, Eli Lilly, Roche/Genentech, and Sanofi-Aventis; and travel support from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, and Roche/Genentech. LP-A or his relative has received consulting fees from Genentech/Roche, Loxo Oncology, Bayer, Eli Lilly, AstraZeneca, Pfizer, Bayer, Merck Sharp & Dohme, Novartis, Amgen, Pharmamar, Boehringer Ingelheim, Celgene, Servier, Sysmex, Incyte, Ipsen, Adacap, Sanofi, and Blueprint Medicines; sponsored research agreements from BMS, AstraZeneca, and Merck Sharp & Dohme; and serves on the board of Genómica. TS has received research grants from Chugai Pharmaceuticals; grants and honoraria from Astellas Pharma, AstraZeneca, Chugai Pharmaceuticals, Eli Lilly Japan, Kissei Pharmaceutical, Merck Sharp & Dohme, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, and Takeda Pharmaceutical; honoraria from Bristol-Myers Squibb, Kyowa Hakko Kirin, Nippon Kayaku, Ono, Roche Singapore, Taiho Pharmaceutical, Thermo Fisher Scientific, and Yakult Honsha; and research grants from Bayer Yakuhin, Daiichi Sankyo, Eisai, LOXO Oncology, and Merck Serono. ATS has served as a compensated consultant or received honoraria from ARIAD, Bayer, Blueprint Medicines, Chugai, Daiichi Sankyo, EMD Serono, Foundation Medicine, Genentech/Roche, Guardant, Ignyta, KSQ Therapeutics, LOXO, Natera, Novartis, Pfizer, Servier, Taiho Pharmaceutical, Takeda, and TP Therapeutics; has received research (institutional) funding from Daiichi Sankyo, Ignyta, Novartis, Pfizer, Roche/Genentech, and Turning Point Therapeutics; and has received travel support from Pfizer and Roche/Genentech. SS is an advisory board member for Amgen, Bayer, Bristol-Myers Squibb, CheckmAb, Celgene, Daiichi Sankyo, Incyte, Merck, Novartis, Roche, and Seattle Genetics. DS is an advisory board member for Celularity, Molecular Stethoscope, and Curematch; is on the speaker bureau for Celgene and Bayer; and has a patent on 'methods of treating a neuroendocrine tumour'. CS has received consulting fees from AbbVie, Merck, EMD Serono, Armo, Bergen Bio and Eli Lilly; and research funds from Vaccinex. DT has received grants from Janssen and Astellas; and support for meeting travel from Sanofi, Pfizer, Janssen, and Astellas. TR, BS, and SE are employees of Genentech. NC was an employee of Genentech. EC-M and AJ were employees of Ignyta. TRW is employed by Genentech and has equity in Roche. MB and GLB report no competing interests.

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Research in context

Evidence before this study

We searched PubMed and major congress abstracts with the search terms “NTRK”, “fusion”, “cancer”, and “inhibitor”, with no publication date or language restrictions. Of the TRK inhibitors currently under development for the treatment of *NTRK* gene fusions, larotrectinib and entrectinib yielded the greatest number of search results. Larotrectinib has shown systemic efficacy in three phase 1–2 trials; based on these data, larotrectinib was granted US Food and Drug Administration approval in November, 2018, for the treatment of adults and children with solid tumours harbouring an *NTRK* gene fusion without a known acquired resistance mutation. However, there is insufficient evidence that this compound can penetrate the CNS and its intracranial efficacy has not been clearly shown. Entrectinib is a potent inhibitor of TRK A, B and C; ROS1; and ALK that was designed to penetrate and remain in the CNS, and which showed clinical activity in phase 1 studies of patients with *NTRK* fusion-positive tumours, including primary CNS cancers.

Added value of this study

In this integrated analysis of three phase 1–2 clinical trials, we report the efficacy and safety of entrectinib in patients with a range of metastatic, locally advanced, or unresectable TRK inhibitor-naïve, *NTRK* fusion-positive solid tumours. Overall, entrectinib treatment was associated with clinically meaningful and durable systemic and intracranial responses, irrespective of tumour type or the presence of baseline CNS lesions. Entrectinib was well tolerated with a manageable safety profile.

Implications of all the available evidence

Entrectinib is a highly effective treatment for patients with *NTRK* fusion-positive solid tumours, with both systemic and CNS activity. On the basis of the results of this integrated analysis, entrectinib could become an effective first-line therapeutic option for patients with *NTRK* fusion-positive solid tumours, with or without CNS involvement.

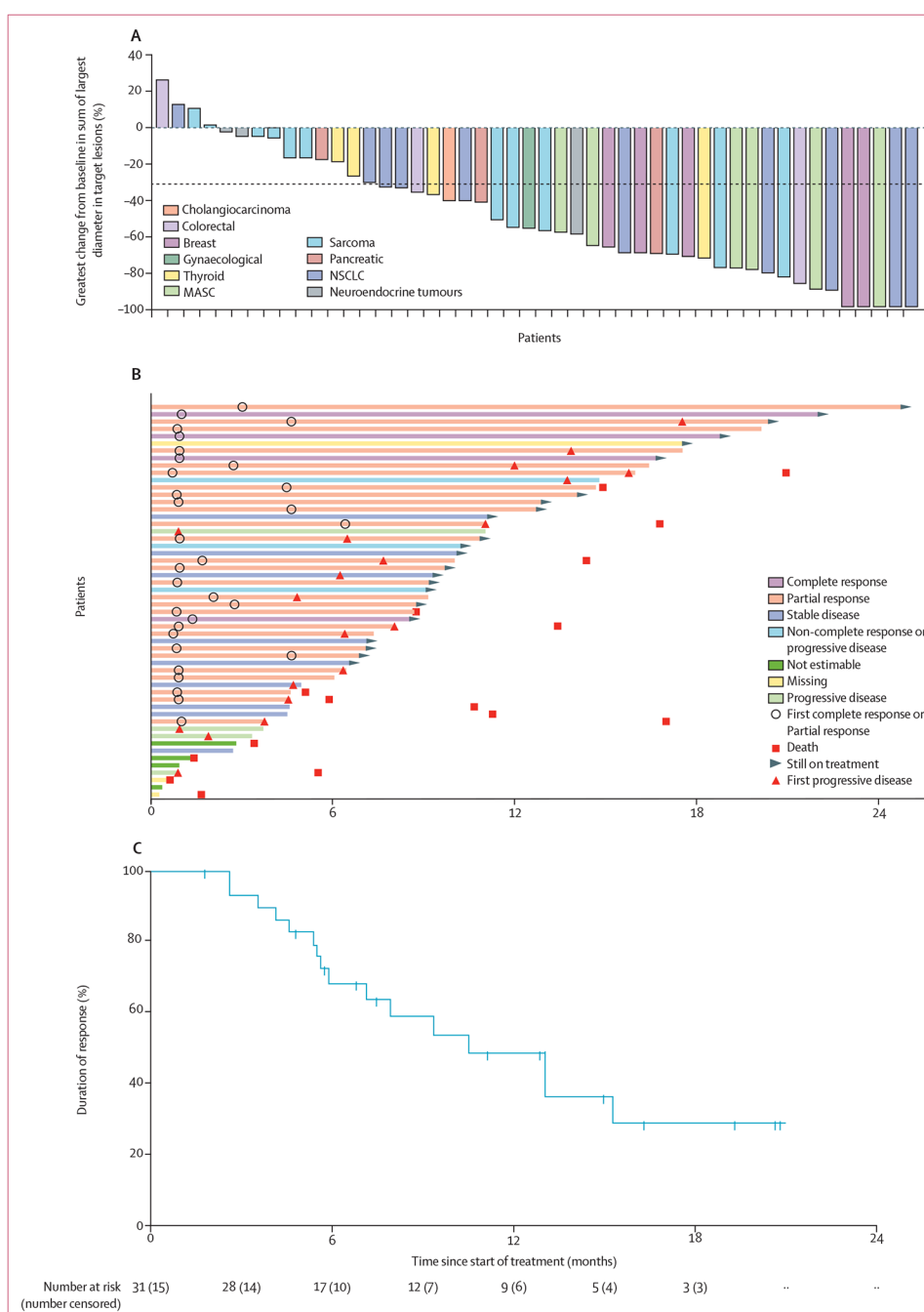


Figure 1: Individual responses by tumour type

(A) Responses in 48 patients with *NTRK* fusion-positive solid tumours (six patients without matched pre-therapy or post-therapy scans were excluded). (B) Duration of response in 54 patients with *NTRK* fusion-positive solid tumours. (C) Kaplan–Meier curve of median duration of response. All assessments shown are based on blinded independent central review. Waterfall plot represents the greatest change at any single timepoint. The dashed horizontal line on figure 1A represents the minimum 30% shrinkage in target lesions that

defines an objective response. NSCLC=non-small-cell lung cancer. MASC=mammary analogue secretory carcinoma

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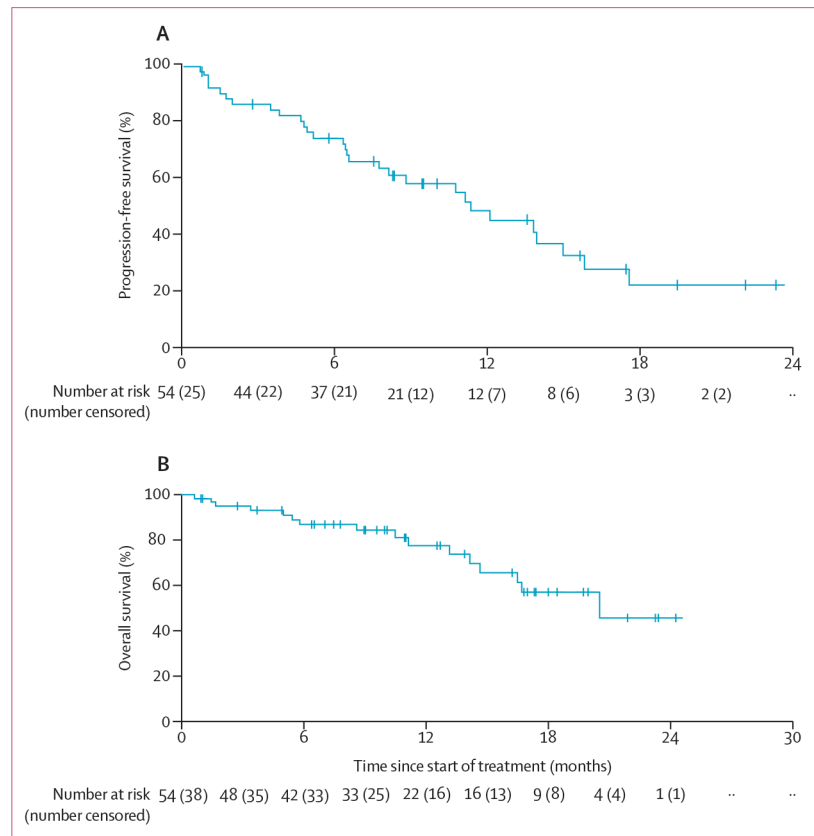


Figure 2: Time to event analyses

(A) Progression-free survival and (B) overall survival in patients with *NTRK* fusion-positive solid tumours in the efficacy-evaluable population (n=54). All assessments shown are based on blinded independent central review.

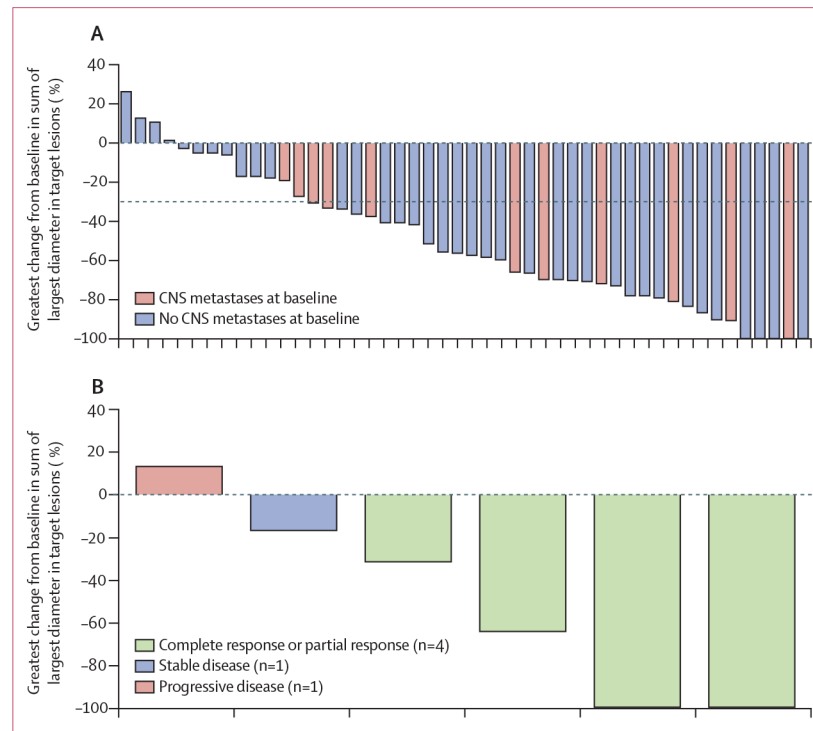


Figure 3: Individual responses by presence or absence of CNS metastases

(A) Response by CNS tumour involvement at baseline (six patients without matched pre-therapy or post-therapy scans were excluded) and (B) Intracranial responses in six patients with measurable CNS metastases at baseline by blinded independent central review (12 patients had CNS metastases at baseline according to investigator assessment, 11 confirmed by blinded independent central review. Of these 11 patients with CNS metastases, seven had measurable disease, of whom one had missing/unevaluable data). All assessments shown are based on blinded independent central review. Waterfall plot represents the best change at any single timepoint.

Table 1:

Baseline characteristics

All patients in <i>NTRK</i> gene fusion-positive efficacy-evaluable population (n=54)	
Age, years	58 (48–67)
Sex	
Female	32 (59%)
Male	22 (41%)
Race	
White	43 (80%)
Asian	7 (13%)
Other	4 (7%)
Eastern Cooperative Oncology Group performance status	
0	23 (43%)
1	25 (46%)
2	6 (11%)
Previous lines of systemic therapy	
0	20 (37%)
1	11 (20%)
2	14 (26%)
3	4 (7%)
4	5 (9%)
Previous treatment *	
Chemotherapy	46 (85%)
Targeted therapy	13 (24%)
Hormonal therapy	9 (17%)
Immunotherapy	7 (13%)
CNS metastases at baseline	
Yes	12 (22%)
No	42 (78%)
Previous radiotherapy to the brain	
Yes	7 (13%)
No	47 (87%)
Time from end of previous radiotherapy of the brain to first dose of entrectinib †	
<2 months	2 (29%)
2 to <6 months	4 (57%)
6 months	1 (14%)
Tumour type	
Sarcoma ‡	13 (24%)
NSCLC	10 (19%)
Mammary analogue secretory carcinoma (salivary)	7 (13%)
Breast	6 (11%)
Thyroid	5 (9%)

All patients in <i>NTRK</i> gene fusion-positive efficacy-evaluable population (n=54)	
Colorectal	4 (7%)
Neuroendocrine	3 (6%)
Pancreatic	3 (6%)
Gynaecological	2 (4%)
Ovarian	1 (2%)
Endometrial	1 (2%)
Cholangiocarcinoma	1 (2%)

Data are median (IQR) and n (%). NSCLC=non-small-cell lung cancer.

* Patient might have received multiple or combination therapies, resulting in the sum of previous treatments being >100%.

[†] Patients with baseline CNS metastases.

[‡] Subtypes of soft tissue sarcoma included cervical adenosarcoma (n=1), dedifferentiated chondrosarcoma (n=1), endometrial stromal sarcoma (n=1), follicular dendritic cell sarcoma (n=1), gastrointestinal stromal tumour (n=1; wild-type gastrointestinal stromal tumour, succinate dehydrogenase complex subunit B immunohistochemistry—tumour cells retain normal expression), malignant peripheral nerve sheath tumour (n=1), and sarcoma not otherwise specified (n=7).

Table 2:

Activity outcomes

	Efficacy-evaluable population[*] (n=54)	Patients with baseline CNS disease[†] (n=12)	Patients with no baseline CNS disease^{*†} (n=42)
Proportion of patients achieving a response	31 (57%)	6 (50%)	25 (60%)
Best overall response			
Complete response	4 (7%)	0	4 (10%)
Partial response	27 (50%)	6 (50%)	21 (50%)
Stable disease	9 (17%)	4 (33%)	5 (12%)
Progressive disease	4 (7%)	0	4 (10%)
Non-complete response or progressive disease	3 (6%)	0	3 (7%)
Missing or unevaluable [‡]	7 (13%)	2 (17%)	5 (12%)
Median duration of response, months	10·4 (7·1-NE)	NE	12·9 (7·1-NE)
Median progression-free survival, months	11·2 (8·0–14·9)	7·7 (4·7-NE)	12·0 (8·7–15·7)

Data are n (%) or median (95% CI). NE=not estimable.

^{*} Systemic response.

[†] CNS disease status determined by the investigator.

[‡] Missing or unevaluable included patients with no post-baseline scans available, missing subsets of scans at all time points, or patients who discontinued before obtaining adequate scans to evaluate or confirm response.

Table 3:

Treatment-related adverse events

	<i>NTRK</i> fusion-positive safety-evaluable population* (n=68)			Overall safety-evaluable population† (n=355)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Dysgeusia	32 (47%)	0	0	146 (41%)	1 (<1%)	0
Constipation	19 (28%)	0	0	83 (23%)	1 (<1%)	0
Fatigue	19 (28%)	5 (7%)	0	89 (25%)	10 (3%)	0
Diarrhoea	18 (27%)	1 (2%)	0	76 (21%)	5 (1%)	0
Oedema peripheral	16 (24%)	1 (2%)	0	49 (14%)	1 (<1%)	0
Dizziness	16 (24%)	1 (2%)	0	88 (25%)	2 (1%)	0
Blood creatinine increased	12 (18%)	1 (2%)	0	52 (15%)	2 (1%)	0
Paraesthesia	11 (16%)	0	0	67 (19%)	0	0
Nausea	10 (15%)	0	0	74 (21%)	0	0
Vomiting	9 (13%)	0	0	48 (14%)	0	0
Arthralgia	8 (12%)	0	0	42 (12%)	2 (1%)	0
Myalgia	8 (12%)	0	0	52 (15%)	2 (1%)	0
Weight increased	8 (12%)	7 (10%)	0	51 (14%)	18 (5%)	0
AST increased	7 (10%)	0	1 (2%)	35 (10%)	3 (1%)	1 (<1%)
ALT increased	6 (9%)	0	1 (2%)	30 (9%)	3 (1%)	1 (<1%)
Muscular weakness	6 (9%)	1 (2%)	0	22 (6%)	3 (1%)	0
Anaemia	5 (7%)	8 (12%)	0	27 (10%)	16 (5%)	0
Asthenia	5 (7%)	0	0	28 (8%)	2 (1%)	0
Peripheral sensory neuropathy	4 (6%)	1 (2%)	0	20 (6%)	4 (1%)	0
Neutrophil count decreased	4 (6%)	0	0	13 (4%)	8 (2%)	0
Rash	4 (6%)	0	0	18 (5%)	2 (1%)	0
Disturbance in attention	3 (4%)	0	0	13 (4%)	1 (<1%)	0
Pain of skin	3 (4%)	0	0	9 (3%)	1 (<1%)	0
Neutropenia	3 (4%)	2 (3%)	0	9 (3%)	9 (3%)	0
Localised oedema	2 (3%)	1 (2%)	0	3 (1%)	1 (<1%)	0
Hyperaesthesia	2 (3%)	0	0	22 (6%)	1 (<1%)	0
Ataxia	2 (3%)	0	0	9 (3%)	3 (1%)	0
Platelet count decreased	2 (3%)	0	0	4 (1%)	0	1 (<1%)
Hyperuricaemia	2 (3%)	0	2 (3%)	13 (4%)	0	5 (1%)
Hypophosphataemia	2 (3%)	2 (3%)	0	6 (2%)	4 (1%)	0
Dehydration	2 (3%)	0	0	5 (1%)	2 (1%)	0
Diplopia	1 (2%)	1 (2%)	0	4 (1%)	1 (<1%)	0
Hypotension	1 (2%)	1 (2%)	0	14 (4%)	2 (1%)	0
Pyrexia	1 (2%)	0	0	7 (2%)	1 (<1%)	0
Lymphocyte count decreased	1 (2%)	0	0	4 (1%)	1 (<1%)	0
Pruritus	1 (2%)	0	0	15 (4%)	1 (<1%)	0
Hypoxia	1 (2%)	0	0	1 (<1%)	1 (<1%)	0

	<i>NTRK</i> fusion-positive safety-evaluable population* (n=68)			Overall safety-evaluable population† (n=355)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fall	1 (2%)	0	0	6 (2%)	1 (<1%)	0
Osteoarthritis	0	1 (2%)	0	2 (1%)	1 (<1%)	0
Blood uric acid increased	0	0	1 (2%)	3 (<1%)	0	1 (<1%)
Dysarthria	0	0	0	5 (1%)	2 (1%)	0
Anorectal disorder	0	0	0	0	0	1 (<1%)
Generalised oedema	0	0	0	5 (1%)	2 (1%)	0
Electrocardiogram QT prolonged	0	0	0	5 (1%)	1 (<1%)	0
Lipase increased	0	0	0	2 (1%)	2 (<1%)	1 (1%)
Amylase increased	0	0	0	1 (<1%)	3 (1%)	0
Blood creatine phosphokinase increased	0	0	0	2 (<1%)	1 (<1%)	1 (<1%)
Hyponatraemia	0	0	0	3 (1%)	2 (1%)	0
Hypermagnesaemia	0	1 (2%)	0	0	1 (<1%)	0
Hypoalbuminaemia	0	0	0	0	1 (<1%)	0
Pulmonary oedema	0	0	0	0	2 (1%)	0
Mental status changes	0	0	0	0	2 (1%)	0
Agitation	0	0	0	0	1 (<1%)	0
Mood altered	0	0	0	0	1 (<1%)	0
Orthostatic hypotension	0	0	0	2 (1%)	1 (<1%)	0
Hypertension	0	0	0	0	1 (<1%)	0
Cardiac failure	0	1 (2%)	0	0	2 (1%)	0
Cardiac failure congestive	0	1 (2%)	0	0	1 (1%)	0
Myocarditis	0	0	0	0	0	1 (<1%)

Data are n (%). Adverse events were encoded using MedDRA (version 21.0). ALT=alanine aminotransferase. AST=aspartate aminotransferase.

* All patients with *NTRK* gene fusions who received 1 dose of entrectinib, regardless of dose or duration of follow-up.

† All patients from STARTRK-1, STARTRK-2, ALKA-372-001, and STARTRK-NG (regardless of tumour type or gene rearrangement) who received 1 dose of entrectinib. No deaths due to adverse events were reported.