ORIGINAL ARTICLE

Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study

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Background: *NTRK1*, *NTRK2* and *NTRK3* gene fusions (*NTRK* gene fusions) occur in a range of adult cancers. Larotrectinib is a potent and highly selective ATP-competitive inhibitor of TRK kinases and has demonstrated activity in patients with tumours harbouring *NTRK* gene fusions.

Patients and methods: This multi-centre, phase I dose escalation study enrolled adults with metastatic solid tumours, regardless of *NTRK* gene fusion status. Key inclusion criteria included evaluable and/or measurable disease, Eastern Cooperative Oncology Group performance status 0–2, and adequate organ function. Larotrectinib was administered orally once or twice daily, on a continuous 28-day schedule, in increasing dose levels according to a standard 3 + 3 dose escalation scheme. The primary end point was the safety of larotrectinib, including dose-limiting toxicity.

Results: Seventy patients (8 with tumours with *NTRK* gene fusions; 62 with tumours without a documented *NTRK* gene fusion) were enrolled to 6 dose cohorts. There were four dose-limiting toxicities; none led to study drug discontinuation. The maximum tolerated dose was not reached. Larotrectinib-related adverse events were predominantly grade 1; none were grade 4 or 5. The most common grade 3 larotrectinib-related adverse event was anaemia [4 (6%) of 70 patients]. A dose of 100 mg twice daily was recommended for phase II studies based on tolerability and antitumour activity. In patients with evaluable TRK fusion cancer, the objective response rate by independent review was 100% (eight of the eight patients). Eight (12%) of the 67 assessable patients overall had an objective response by investigator assessment. Median duration of response was not reached. Larotrectinib had limited activity in tumours with *NTRK* mutations or amplifications. Pharmacokinetic analysis showed exposure was generally proportional to administered dose.

Conclusions: Larotrectinib was well tolerated, demonstrated activity in all patients with tumours harbouring *NTRK* gene fusions, and represents a new treatment option for such patients.

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Key words: larotrectinib, adult, phase I, *NTRK* gene fusion, TRK fusion cancer

Introduction

Chromosomal rearrangements involving the *NTRK1*, *NTRK2* and *NTRK3* genes (*NTRK* gene fusions), which encode a family of receptor tyrosine kinases (TRKA/B/C) involved in neuronal development [1, 2], have been identified in a broad range of adult and paediatric tumour types [3]. Typically in such rearrangements, the 5′ region of an unrelated gene expressed in the tumour cell is joined in frame with the 3′ region of the *NTRK* gene, with the fusion transcript encoding a protein comprising the N terminus of the fusion partner joined to the C-terminus of the TRK protein, including the tyrosine kinase domain [4].

NTRK gene fusions occur at high frequency in several uncommon tumours, including infantile fibrosarcoma [5], congenital mesoblastic nephroma [6], paediatric papillary thyroid carcinoma [7], secretory breast carcinoma [8] and mammary analogue secretory carcinoma the salivary gland [9]. In addition, *NTRK* gene fusions have been identified at low frequency in a wide range of common adult cancers, including non-small-cell lung cancer (NSCLC), breast cancer, colorectal cancer, soft tissue sarcoma, papillary thyroid cancer, melanoma, and glioblastoma [3, 10–13]. *NTRK* gene fusions may therefore represent one of the first tissue-agnostic and age-agnostic oncogenic drivers.

Larotrectinib is a potent and highly selective ATP-competitive inhibitor of TRKA, B and C receptor tyrosine kinases, with a 50% inhibitory concentration (IC_{50}) of 5–11 nM [14]. *In vitro* analyses have shown that tumour cell lines harbouring different *NTRK* gene fusions are sensitive to larotrectinib with IC_{50} values in the low nanomolar range.

Robust and durable responses to larotrectinib in paediatric and adult patients with TRK fusion cancer were recently reported [14]. In this first-in-human, phase I dose-escalation study, which contributed patients to this combined analysis, we report the safety, tolerability, pharmacokinetic properties, and preliminary activity of larotrectinib in adult patients with advanced solid tumours. These data determined the recommended phase II larotrectinib dose currently under clinical investigation.

Methods

Study design and participants

This multi-centre, open-label, phase I, dose-escalation study enrolled patients at eight investigative sites in the United States. Adult patients, at least 18 years of age, with a locally advanced or metastatic solid tumour refractory to standard therapies were eligible. Other major inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0–2, life expectancy of at least 3 months, and adequate organ function (absolute neutrophil count $\geq 1.5 \times 10^9$/l independent of growth factor support for at least 7 days before screening; platelet count $\geq 100 \times 10^9$/l independent of transfusion support for at least 7 days before screening; alanine aminotransferase and aspartate aminotransferase $< 2.5 \times$ the upper limit of normal (ULN) or $< 5 \times$ ULN with documented liver metastases; total bilirubin $< 1.5 \times$ ULN, and an estimated glomerular filtration rate ≥ 30 ml/min according to the Cockroft-Gault formula). *NTRK* gene fusion status determination was not an eligibility criterion for enrolment. Key exclusion criteria included receipt of an investigational or anticancer therapy within 2 weeks, or major surgery within 4 weeks, before enrolment, clinically significant active cardiovascular disease or history of myocardial infarction within 6 months before enrolment, or active, uncontrolled systemic infection. Patients with primary central nervous system (CNS) tumours or metastasis who were neurologically stable, and did not require steroid management of CNS symptoms within the 2 weeks before study entry, were allowed to enrol.

The protocol was approved by the institutional review boards of all participating centres. The study was conducted in accordance with the protocol and the principles expressed in the Declaration of Helsinki. All patients provided written informed consent before any study specific procedures were conducted.

Procedures

Patients were enrolled to six cohorts according to a standard $3 + 3$ dose escalation scheme. A safe starting dose of 50 mg once daily (QD) was determined based on data from animal toxicity studies. Larotrectinib was administered orally, as a QD or twice daily (b.i.d.) dose for continuous 28-day cycles. Treatment was continued until disease progression, the occurrence of unacceptable toxicity, or the withdrawal of patient consent. Dose escalation was to proceed through planned dose levels (supplementary Table S1, available at *Annals of Oncology* online), according to the occurrence of dose-limiting toxicity (DLT) in cycle 1, until the maximum tolerated dose (MTD) was reached. Expansion of the cohort treated at the MTD, or at a dose level deemed by the sponsor to provide significant TRK inhibition was permitted to better characterise safety and efficacy in specific patient groups. Dose interruptions of up to 4 weeks to allow for recovery were specified for clinically significant adverse events. Upon recovery, patients could either continue at the assigned dose of larotrectinib or have the dose reduced. Patients who had drug-related toxicity requiring a recovery period longer than 4 weeks were to be withdrawn from study drug administration, unless there was compelling evidence of response and no alternative treatment.

Study assessments

Disease status was assessed by investigators according Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15], at baseline and then on day 1 of every other cycle. Patients with a history of CNS metastases were to additionally have head computed tomography/magnetic resonance imaging carried out at each tumour assessment. Response in one patient has previously been described [16]. Blinded independent central review of imaging was subsequently carried out in patients with tumours harbouring *NTRK* gene fusions. Adverse events were monitored throughout the study and for 28 days after treatment and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Laboratory monitoring for toxicity and symptom directed neurological examinations for close monitoring of neurological toxicities were carried out weekly during cycle 1 and every 4 weeks thereafter.

Serial blood samples were collected for pharmacokinetic analyses. Plasma concentrations of larotrectinib were determined by liquid chromatography–mass spectrometry. The lower limit of quantification was 1 ng/ml. The appropriate noncompartmental pharmacokinetic parameters were calculated from the plasma concentration–time data with Phoenix® WinNonlin® Version 6.4. $AUC_{0–24}$ was calculated using the linear trapezoidal rule for QD cohorts. $AUC_{0–24}$ was estimated as two times $AUC_{0–12}$ for b.i.d. cohorts, with trough concentrations imputed from the pre-dose concentration. Actual sample times were used in the calculations.

Tumour *NTRK* gene status was assessed locally in a clinical laboratory improvement amendments (CLIA)-certified laboratory, before enrolment, by next generation sequencing, and was not centrally tested. If patients did not have tumour available for such analyses ($n = 18$), they were considered not to have *NTRK* gene fusions.

Outcomes

The primary end point was the safety of oral larotrectinib, including the MTD and recommended dose for further clinical investigation. Secondary end points included pharmacokinetics, objective response and duration of response. A post hoc analysis of the objective response rate (ORR) in patients with TRK fusion cancer was carried out.

DLT was assessed during the dose escalation phase and was defined as any of the following treatment-emergent adverse events, if they occurred during the first cycle: grade 3 or 4 non-haematological toxicity, with the exception of fatigue, asthenia, nausea or other manageable constitutional symptom; grade 3 or 4 vomiting or diarrhoea persisting for more than 24 h; any toxicity, regardless of grade, resulting in discontinuation or dose reduction of larotrectinib; grade 4 thrombocytopenia or grade 3 thrombocytopenia with grade 1 or worse bleeding; grade 4 anaemia lasting more than 7 days; or grade 4 neutropenia lasting more than 7 days.

Statistical considerations

Safety and antitumour activity data were summarised descriptively. Adverse events were summarised using the standardised preferred term assigned by the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The safety population comprised all patients who received one or more doses of larotrectinib. It was anticipated that enrolment of up to 60 patients might be required to define the MTD of larotrectinib, with the actual number dependent on the safety profile. A safety review committee considered safety and pharmacokinetic data and rendered dose-escalation decisions before each dose escalation. Antitumour activity was assessed in all enrolled patients; the ORR was calculated as the proportion of patients with measurable disease at baseline by RECIST v1.1 with a complete or partial response. Statistical analyses were carried out using SAS (version 9.4).

Results

Between 1 May 2014 and 24 August 2017, 70 patients with a median age of 59.5 years (IQR 50–66, range 19–82 years) were enrolled to 6 cohorts. Four patients were enrolled to cohort 1 (50 mg QD), five to cohort 2 (100 mg QD), 43 to cohort 3 (100 mg b.i.d.), 4 to cohort 3a (200 mg QD), 7 to cohort 4 (150 mg b.i.d.), and 6 to cohort 5 (200 mg b.i.d.). The trial profile is summarised in supplementary Figure S1, available at *Annals of Oncology* online. Patient characteristics at baseline are summarised in Table 1. Patients were in general heavily pre-treated, with 44 (63%) of 70 having at least three prior systemic therapies. The data cut-off date for the present analysis was 19 February 2018.

NTRK gene fusions were identified in the tumours of eight patients; six were *ETV6-NTRK3* fusions, one an *LMNA-NTRK1* fusion, and one a *TPR-NTRK1* fusion (Table 1). Additional oncogenic driver mutations were not identified in any of the TRK fusion tumours. Patients with 23 unique cancer diagnoses were included in this dose escalation study, as summarised in supplementary Table S2, available at *Annals of Oncology* online, according to *NTRK* gene fusion status.

All enrolled patients were assessable for safety. During the dose-escalation phase, no DLTs occurred at the first two dose levels. A DLT (dizziness) was reported in one of the first six patients treated at 100 mg b.i.d. and none were seen at 200 mg QD. DLTs occurred in one of seven patients treated at 150 mg b.i.d. (alanine aminotransferase increased and aspartate aminotransferase increased) and one of six patients treated at 200 mg b.i.d. (dizziness). The MTD was consequently not reached, and the 100 mg

b.i.d. dosing schedule was chosen as the recommended phase II dose based on its tolerability and the durability of response in patients with *NTRK* gene fusions; cohort 3 was subsequently expanded to further explore the safety and efficacy of larotrectinib.

The most commonly occurring treatment-emergent adverse events of any grade were fatigue, dizziness and anaemia (Table 2). Forty-two (60%) of 70 patients had grade 3 or worse treatment-emergent adverse events, with the most common being anaemia, fatigue and aspartate aminotransferase increased. Adverse events with an outcome of death were reported for five patients; all were related to disease progression. Most treatment-related adverse events were grade 1 or 2 (supplementary Table S3, available at *Annals of Oncology* online); 13 (19%) of the 70 patients experienced grade 3 treatment-related adverse events, the most common of which was anaemia [4 (6%) of 70 patients]. No patients had grade 4 or 5 treatment-related adverse events. Serious adverse events were reported in 32 (46%) of the 70 patients overall and in 17 (40%) of 43 patients in the 100 mg b.i.d. cohort. These were predominantly related to disease progression. Three (4%) of the 70 patients, none with an *NTRK* gene fusion, discontinued treatment due to larotrectinib-related adverse events (amylase increased, enterocutaneous fistula, lipase increased, and muscular weakness). Adverse events leading to dose interruption or

Table 1. Patient characteristics at baseline	
	All patients (*N* = 70)
Age, years	
Median (IQR)	59.5 (50–66)
Range	19–82
Median (IQR) for patients with tumour *NTRK* gene fusions (*n*=8)	48 (36–57.5)
Median (IQR) for patients without tumour *NTRK* gene fusions (*n*=62)	61 (52–67)
Sex	
Male	35 (50)
Female	35 (50)
ECOG performance status	
0	21 (30)
1	47 (67)
2	2 (3)
NTRK gene fusion (*n*=8)	
ETV6-NTRK3	6 (9)
LMNA-NTRK1	1 (1)
TPR-NTRK1	1 (1)
Prior anticancer treatments	
Systemic therapy	68 (97)
Surgery	61 (87)
Radiotherapy	40 (57)
Number of prior systemic therapies	
0	2 (3)
1–2	24 (34)
≥3	44 (63)

Data are *n* (%), unless otherwise stated.
ECOG, Eastern Cooperative Oncology Group.

Table 2. Treatment-emergent adverse events				
	All patients, *n* = 70			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**
Fatigue	28 (40)	5 (7)	0	0
Dizziness	22 (31)	1 (1)	0	0
Anaemia	12 (17)	10 (14)	0	0
Nausea	20 (29)	0	0	0
Constipation	17 (24)	1 (1)	0	0
Dyspnoea	15 (21)	3 (4)	0	0
Cough	16 (23)	0	0	0
Vomiting	14 (20)	1 (1)	0	0
Diarrhoea	13 (19)	1 (1)	0	0
Decreased appetite	10 (14)	3 (4)	0	0
Oedema peripheral	13 (19)	0	0	0
Myalgia	11 (16)	1 (1)	0	0
Arthralgia	10 (14)	1 (1)	0	0
Pyrexia	11 (16)	0	0	0
Aspartate aminotransferase increased	6 (9)	4 (6)	0	0
Muscular weakness	10 (14)	0	0	0
Abdominal pain	7 (10)	2 (3)	0	0
Dysgeusia	9 (13)	0	0	0
Back pain	8 (11)	0	0	0
Hypertension	6 (9)	2 (3)	0	0
Blood alkaline phosphatase increased	6 (9)	1 (1)	0	0
Gait disturbance	6 (9)	1 (1)	0	0
Hypoalbuminaemia	6 (9)	1 (1)	0	0
Insomnia	7 (10)	0	0	0
Memory impairment	7 (10)	0	0	0
Paraesthesia	7 (10)	0	0	0

Data are *n* (%). Table shows adverse events occurring in ≥10% of patients at any grade.

modification were recorded in 30 (43%) of 70 patients; the most common were dizziness (5 patients; 7%) aspartate aminotransferase increased and pyrexia (3 patients; 4%). Utilising *NTRK* gene fusion status as a surrogate for safety related to long-term exposure, there was no meaningful difference in treatment-related adverse event profiles for patients with or without *NTRK* gene fusions (supplementary Table S3, available at *Annals of Oncology* online).

Steady-state pharmacokinetic parameters for larotrectinib across the six dose escalation cohorts are summarised in supplementary Table S4 and Figure S2, available at *Annals of Oncology* online. The rate and extent of exposure to larotrectinib following QD and b.i.d. administration at doses up to 200 mg increased with increasing dose. The estimates of exposure were generally proportional to the administered dose. Larotrectinib was rapidly eliminated from plasma and its half-life appeared to be independent of the administered dose. Following repeated administration of larotrectinib, minimal accumulation was evident in plasma, consistent with its short half-life.

Of the 70 patients enrolled, 67 patients were assessable for objective response, with measurable disease by RECIST 1.1 at enrolment; 3 patients without measurable disease were excluded from this assessment. The ORR among assessable patients as assessed by investigators was 12% (8 of the 67 patients); responses were seen in 7 of 8 patients with tumours harbouring *NTRK* gene fusions and in one patient with a tumour harbouring an *NTRK1* gene amplification. The responding patient with the *NTRK1* gene amplification had a single, small target lesion (11 mm) that shrank by 5 mm (45.5%) and a duration of response of 3.7 months. None of the patients with *NTRK* point mutations had an objective response, consistent with prior analyses suggesting that *NTRK* point mutations are generally not activating oncogenic events [17]. Following independent, central radiology review, eight (100%) of eight patients with tumours harbouring *NTRK* gene fusions were deemed to have had an objective response, including two with complete responses and six with partial responses (Table 3; supplementary Figure S3, available at *Annals of Oncology* online).

Reductions in tumour burden were observed in all patients with tumours harbouring an *NTRK* gene fusion. Figure 1A and supplementary Figure S4A, available at *Annals of Oncology* online show the best change in target lesion size in these patients according to independent assessment; Figure 1B and supplementary Figure S4B, available at *Annals of Oncology* online show the timing of response. Six of eight patients with TRK fusion cancer remained on treatment at 19 February 2018 cut-off. The median

Table 3. Investigator and independent central assessments of response in patients with TRK fusion cancer		
	Investigator assessment (n = 8)	Independent central assessment (n = 8)
Objective response rate, % (95% CI)	88% (47–100)	100% (63–100)
Complete response, n (%)	2 (25)	2 (25)
Partial response, n (%)	5 (63)	6 (75)
Stable disease, n (%)	1 (13)	0
Time to first response, median (min, max)	1.8 months (1.0, 3.7)	1.9 months (1.0, 14.5)
Duration of response, median (range), months	NR (14.7+ to 33.2+)	NR (8.2 to 33.1+)
Median follow-up, months	26.9	27.0

NR, not reached.
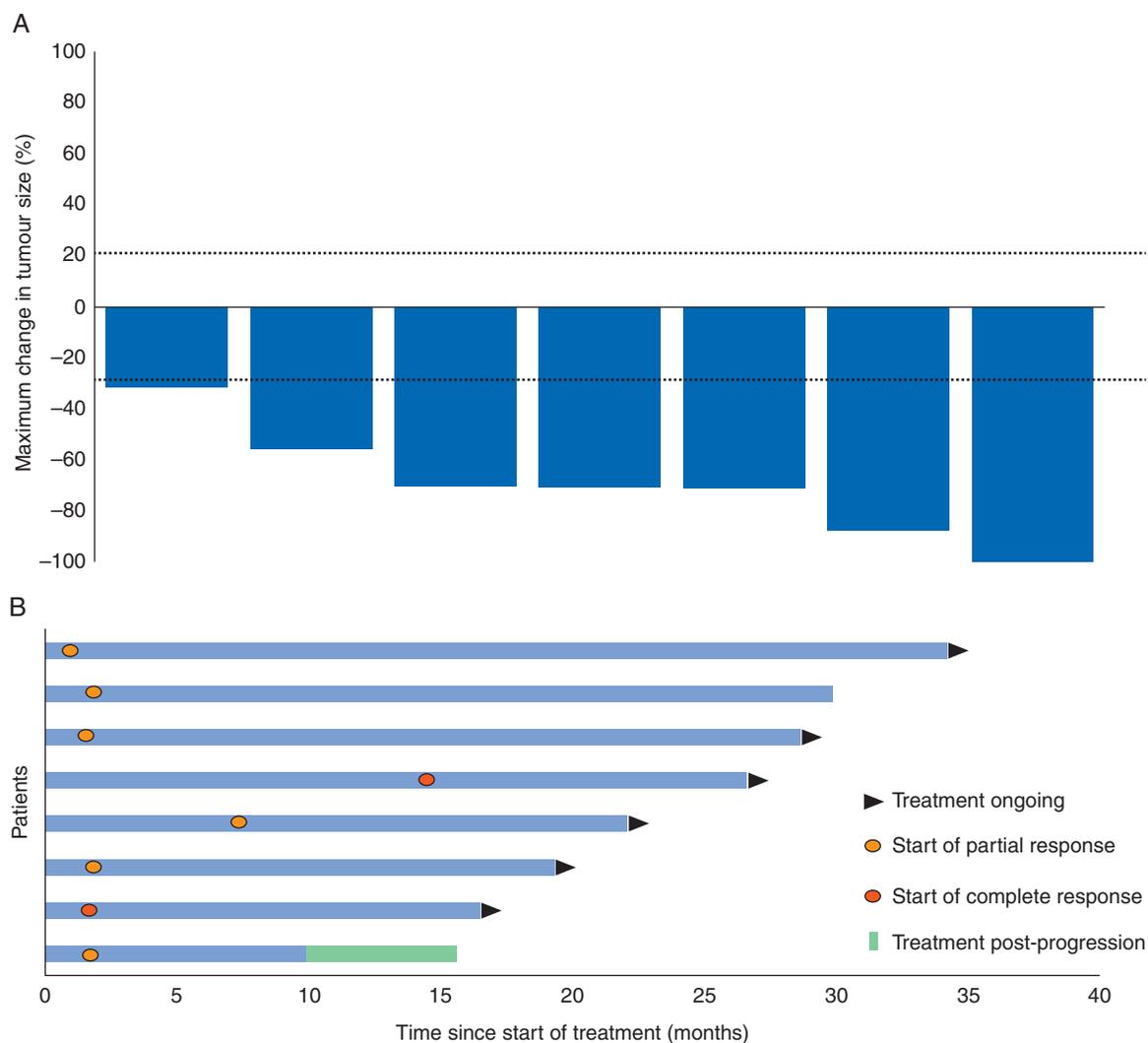
Figure 1. Independent review committee assessment of response in patients with TRK fusion cancer. (A) Waterfall plot of maximum percentage change in tumour size of target lesions in patients with TRK fusion cancer. Outcome for one patient with a complete response is not shown as the independent review committee assessed this patient as having non-measurable disease at baseline. (B) Swimmer plot showing time on treatment and timing of objective response for patients with tumours harbouring *NTRK* gene fusions.

time on treatment of patients with TRK fusion cancer was 28.4 months (IQR 20.2–29.9) with a maximum of 35.2 months ongoing at the time of data analysis, compared with a median of 1.8 months (IQR 0.9–2.8) and a maximum of 27.0 months for patients whose tumours did not harbour an *NTRK* gene fusion. The median duration of follow up for patients with TRK fusion cancer on larotrectinib was 26.9 months; the median duration of response was not reached (supplementary Figure S5, available at *Annals of Oncology* online).

Following an initial response to treatment, a 29-year-old male with NSCLC and a 58-year-old male with a gastrointestinal stromal tumour (GIST) progressed after developing acquired resistance mutations; solvent-front (TRKA G595R) and xDFG (TRKA G667S) mutations in the case of the patient with NSCLC, and a gatekeeper mutation (TRKC F617L) in the case of the patient with GIST.

Discussion

We found that in adults, larotrectinib was safe and well tolerated. Larotrectinib-related toxicities were most often grade 1 or 2, were reversible, and were easily managed. Since the MTD was not reached, 100 mg b.i.d. was set as the recommended phase II dose based on its tolerability and on the durability of response in patients with TRK fusion cancer. The 100 mg b.i.d. dosing regimen has since been investigated in a combined analysis of larotrectinib administered to 55 adult and paediatric patients with tumours harbouring *NTRK* gene fusions [14].

By independent radiology review, all eight patients with TRK fusion cancer were deemed to have had an objective response. One patient had punctate brain metastases at baseline that appeared to respond while on treatment, which suggests that larotrectinib can cross the blood–brain barrier. Indeed, the larotrectinib phase I paediatric study confirmed the presence of free drug within the CNS [18]. Six of eight patients are continuing on larotrectinib with a median time on treatment of 28.4 months, which is markedly longer than observed for patients whose tumours did not harbour *NTRK* gene fusions (1.8 months). These data demonstrate the significantly robust and prolonged durability of response to larotrectinib in patients with TRK fusion cancer, consistent with the findings of the paediatric phase I/II trial [18] and the ongoing phase II larotrectinib adult/adolescent basket trial (NCT02576431).

Our next generation sequencing data suggest that patients with TRK fusion cancer are unlikely to harbour other actionable alterations within their tumours. This argues for careful consideration when screening patients. In particular, it is crucial that the specific platform chosen for genetic screening is able to capture the entire spectrum of *NTRK* gene fusions.

The combined results of the current study and the paediatric larotrectinib trial [18] show that larotrectinib is effective against TRK fusion cancer, regardless of patient age. These studies also demonstrate the robust efficacy of larotrectinib against 17 unique TRK fusion tumour types [14, 18], regardless of *NTRK* gene and 5′ fusion partner.

In conclusion, larotrectinib was well tolerated and provided consistent and durable antitumour activity in adults with TRK fusion cancer, giving an ORR of 100% (eight of eight patients) by independent central assessment. This first-in-class, highly selective TRK inhibitor is the only one of its kind, to our knowledge, that is currently in clinical development simultaneously for both adult and paediatric cancers. Larotrectinib offers a potential new standard of care for patients with TRK fusion cancer, which is contingent on effective tissue-agnostic routine screening to detect tumours harbouring *NTRK* gene fusions.

Disclosure

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