THE LANCET
Oncology

www.thelancet.com/oncology

Reprint

Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials

Alexander Drilon, Salvatore Siena, Rafal Dziadziuszko, Fabrice Barlesi, Matthew G Krebs, Alice T Shaw, Filippo de Braud, Christian Rolfo, Myung-Ju Ahn, Jürgen Wolf, Takashi Seto, Byoung Chul Cho, Manish R Patel, Chao-Hua Chiu, Thomas John, Koichi Goto, Christos S Karapetis, Hendrick-Tobias Arkenau, Sang-We Kim, Yuichiro Ohe, Yu-Chung Li, Young K Chae, Christine H Chung, Gregory A Otterson, Haruyasu Murakami, Chia-Chi Lin, Daniel S W Tan, Hans Prenen, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, Robert C Doebele, on behalf of the trial investigators†

Lancet Oncol 2020; **21:** 261–70

Account Manager
David Velázquez
T: +34 914021212
d.velazquez@elsevier.com

The Lancet Oncology is a monthly subscription journal. For further information on how to subscribe please contact our Subscription Department
T: +44 (0) 1865 843077
F: +44 (0) 1865 843970
custserv@lancet.com

(North America)
T: +1 (800) 462 6198
F: +1 (800) 327 9021
USLancetCS@elsevier.com

Printed by

Elsevier España, S.L.U.
(A member of Elsevier)
Josep Tarradellas, 20-30, 1ª pl.
08029 Barcelona
Tel. 93 2000711
Fax 93 2091136

Publication information *The Lancet Oncology* (ISSN 1470-2045) is published monthly by Elsevier (The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK). Periodicals postage paid at Rahway, NJ, USA. POSTMASTER: send address corrections to *The Lancet Oncology* c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials

Alexander Drilon, Salvatore Siena*, Rafal Dziadziuszko, Fabrice Barlesi, Matthew G Krebs, Alice T Shaw, Filippo de Braud, Christian Rolfo, Myung-Ju Ahn, Jürgen Wolf, Takashi Seto, Byoung Chul Cho, Manish R Patel, Chao-Hua Chiu, Thomas John, Koichi Goto, Christos S Karapetis, Hendrick-Tobias Arkenau, Sang-We Kim, Yuichiro Ohe, Yu-Chung Li, Young K Chae, Christine H Chung, Gregory A Otterson, Haruyasu Murakami, Chia-Chi Lin, Daniel S W Tan, Hans Prenen, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, Robert C Doebele, on behalf of the trial investigators†*

Summary

Background Recurrent gene fusions, such as *ROS1* fusions, are oncogenic drivers of various cancers, including non-small-cell lung cancer (NSCLC). Up to 36% of patients with *ROS1* fusion-positive NSCLC have brain metastases at the diagnosis of advanced disease. Entrectinib is a ROS1 inhibitor that has been designed to effectively penetrate and remain in the CNS. We explored the use of entrectinib in patients with locally advanced or metastatic *ROS1* fusion-positive NSCLC.

Methods We did an integrated analysis of three ongoing phase 1 or 2 trials of entrectinib (ALKA-372-001, STARTRK-1, and STARTRK-2). The efficacy-evaluable population included adult patients (aged ≥18 years) with locally advanced or metastatic *ROS1* fusion-positive NSCLC who received entrectinib at a dose of at least 600 mg orally once per day, with at least 12 months' follow-up. All patients had an Eastern Cooperative Oncology Group performance status of 0–2, and previous cancer treatment (except for ROS1 inhibitors) was allowed. The primary endpoints were the proportion of patients with an objective response (complete or partial response according to Response Evaluation Criteria in Solid Tumors version 1.1) and duration of response, and were evaluated by blinded independent central review. The safety-evaluable population for the safety analysis included all patients with *ROS1* fusion-positive NSCLC in the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). These ongoing studies are registered with ClinicalTrials.gov, NCT02097810 (STARTRK-1) and 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), 41 (77%; 95% CI 64–88) of 53 patients in the efficacy-evaluable population had an objective response. Median follow-up was 15·5 months (IQR 13·4–20·2). Median duration of response was 24·6 months (95% CI 11·4–34·8). In the safety-evaluable population, 79 (59%) of 134 patients had grade 1 or 2 treatment-related adverse events. 46 (34%) of 134 patients had grade 3 or 4 treatment-related adverse events, with the most common being weight increase (ten [8%]) and neutropenia (five [4%]). 15 (11%) patients had serious treatment-related adverse events, the most common of which were nervous system disorders (four [3%]) and cardiac disorders (three [2%]). No treatment-related deaths occurred.

Interpretation Entrectinib is active with durable disease control in patients with *ROS1* fusion-positive NSCLC, and is well tolerated with a manageable safety profile, making it amenable to long-term dosing in these patients. These data highlight the need to routinely test for *ROS1* fusions to broaden therapeutic options for patients with *ROS1* fusion-positive NSCLC.

Funding Ignyta/F Hoffmann-La Roche.

Introduction

Recurrent gene fusions are oncogenic drivers of various cancers.[1] *ROS1* fusions include the kinase domain-containing 3′ region of *ROS1* fused to various 5′ or upstream partners, the most common of which is *CD74*.[2] The resultant oncoprotein is characterised by constitutive kinase activation, increased downstream signalling, and ultimately tumour growth.[3] *ROS1* fusions are enriched in non-small-cell lung cancers (NSCLCs) and are present in 1–2% of cases.[4] Typically, *ROS1* fusions do not overlap with other canonical drivers, including *NTRK* fusions, in NSCLCs.[5]

Targeted therapy for patients with *ROS1* fusion-positive NSCLC requires effective coverage of the CNS, a common site of metastases. Up to 36% of patients with *ROS1* fusion-positive NSCLCs have brain metastases at the diagnosis of advanced disease, and many others will subsequently develop intracranial metastases.[6] The

Lancet Oncol 2020; 21: 261–70

Published Online December 11, 2019 https://doi.org/10.1016/S1470-2045(19)30690-4

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on January 30, 2020

See Comment page 193

*Joint first authors

†Trial investigators listed in the appendix

Weill Cornell Medical College, New York, NY, USA (A Drilon MD); **Memorial Sloan Kettering Cancer Center, New York, NY, USA** (A Drilon); **Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy** (Prof S Siena M D); **Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy** (Prof S Siena); **Institute of Cancer Sciences, Medical University of Gdansk, Gdansk, Poland** (R Dziadziuszko MD); **Aix Marseille University, INSERM, CNRS, CRCM, Assistance Publique-Hôpitaux de Marseille, Marseille, France** (F Barlesi MD); **Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK** (M G Krebs MD); **The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK** (M G Krebs); **Institute of Cancer Sciences, Massachusetts General Hospital, Boston, MA, USA** (Prof A T Shaw MD); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (Prof F de Braud MD); **Department of Oncology and Hemato-Oncology, Università deli Studi di Milano, Milan,**

Italy (Prof F de Braud)**; Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA** (C Rolfo MD)**; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea** (M-J Ahn MD)**; Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany** (Prof J Wolf MD)**; National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan** (T Seto MD)**; Yonsei Cancer Center, Seoul, South Korea** (Prof B C Cho MD)**; University of Minnesota, Department of Medicine, Minneapolis, MN, USA** (M R Patel MD)**; Taipei Veterans General Hospital, Taipei, Taiwan** (C-H Chiu MD)**; Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia** (T John MD)**; National Cancer Center Hospital East, Kashiwa, Japan** (K Goto MD)**; Flinders Medical Centre and Flinders University, Adelaide, SA, Australia** (Prof C S Karapetis MD)**; Sarah Cannon Research Institute and Cancer Institute University College London, London, UK** (H-T Arkenau MD)**; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (S-W Kim MD)**; National Cancer Center Hospital, Tokyo, Japan** (Y Ohe MD)**; Hong Kong United Oncology Centre, Hong Kong Special Administrative Region, China** (Y-C Li MD)**; Department of Medicine, Northwestern University, Chicago, IL, USA** (Y K Chae MD)**; Moffitt Cancer Center, Tampa, FL, USA** (Prof C H Chung MD)**; Arthur G James Cancer Hospital and Richard J Solove Research Institute, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA** (Prof G A Otterson MD)**; Shizuoka Cancer Center, Tokyo, Japan** (H Murakami MD)**; National Taiwan University Hospital, Taipei, Taiwan** (C-C Lin MD)**; National Cancer Centre, Singapore** (D S W Tan MD)**; University Hospital Antwerp, Edegem, Belgium** (Prof H Prenen MD)**; Genentech, South San Francisco, CA, USA** (T Riehl PharmD, B Simmons PharmD, N Cui PhD,

Research in context

Evidence before this study

We searched PubMed and major congress abstracts for reports relating to the treatment of *ROS1* fusion-positive non-small-cell lung cancer (NSCLC) using terms including "ROS1", "fusion OR rearrangement" and "lung OR NSCLC", with no publication date or language restrictions. Data from several studies, including a pivotal phase 1 trial, showed that the ROS1 inhibitor crizotinib has anti-tumour activity in patients with *ROS1* fusion-positive NSCLC. Unfortunately, about half of patients with *ROS1* fusion-positive NSCLC experience disease progression solely in the CNS, likely due to poor drug penetration of the blood–brain barrier. Additionally, up to 36% of patients with *ROS1* fusion-positive NSCLC already have CNS metastases at the time of diagnosis, further highlighting the need for alternative treatment options with CNS activity.

Added value of this study

Entrectinib is a potent inhibitor of ROS1 that was designed to penetrate and remain in the CNS. In this integrated analysis of three phase 1–2 clinical trials, the proportion of patients having a response with entrectinib was high and disease control was durable (overall and in the CNS) in patients with ROS1 inhibitor-naive, *ROS1* fusion-positive NSCLCs. These data provide clear evidence for the substantial intracranial and extracranial activity of entrectinib. The drug had a manageable safety profile.

Implications of all the available evidence

Entrectinib is an important therapeutic option for patients with ROS1 inhibitor-naive, *ROS1* fusion-positive NSCLC. The intracranial activity of entrectinib is of particular importance because of the frequency of CNS involvement in *ROS1* fusion-positive NSCLC and the suboptimal ability of crizotinib to penetrate the CNS.

tyrosine kinase inhibitor (TKI) crizotinib is approved by several regulatory agencies for the treatment of patients with advanced *ROS1* fusion-positive NSCLC.[7] Unfortunately, crizotinib has suboptimal CNS penetration, as has been observed in *ALK* fusion-positive NSCLC.[8,9] Consistent with this finding, the CNS is the first and sole site of progression in almost half of patients with *ROS1* fusion-positive NSCLC who are treated with crizotinib.[6,10] This fact highlights the need for novel ROS1 inhibitors with potent intracranial activity.

Entrectinib is a multikinase inhibitor with activity against ROS1 (in addition to tropomyosin receptor kinase [TRK] A, B, and C and ALK).[11–13] In *ROS1* fusion-containing cancer models, entrectinib is 40 times more potent than crizotinib in vitro.[13] Moreover, it was designed with the ability to effectively cross the blood–brain barrier and be retained in the CNS.[13] In preclinical studies, entrectinib achieved substantial concentrations in the CNS, with a blood-to-brain ratio of 0·4–1·9 in mice, rats, and dogs.[14] Entrectinib was detected in brain homogenates of these species after single or multiple doses.[15]

Consistent with these findings, entrectinib was found to prolong survival and delay intracranial progression compared with vehicle in orthotopic CNS xenografts of models that harbour established fusion targets of the drug such as NCI-H228 (in NSCLC),[13] BNN2/4 (in glioblastoma),[16] and KM12SM (in colorectal cancer).[17] In the NCI-H228 model, entrectinib resulted in increased survival compared with that with crizotinib.[13] These data established preclinical proof-of-principle of the activity of this drug in the CNS.

In this context, the use of entrectinib in patients with TKI-naive *ROS1* fusion-positive NSCLC was explored in three prospective phase 1 or 2 clinical trials. The goal of this programme was to provide a more potent and CNS-active, ROS1-targeted therapy for patients with *ROS1* fusion-positive NSCLC.

Methods

Study design and participants

Patients (aged ≥18 years) with locally advanced or metastatic solid tumours harbouring *ROS1* fusions were enrolled in one of two phase 1 studies (ALKA-372-001 or STARTRK-1)[11] 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 hospital and seven cancer centres in the USA, one hospital in Spain, one centre in South Korea. STARTRK-2 is ongoing at more than 150 sites (ie, cancer and medical centres, research institutes, hospitals, and universities) in 15 countries (appendix pp 2–10).

Patients included in this prespecified integrated efficacy analysis met the following criteria: they had locally advanced or metastatic NSCLC harbouring a *ROS1* fusion, they were ROS1 TKI naive, they had measurable disease (investigator assessed, according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), they had a Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and they had received at least 600 mg (one dose) of entrectinib.[11] The safety analysis set included 134 patients with NSCLC who were not all TKI naive. The safety population was much larger than the efficacy population because it included 47 patients with less than 12 months of follow-up, 27 patients who previously had received a ROS1 inhibitor (which was not allowed for the efficacy analysis), three patients with an ECOG performance status of 2 or more, and one patient with ROS1

biomarker ineligibility—these patients were not eligible for the efficacy analysis but were eligible for the safety analysis because they had all received at least one dose of entrectinib. 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; used to detect the presence of *ROS1* fusions). Local testing could include fluorescence in-situ hybridisation tests, quantitative PCR, or DNA-based or RNA-based next-generation sequencing (appendix p 11). In ALKA-372-001 and STARTRK-1, patients were enrolled on the basis of local testing only. In STARTRK-2, patients enrolled via local testing were required to provide tumour tissue (unless a biopsy was medically contraindicated) for independent central next-generation sequencing testing following enrolment.

Patients had 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. The presence of brain metastases, which were either asymptomatic or previously treated and controlled, was permitted. In ALKA-372-001, previous cancer therapy was allowed (excluding previous ROS1 inhibitors); in STARTRK-1, previous cancer therapy was allowed, including crizotinib, ceritinib, and investigational drugs; and in STARTRK-2, previous anticancer therapy was allowed (excluding approved or investigational ROS1 inhibitors). All patients, irrespective of line of therapy, had measurable disease as assessed locally according to RECIST (version 1.1). 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 TKI-induced pneumonitis; or peripheral neuropathy grade 2 or worse. Full general and study-specific eligibility criteria are provided in the appendix pp 16–17.

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 protocols are provided in the appendix.

Procedures

In all three trials patients received capsule form entrectinib (in a fasted state in ALKA-372-001 and fed state in STARTRK-1 and STARTRK-2) once daily. In ALKA-372-001 (dose escalation trial) patients received 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, or 1600 mg; in STARTRK-1 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg; and in STARTRK-2: 600 mg. Entrectinib was administered on intermittent or continuous dose schedules. Patients in all trials continued treatment until documented radiographic progression, unacceptable toxicity, or withdrawal of consent.

Imaging assessments of all known disease sites (including the brain, as applicable) were done by CT or MRI scanning at the end of cycle 1 (4 weeks), and every two cycles (8 weeks) thereafter. In all three trials patients received treatment in 4-week cycles. Serial CNS imaging was required only when intracranial disease was known to be present at baseline. Methods used for CNS evaluation were consistent across all three trials. All CT and MRI scans were submitted for blinded independent central review according to RECIST (version 1.1). Intracranial evaluations were limited to only intracranial lesions. Any progressive disease outside the brain was censored, unless the patient continued treatment beyond progression.

Safety was assessed by physical examination, laboratory tests, and adverse event monitoring. Adverse events were coded using Medical Dictionary for Regulatory Activities (version 14.0 or higher for individual studies; version 21.0 for the integrated safety analysis) 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 select patient visits (days 1 and 15 of cycles 1–3, and day 1 of cycle 4 and of each subsequent cycle thereafter). If needed, dose reductions due to toxicity or treatment-related adverse events could occur in decrements of 200 mg, but no more than two dose reductions were allowed.

Outcomes

For this integrated analysis, the co-primary endpoints of this integrated analysis were objective response (defined as the proportion of patients with a complete response or partial response) to measure the direct antitumour activity of entrectinib, and duration of response to measure the durability of antitumour activity (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); both endpoints were measured by blinded independent central review. Key secondary endpoints were 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), overall survival (defined as the time from the first dose of entrectinib to the date of death due to any cause at the time of data cutoff) per blinded independent central review, and safety. Additional prespecified secondary endpoints evaluated in patients with baseline CNS disease per blinded independent central review were intracranial response, intracranial duration of response, and intracranial progression-free survival. Time to CNS progression in patients presenting with measurable CNS disease at baseline was a predefined secondary endpoint.

S Eng PharmD, T R Wilson PhD); **Ignyta, San Diego, CA, USA** (E Chow-Maneval PhD, A Johnson MS)**; and School of Medicine, University of Colorado, Aurora, CO, USA** (R C Doebele MD)

Correspondence to:
Dr Robert C Doebele, University of Colorado, Aurora, CO 80045, USA
robert.doebele@cuanschutz.edu

See **Online** for appendix

Statistical analysis

For response data, the number, percentage, and corresponding two-sided 95% Clopper–Pearson exact CIs were summarised. The sample size for the integrated analysis was calculated based on the objective response endpoint, with assumptions based on the clinically meaningful response threshold and target response. Under the assumption that the true objective response by blinded independent central review was 70%, a sample size of 50 or more patients would yield a two-sided 95% CI with precision of at least 17% (excluding a lower limit of 50% as observed with standard-of-care *ROS1* fusion-positive NSCLC treatment, as determined in consultation with the US Food and Drug Administration). A response of 50% or higher is considered clinically meaningful. There was no formal hypothesis testing and significance tests were not done; there was no α spending for the objective response and duration of response endpoints. The Kaplan–Meier method was used to estimate the time-to-event endpoints (duration of response, progression-free survival, and overall survival), with corresponding 95% CIs.

For the primary and secondary outcomes, the integrated efficacy-evaluable population included patients with *ROS1* fusion-positive NSCLC, who were ROS1 inhibitor naive, had measurable disease at baseline, and at least 12 months' follow-up from the onset of treatment; patients were not assessable if they did not have measurable disease at baseline. The safety-evaluable population in this integrated analysis included all patients with *ROS1* fusion-positive NSCLC from all three studies who had received at least one dose of entrectinib, irrespective of dose. Safety data from all three studies were summarised descriptively. The statistical evaluation was done with the software package SAS (version 9.3 or higher). No interim analyses were planned. Investigator assessments were used for sensitivity analyses, which are not reported here.

These studies are registered as follows: ALKA-372-001, EudraCT 2012–000148–88; STARTRK-1 with Clinicaltrials.gov, NCT02097810; and STARTRK-2 with Clinicaltrials.gov, NCT02568267.

	All patients in integrated analysis (n=53)
Age, years	53 (46–61)
Sex	
Female	34 (64%)
Male	19 (36%)
Ethnicity	
White	31 (59%)
Asian	19 (36%)
Black or African–American	3 (6%)
Eastern Cooperative Oncology Group performance status	
0	20 (38%)
1	27 (51%)
2	6 (11%)
Smoking status	
Never smoker	31 (59%)
Previous or current smoker	22 (42%)
Histology*	
Adenocarcinoma	52 (98%)
Other†	1 (2%)
CNS disease present at baseline‡	23 (43%)
Measurable	5 (9%)
Not measurable	18 (34%)
Previous CNS disease treatment§	8 (35%)
Stereotactic radiotherapy	3 (13%)
Whole brain with or without stereotactic radiotherapy	5 (22%)
No previous CNS disease treatment§	15 (65%)
Number of previous systemic therapies	
0	17 (32%)
1	23 (43%)
2 or more	13 (25%)
Gene fusion	
CD74–ROS1	21 (40%)
SLC34A2–ROS1	7 (13%)
SDC4–ROS1	6 (11%)
EZR–ROS1	5 (9%)
TPM3–ROS1	2 (4%)
Unknown¶	12 (23%)

Data are median (IQR) or n (%). *Percentage calculated out of 46 patients with available histological data. †Carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (n=1). ‡Baseline CNS disease featured in the table was as per investigator assessment, for which 23 patients with CNS disease were identified. However, according to blinded independent central review, the number of patients with CNS disease was 20. §Percentage calculated out of the 23 patients with CNS disease at baseline (according to investigator assessment). ¶Patients enrolled via a *ROS1* fluorescence in-situ hybridisation assay, which does not provide information on fusion partner.

Table 1: **Baseline characteristics of the integrated efficacy analysis population**

Role of the funding source

The studies were designed by the funders and study investigators. Data were collected, analysed, and interpreted by the funders, with the authors and investigators. TR, EC-M, BS, NC, AJ, SE, and TRW had full access to the raw data. All authors contributed to the writing and approval of this report. Professional medical writing assistance was funded by F Hoffmann-La Roche. The lead (AD and SS) and corresponding (RCD) authors had full access to all the data and had final responsibility for the decision to submit for publication.

Results

53 ROS1 inhibitor-naive patients with *ROS1* fusion-positive NSCLC were included in the integrated efficacy analysis population (appendix p 12). 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). All three studies were ongoing

on May 31, 2018, which was the data cutoff date for this integrated analysis. All 53 patients received treatment and the safety population included 134 patients who had received at least one dose of treatment.

Table 1 summarises the clinical characteristics of all patients. The median age was 53 years (IQR 46–61). Two patients from STARTRK-2 received previous crizotinib (one had previously received 4 cycles of crizotinib that was discontinued due to toxicity, and one was a protocol violation; both included in analysis).

The upstream *ROS1* fusion partner was known for 41 (77%) patients (table 1). The remaining 12 (23%) patients were enrolled by fluorescence in-situ hybridisation, with no (11 [21%]) or insufficient (one [2%]) tissue for central next-generation sequencing testing for fusion partner determination. Although 23 patients had baseline CNS metastases according to investigator assessment (table 1), 20 (38%) patients had baseline CNS metastases as assessed by blinded independent central review. Of these 20 patients, 12 had measurable CNS disease and eight patients did not have measurable CNS disease (their lesions were <1 cm in size). Six of the 12 patients with measurable CNS disease had no previous brain radiotherapy and one received radiotherapy more than 2 months before starting entrectinib. The median follow-up was 15·5 months (IQR 13·4–20·2).

41 (77%; 95% CI 64–88) of 53 patients in the integrated efficacy-evaluable population had a response at the data cutoff. Among the 53 patients, three (6%) had a complete response, 38 (72%) had a partial response, and one (2%) had stable disease as their best objective response to entrectinib (table 2). Most patients who were given entrectinib had disease regression in target lesions (figure 1A), including those with baseline CNS metastases (figure 1B). Response to entrectinib did not differ by upstream gene partner type (prespecified subgroup analysis; appendix p 13). 18 (86%) of 21 patients with *CD74–ROS1* fusions had a response compared with 13 (65%) of 20 for non-*CD74–ROS1* fusions, and 10 (83%) of 12 in those with unknown fusions. Responses occurred early; most responses occurred at the first follow-up imaging assessment (appendix p 15). Time on therapy did not differ by upstream gene partner (prespecified subgroup analysis; appendix p 14). The median treatment duration was 14·6 months (IQR 7·2–18·1) for patients with *CD74–ROS1* fusions versus 14·2 months (3·1–15·4) for those with non-*CD74–ROS1* fusions and 21·5 months (13·0–20·2) for those with unknown fusions (prespecified subgroup analysis).

Of the 20 patients with baseline CNS metastases by blinded independent central review, 11 (55%, 95% CI 32–77) patients had an intracranial response (table 2). Most patients with measurable intracranial disease had disease regression (figure 1C). Of the seven patients with measurable CNS disease at baseline who had no previous radiotherapy or had received radiotherapy more than 2 months before starting entrectinib, five (71%) had an intracranial response and two (29%) had no intracranial response. Four (80%) of five patients who had received radiotherapy within 2 months before entrectinib treatment had an intracranial response.

In the 41 responding patients in the overall integrated efficacy-evaluable population, median duration of response by blinded independent central review was 24·6 months (95% CI 11·4–34·8; figure 2A). Of the 53 patients in the integrated efficacy-evaluable population there were 25 patients with a progression-free survival event and the median progression-free survival by blinded independent central review was 19·0 months (95% CI 12·2–36·6; figure 2B). Of the 20 patients with baseline CNS metastases assessed by blinded independent central review, 11 patients had a progression-free survival event, and the median overall progression-free survival was 13·6 months (95% CI 4·5 to not estimable) whereas in 30 patients without baseline CNS metastases (according to investigator assessment) 14 patients had a progression-free survival

	Integrated efficacy-evaluable population (n=53)	Patients with baseline CNS disease (n=23)*	Patients with no baseline CNS disease (n=30)*
Objective responses, n; % (95% CI)	41; 77% (64–88)	17; 74% (52–90)	24; 80% (61–92)
Best overall response			
Complete response, n (%)	3 (6%)†	0	3 (10%)
Partial response, n (%)	38 (72%)†	17 (74%)	21 (70%)
Stable disease, n (%)	1 (2%)	0	1 (3%)
Progressive disease, n (%)	4 (8%)	4 (17%)	0
Non-complete response or non-progressive disease, n (%)	3 (6%)	0	3 (10%)
Missing or unevaluable, n (%)‡	4 (8%)	2 (9%)	2 (7%)
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)
Intracranial activity	..	20·0‡	..
Overall response, n; % (95% CI)	..	11; 55% (32–77)	..
Best intracranial response			
Complete response, n (%)	..	4 (20%)	..
Partial response, n (%)	..	7 (35%)	..
Stable disease, n (%)	..	0	..
Progressive disease, n (%)	..	3 (15%)	..
Non-complete response or non-progressive disease, n (%)	..	4 (20%)	..
Missing or unevaluable, n (%)§	..	2 (10%)	..

Shown are the proportion of patients achieving a response, duration of response, and progression-free survival (RECIST version 1.1 by blinded independent central review) in the integrated efficacy population (patients with *ROS1* fusion-positive and ROS1 inhibitor-naive non-small-cell lung cancer) and intracranial response, duration of response, and progression-free survival in patients with CNS disease at baseline (RECIST version 1.1, according to blinded independent central review). NE=not estimable. RECIST=Response Evaluation Criteria in Solid Tumors. *CNS disease status determined by investigator. †These percentages do not equal 77% due to rounding. ‡CNS disease status determined by BICR. §Missing or unevaluable included patients with no post-baseline scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to evaluate or confirm response.

Table 2: **Efficacy outcomes**

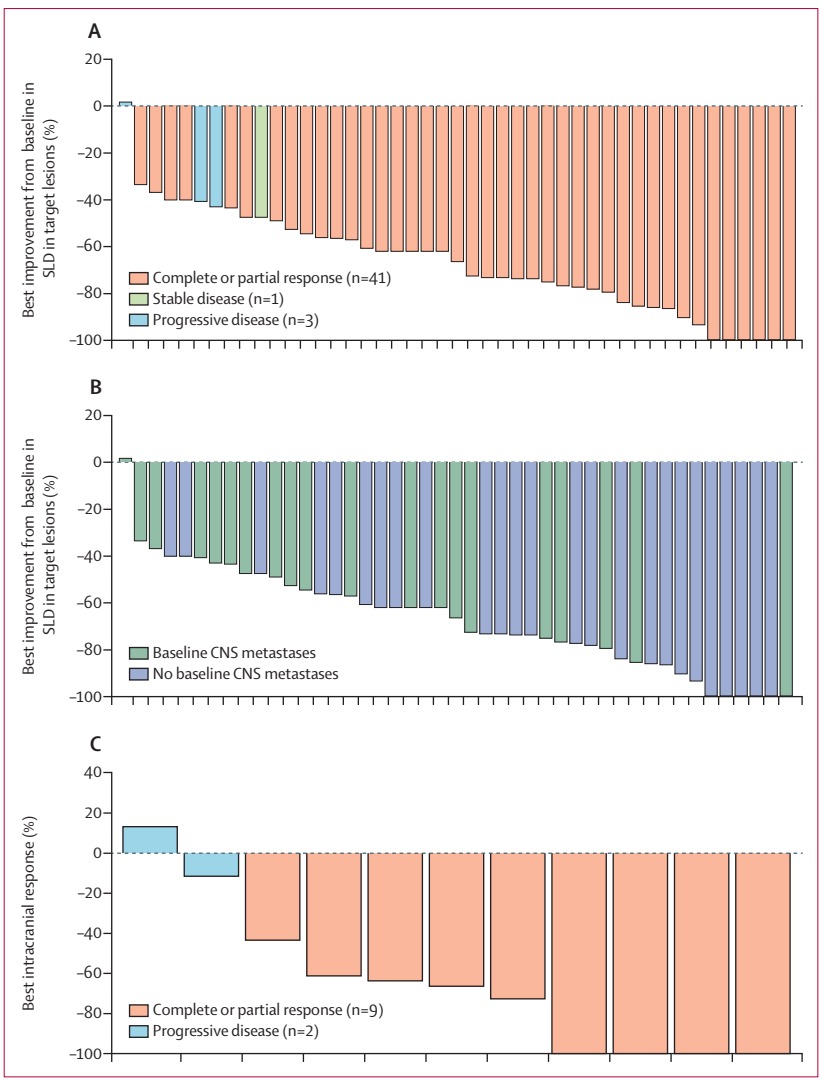

Figure 1: **Responses to entrectinib**

(A) Best responses to entrectinib in the efficacy-evaluable population. (B) Best responses for patients with and without baseline CNS disease. (C) Best intracranial responses in patients with measurable CNS disease at baseline. According to blinded independent central review, 11 patients were responders. The best response to entrectinib in ROS1 inhibitor-naive patients with *ROS1* fusion-positive lung cancers is shown as the maximum percentage improvement in the sum of longest diameters of identified target lesions compared with baseline. At baseline eight patients had lesions of less than 1 cm, which were considered unmeasurable. These eight patients were evaluated as having only non-target lesions and could only have complete responses or progressive disease, therefore results for 45 patients are shown in A and B. All assessments shown were based on blinded independent central review. SLD=sum of longest diameters.

event and median progression-free survival was 26·3 months (15·7–36·6; table 2). In both groups, the presence of CNS metastases at baseline was by investigator assessment. The median overall survival was not estimable (95% CI 15·1 to not estimable; figure 2C). At the time of data cutoff, nine (17%) of 53 patients had died. 45 (85%; 95% CI 74–95) patients were alive at 12 months and 43 (82%; 70–93) were alive at 18 months. The median duration of intracranial response in 20 patients with CNS disease by blinded independent review was 12·9 months (95% CI 5·6 to not estimable), and the median intracranial progression-free survival was 7·7 months (95% CI 3·8–19·3; 13 patients with an event; table 2).

At data cutoff, 18 (34%) of 53 patients had a CNS progression event. Median time to CNS progression was not estimable (95% CI 15·1 to not estimable; figure 2D), with a median follow-up for progression or death of 15·5 months (IQR 8·3 to not estimable).

In the safety-evaluable population of 134 patients with *ROS1* fusion-positive NSCLC, the median duration of treatment was 8·3 months (IQR 4·6–14·6). All 134 patients reported at least one treatment-emergent adverse event of any grade regardless of causality; most were grade 1 or 2 in severity. The full list of all-cause adverse events reported in more than 5% of patients is shown in appendix (pp 18–19). We observed on-target treatment-emergent adverse events, presumed to be secondary to the concurrent inhibition of TRKA, B, and C by entrectinib: three (2%) of 134 patients had a dose reduction for adverse events including confusion, depression, and mental status change; and 20 (15%) had a dose reduction for a broader range of nervous system disorders, the most common being dizziness (eight [6%]) and paraesthesia (three [2%]).

Most (79 [59%]) treatment-related adverse events were grade 1 or 2 (table 3). Grade 3 treatment-related adverse events occurred in 41 (31%) patients and grade 4 in five (4%). The most common grade 3–4 adverse events were weight increase (ten [8%]) and neutropenia (five [4%]). No deaths due to adverse events occurred. 21 serious treatment-related adverse events were reported in 15 (11%) patients. The most frequently reported events were nervous system disorders (in four [3%] patients) and cardiac disorders (three [2%]). Other treatment-related adverse events occurring in less than three patients included pyrexia, hypotension, anorectal disorder, blood creatinine increased, dehydration, and mental status changes. Treatment-related adverse events led to dose reduction in 46 (34%) of 134 patients, and discontinuation in seven (5%). Adverse events leading to discontinuation were cardiac tamponade (one patient [<1%]), cardiogenic shock (one [<1%]), myocarditis (one [<1%]), pericardial effusion(one [<1%]), dyspnoea (one [<1%]), pneumonitis (one [<1%]), pulmonary embolism (one [<1%]), oedema peripheral (one [<1%]), pneumonia (one [<1%]), anorectal disorder (one [<1%]), diarrhoea (one [<1%]), large intestine perforation (one [<1%]), vomiting (one [<1%]), limbic encephalitis (one [<1%]), and myoclonus (one [<1%]). At the time of data cutoff, there were nine (7%) deaths in the *ROS1* fusion-positive NSCLC safety population—all deemed unrelated to treatment (dyspnoea (one [<1%] patient), metastases to meninges (two [<1%]), pneumonia (one [<1%]), sepsis (one [<1%]), cardiogenic shock (one [<1%]), cerebral infarction (one [<1%]), large intestine perforation (one [<1%]), and pulmonary embolism (one [<1%]).

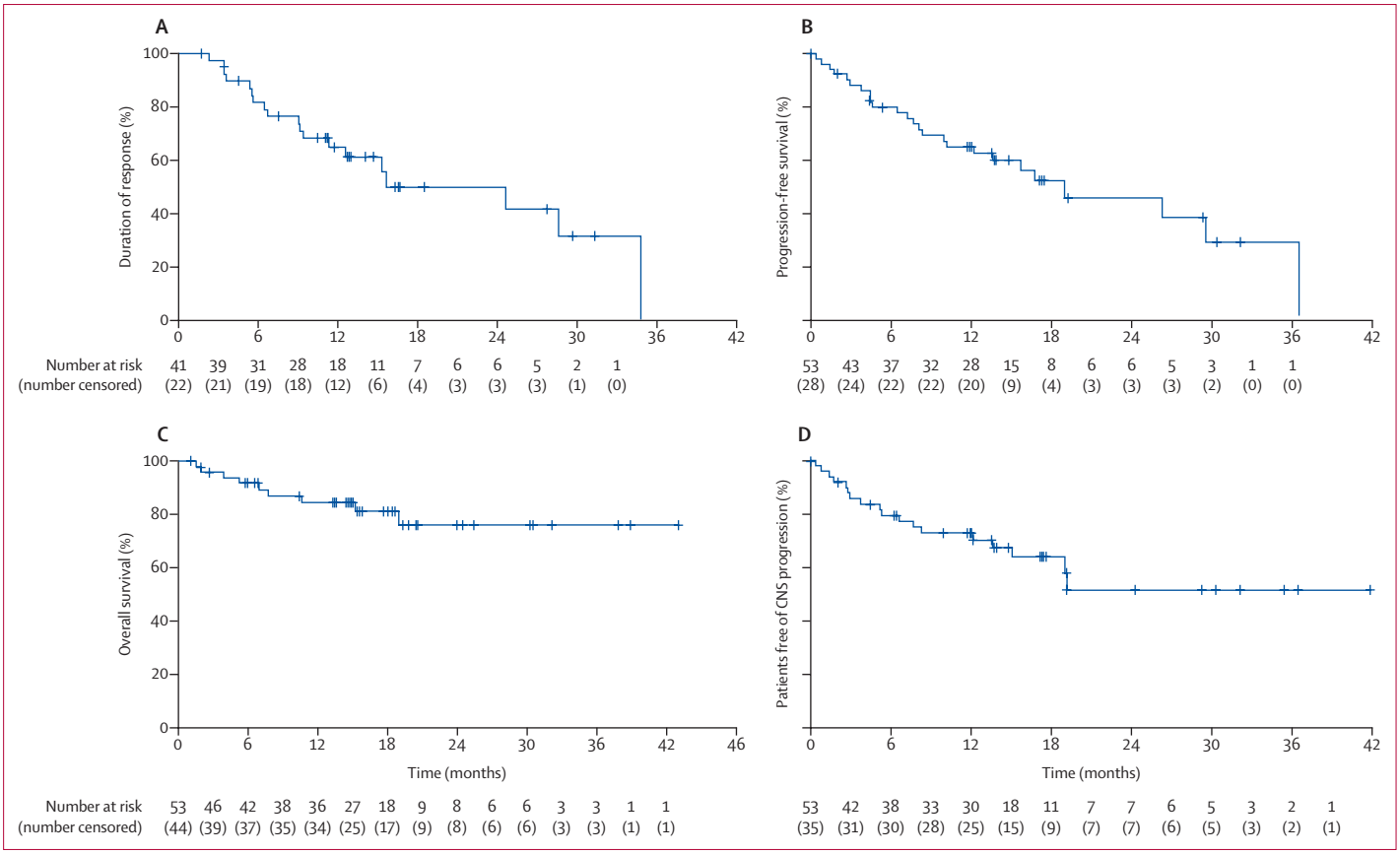

Figure 2: **Time-to-event analyses**
Kaplan–Meier curves of (A) duration of response, (B) progression-free survival, (C) overall survival, and (D) time to CNS progression. All assessments shown were based on blinded independent central review. Tick marks indicate censored patients.

Discussion

In this integrated analysis of a prospective, global, multicentre dataset, we have shown that entrectinib is active both systemically and in the CNS in patients with advanced, ROS1 inhibitor-naive, *ROS1* fusion-positive NSCLC. 41 (77%) of 53 patients had a response to entrectinib. Response to therapy was brisk (response occurred at the first follow-up imaging assessment in most patients) and did not differ by upstream fusion partner (*CD74 vs* non-*CD74*). Disease control was durable, with a median progression-free survival of 19 months and a median duration of response of 24·6 months. These outcomes exceed the activity of first-line chemotherapy and immunotherapy in NSCLC,[18] supporting the current standard of care for *ROS1* fusion-positive NSCLC for which a ROS1 TKI is recommended in the first-line setting. On the basis of these data, entrectinib was granted approval by the US Food and Drug Administration in August, 2019, for the treatment of patients with metastatic *ROS1* fusion-positive NSCLC.

This dataset had a high proportion of patients with baseline intracranial disease (>40%) when compared with previously reported prospective trials of early-generation ROS1 TKIs such as crizotinib and ceritinib (listed as a potential first-line TKI for *ROS1* fusion-positive NSCLC in the National Cancer Center Network Guidelines) in TKI-naive, *ROS1* fusion-positive NSCLC. Notably, the PROFILE 1001 study, a phase 1 trial of crizotinib in the same setting, did not report data on whether enrolled patients had evidence of brain metastases.[19,20] In phase 2 studies on crizotinib done in East Asian patients who were TKI naive (OxOnc study) and on ceritinib in Korean patients who were crizotinib naive, the frequency of patients with brain metastases at baseline were 18% and 25%, respectively.[21,22] Patients with intracranial metastases represent a subpopulation known to have a shorter overall duration of disease control than patients without intracranial disease.[23]

Despite the fact that study populations in this pooled analysis were enriched with patients with poorer prognoses, the proportion of patients having a response and median progression-free survival with entrectinib remained similar to the outcomes previously achieved with crizotinib (responses achieved in 72% patients and median progression-free survival 15·9 months) and ceritinib (responses in 67% patients and median progression-free survival 19·3 months) in patients who

	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	19 (14%)	0	0
Blood creatinine increase	17 (13%)	1 (<1%)	0
Aspartate aminotransferase increase	14 (10%)	2 (2%)	0
Alanine aminotransferase increase	13 (10%)	3 (2%)	0
Hyperaesthesia	12 (9%)	1 (<1%)	0
Arthralgia	12 (9%)	1 (<1%)	0
Anaemia	11 (8%)	1 (<1%)	0
Hyperuricaemia	11 (8%)	0	1 (<1%)
Rash	9 (7%)	2 (1%)	0
Pruritus	9 (7%)	1 (<1%)	0
Peripheral sensory neuropathy	8 (6%)	1 (<1%)	0
Cognitive disorder	8 (6%)	1 (<1%)	0
Muscular weakness	6 (4%)	1 (<1%)	0
Hypotension	6 (4%)	1 (<1%)	0
Neutropenia	5 (4%)	5 (4%)	0
Neutrophil count decrease	5 (4%)	3 (2%)	0
Ataxia	5 (4%)	1 (<1%)	0
Pyrexia	5 (4%)	1 (<1%)	0
Dysarthria	4 (3%)	1 (<1%)	0
Pain of skin	4 (3%)	1 (<1%)	0
Lymphocyte count decrease	2 (1%)	1 (<1%)	0
Blood creatine phosphokinase increase	2 (1%)	1 (<1%)	1 (<1%)
Hypophosphataemia	2 (1%)	1 (<1%)	0
Orthostatic hypotension	2 (1%)	1 (<1%)	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0
Amylase increased	1 (<1%)	1 (<1%)	0
Dehydration	0	2 (1%)	0
Limbic encephalitis	0	0	1 (<1%)
Anorectal disorder	0	0	1 (<1%)
Myocarditis	0	0	1 (<1%)
Myoclonus	0	1 (<1%)	0
Hypoxia	0	1 (<1%)	0
Hypertension	0	1 (<1%)	0
Cardiac failure	0	1 (<1%)	0

The safety population includes all patients with *ROS1* fusion-positive NSCLC across the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). All treatment-related adverse events observed are shown. Data are n (%) of patients. Adverse events were encoded using Medical Dictionary for Regulatory Activities (version 21.0). NSCLC=non-small-cell lung cancer.

Table 3: **Treatment-related adverse events in the safety-evaluable population with *ROS1* fusion-positive NSCLC (n=134)**

were ROS1 TKI naive.[21,22] The median duration of response with entrectinib (24·6 months) surpassed that of crizotinib in the OxOnc study (19·7 months),[21] the largest series of *ROS1* fusion-positive NSCLCs treated with this drug, and of ceritinib in patients who were crizotinib naive in the same setting (21·0 months).[22] It was similar to the median duration of response (24·7 months) reported with crizotinib in the PROFILE 1001 study.[23] Notably, whereas the activity of lorlatinib has also been explored in patients who were ROS1 TKI naive, the clinical outcomes reached with this drug in a smaller series of patients (n=13, of whom 62% achieved a response, with a median duration of response of 19·6 months) were also similar to the outcomes reported with entrectinib.[24] Although the limitations of these cross-trial comparisons should be recognised, to run a randomised controlled trial of entrectinib versus crizotinib in this population would be challenging because of the low frequency of *ROS1* fusions in NSCLC.

These favourable overall outcomes in a population enriched for brain metastases also underscore the CNS activity of entrectinib. Although a good estimate of the intracranial response of crizotinib is not available, the intracranial response of 55% in patients with baseline CNS metastases according to blinded independent central review with entrectinib was higher than that of ceritinib (25%).[22] The median overall progression-free survival with entrectinib in patients with baseline brain metastases was longer than that reported with crizotinib in the OxOnc study (13·6 months *vs* 10·2 months); this was similarly longer than that for crizotinib in patients without brain metastases in the same study (26·3 months *vs* 18·8 months).[21] Our integrated entrectinib dataset arguably features the most well-characterised CNS-specific outcomes of any early-generation ROS1 TKI in *ROS1* fusion-positive NSCLC. Moreover, to our knowledge, this study is the first prospective analysis of time to CNS progression on any ROS1 TKI in *ROS1* fusion-positive NSCLC. The median time to CNS progression with entrectinib was not reached.

Entrectinib was well tolerated. Most of the treatment-related adverse events were low grade. High-grade and serious side-effects were uncommon and managed with dose interruption or dose reduction. The number of treatment discontinuations was low, and no deaths were deemed to be related to entrectinib. Because entrectinib is also a potent TRKA, B, and C inhibitor,[13] the occurrence of adverse events potentially related to TRK inhibition—such as dizziness, weight gain, paraesthesias, and cognitive changes—was not unexpected. These events were consistent with the drug's profile in the larger safety dataset, which includes patients whose cancers did not harbour *ROS1* fusions.[11,25]

Limitations to this study include the single-arm design and sample size. Furthermore, post-progression biopsies were not mandatory and the profile of acquired resistance to entrectinib has yet to be fully characterised. Resistance

to crizotinib and other ROS1 inhibitors that is mediated by *ROS1* kinase domain mutations has been reported in 8–53% of patients,[10,26] suggesting that next-generation ROS1 inhibition might benefit patients who progress on crizotinib or entrectinib.[10,26] ROS1 TKIs that can potentially re-establish disease control after progression on a previous ROS1 inhibitor are under clinical evaluation, including lorlatinib (listed in the National Comprehensive Cancer Network Guidelines for patients who have previously been treated with a ROS1 TKI), repotrectinib, and cabozantinib.[27,28] In patients who previously received a ROS1 TKI, 27% of patients had a response with lorlatinib and 39% had a response with repotrectinib,[24,29] recognising that these responses were largely observed in patients who had progressed on crizotinib. Prospective data for cabozantinib in a substantial number of patients have yet to be reported.

In conclusion, entrectinib is a promising therapy for ROS1 TKI-naive patients with advanced *ROS1* fusion-positive NSCLC. The drug has shown both systemic and intracranial activity. The safety profile of entrectinib is favourable, making it amenable to long-term dosing in this population in which durable disease control was observed. These results underscore the need to routinely test for *ROS1* fusions in the clinic to broaden therapeutic options for patients as is already recommended by several independent groups.[30]

Contributors

AD, EC-M, SS, and RD contributed to study conception and design. AD, SS, RCD, FB, MGK, ATS, FdB, CR, JW, TS, BCC, MRP, C-HC, TJ, KG, CSK, H-TA, S-WK, YO, Y-CL, YKC, CHC, GAO, HM, C-CL, DSWT, HP, and RD contributed to patient recruitment. AD, SS, RCD, FB, MGK, ATS, FdB, CR, M-JA, JW, TS, BCC, MRP, C-HC, TJ, KG, CSK, H-TA, S-WK, YO, Y-CL, YKC, CHC, GAO, HM, C-CL, DSWT, and RD were principal investigators at contributing sites. AD, RCD, MGK, EC-M, Y-CL, C-CL, DSWT, NC, and RD were involved in data collection. AD, CHC, GAO, DSWT, HP, TR, EC-M, BS, NC, AJ, SE, TRW, and RD were involved in data analysis. All authors contributed to data interpretation, drafting of the report, and approval of the final version for submission.

Declaration of interests

AD has received honoraria and consulting fees for advisory boards from Ignyta/Roche/Genentech, Loxo/Bayer/Lily, TP Therapeutics, AstraZeneca, Pfizer, Blueprint, Takeda/Ariad/Millennium, Helsinn, BeiGene, BerGenBio, Hengrui, Exelixis, Tyra, Verastem, MORE Health, Puma, and GlaxoSmithKline; associated research funding paid to institution by Pfizer, Exelixis, Taiho, Teva, and Pharmamar; research funding from Foundation Medicine; and royalties from Wolters Kluwer. SS is an advisory board member for Amgen, Bayer, BMS, CheckMab, Celgene, Daiichi Sankyo, Incyte, Merck, Novartis, Roche, and Seattle Genetics. RCD has received consulting fees from Ignyta, Genentech and 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, Chugai, Foundation Medicine, and Black Diamond; and has stock ownership in Rain Therapeutics. FB has personal financial interests in AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F Hoffmann-La Roche, Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda; and institutional financial interests in AbbVie, ACEA, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eisai, Eli Lilly Oncology, F Hoffmann-La Roche, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, Merck Sharp and Dohme, Pierre Fabre, Pfizer, Sanofi-Aventis, and Takeda. MGK has received honoraria for advisory boards from Roche, Janssen, Octimet, and Achilles Therapeutics; travel grants from AstraZeneca and BerGenBio; and research funding from Roche and BerGenBio. 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 TP Therapeutics; and has received travel support from Pfizer and Genentech/Roche. FdB serves as an advisory board or board of directors member for Tiziana Life Sciences, Bristol-Myers Squibb, Celgene, Novartis, Servier, Pharm Research Associated, Daiichi Sankyo, Ignyta, Amgen, Pfizer, Octimet Oncology, Incyte, Teofarma, Pierre Fabre, Roche, and EMD Serono; and has received honoraria from Bristol-Myers Squibb, Eli Lilly, Roche, Amgen, AstraZeneca, Istituto Gentili, Fondazione Internazionale Menarini, Novartis, Merck Sharp & Dohme, Ignyta, Bayer, Noema, ACCMED, Dephaforum, Nadirex, Roche, Biotechspert, prIME Oncology, and Pfizer. CR is a speaker for Merck Sharp and Dohme, Novartis, and Guardant Health; a scientific advisor for Mylan, Oncompass, and AstraZeneca; and has research collaborations with OncoDNA and Guardant Health. M-JA has received consultant fees and honoraria from AstraZeneca, Lilly, Takeda, Roche, MSD, Merck, Boehringer Ingelheim, Ono Pharmaceutical, Bristol-Myers Squibb, and Alpha Pharmaceutical. JW is an advisory board member for AbbVie, AstraZeneca, Blueprint, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai, Ignyta, Janssen, Lilly, Loxo, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; and has conducted research projects sponsored by Merck Sharp & Dohme, Novartis, Bristol-Myers Squibb, Janssen, and Pfizer. TS has received research grants from Bayer Yakuhin, Daiichi Sankyo, Eisai, LOXO Oncology, Merck Serono, and Chugai Pharmaceuticals; and grants and honoraria from Astellas Pharma, AstraZeneca, Chugai Pharmaceuticals, Eli Lilly Japan, Kissei Pharmaceutical, Merck Sharp & Dohme, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Takeda Pharmaceutical, Bristol-Myers Squibb, Kyowa Hakko Kirin, Nippon Kayaku, Ono, Roche Singapore, Taiho Pharmaceutical, Thermo Fisher Scientific, and Yakult Honsha. BCC has received research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and Merck Sharp & Dohme; has had consulting roles for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD; owns stocks from TheraCane Vac; and has received royalties from Champions Oncology. MRP is an advisory board member for Nektar Therapeutics, and has received research funding from Vyriad and Fate Therapeutics. C-HC has received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, and Takeda. TJ has received advisory or consulting fees for advisory boards from Roche, Ignyta, Pfizer, AstraZeneca, Boehringer Ingelheim, Merck, Takeda, Novartis, and Bristol-Myers Squibb. KG has received research grants and personal fees from Chugai and personal fees from Roche. CSK has received personal fees from Roche, AstraZeneca, Eisai, MSD, and Merck. S-WK has received clinical research funding from AstraZeneca, Lilly, and Boehringer Ingelheim; and attended an advisory meeting for AstraZeneca, Lilly, and Boehringer Ingelheim. YO has received honoraria from AstraZeneca, Chugai, Lilly, Ono, BMS, Boehringer Ingelheim, Bayer, Pfizer, MSD, and Taiho; has had advisory or consultancy roles for AstraZeneca, Chugai, ONO, Bristol-Myers Squibb, Kyorin, Celltrion, and Amgen; and has received grants or research funding from AstraZeneca, Chugai, Lilly, ONO, Bristol-Myers Squibb, Kyorin, Dainippon Sumitomo, Pfizer, Taiho, Novartis, Ignyta, Takeda, Kissei, Daiichi Sankyo, and Janssen. Y-CL has received travel grants from Roche Hong Kong. YKC has received research grants from AbbVie, BMS, Biodesix, Lexent Bio, and Freenome; and honoraria for his participation as an advisory board member from Roche/Genentech, AstraZeneca, Foundation Medicine, Counsyl, NeoGenomics, Guardant Health, Boehringer Ingelheim, Biodesix, ImmuneOncia, Lilly Oncology, Merck, and Takeda. CHC received honoraria for ad-hoc scientific advisory boards from AstraZeneca, Bristol-Myers Squibb, Lilly, Celgene, Ignyta, and CUE Biopharma. GAO has received consulting fees from Pfizer, Genentech, AstraZeneca, Takeda, and Novocure; and research funding (to the institution) from AstraZeneca, Pfizer, Bristol-Myers Squibb, Genentech,

Ignyta, and Merck. HM has received personal fees from AstraZeneca, Chugai, Lilly Japan, Merck Sharp & Dohme, Taiho Pharmaceutical, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Boehringer Ingelheim, Pfizer, and Novartis. C-CL has received personal fees from Roche and Pfizer. DSWT has received grants from Novartis, Bayer, AstraZeneca, Pfizer, and GlaxoSmithKline; personal fees from Novartis, Bayer, Boehringer Ingelheim, Celgene, AstraZeneca, Eli Lilly, and Loxo; and non-financial support from Novartis, Boehringer Ingelheim, Celgene, Merck, Pfizer, Roche, and Takeda. HP has received honoraria and/or travel grants from Roche, Bayer, Amgen, Ipsen, Pfizer, Novartis, Sanofi, Merck, Vifor Pharma, Terumo, and Lilly. TR is employed by Genentech and has equity in Roche. EC-M and AJ were employees of Ignyta during the conduct of the study. BS, NC, SE, and TRW are employed by Genentech and have equity in Roche. RD reports personal fees from Roche during the conduct of the study; non-financial support from Roche and AstraZeneca; and personal fees from Roche, AstraZeneca, Novartis, Pfizer, Foundation Medicine, Bristol-Myers Squibb Merck, and Boehringer-Ingelheim. H-TA declares no competing interests.

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

For the **Roche policy on data sharing** see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

Acknowledgments

The studies were funded by Ignyta/F Hoffmann-La Roche. Third-party medical writing assistance, under the direction of the authors, was provided by Charlotte Kennerley and Caroline Loder of Gardiner-Caldwell Communications, Macclesfield, UK, and was funded by F Hoffmann-La Roche. The authors thank the patients, their families, and the participating study centres. Data and statistical analysis were overseen by Na Cui (Genentech, San Francisco, CA, USA). Salvatore Siena is supported by Fondazione Oncologia Niguarda Onlus. Matthew Krebs acknowledges support by National Institute of Health Research Manchester Biomedical Research Centre and NIHR Manchester Clinical Research Facility and Manchester Experimental Cancer Medicine Centre (Manchester, UK).

References

1 Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. *Nat Commun* 2014; **5:** 4846.

2 Bubendorf L, Buttner R, Al-Dayel F, et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. *Virchows Arch* 2016; **469:** 489–503.

3 Shaw AT, Hsu PP, Awad MM, Engelman JA. Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat Rev Cancer* 2013; **13:** 772–87.

4 Davies KD, Doebele RC. Molecular pathways: ROS1 fusion proteins in cancer. *Clin Cancer Res* 2013; **19:** 4040–45.

5 Farago AF, Taylor MS, Doebele RC, et al. Clinicopathologic features of non-small-cell lung cancer harboring an *NTRK* gene fusion. *JCO Precis Oncol* 2018; published online July 23. DOI:10.1200/PO.18.00037

6 Patil T, Smith DE, Bunn PA, et al. The incidence of brain metastases in stage IV ROS1-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib. *J Thorac Oncol* 2018; **13:** 1717–26.

7 US Food and Drug Administration. Highlights of prescribing information: XALKORI (crizotinib) capsules. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202570s021lbl.pdf (accessed April 29, 2019).

8 Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol* 2018; **29:** 2214–22.

9 Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med* 2018; **379:** 2027–39.

10 Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol* 2017; published online Aug 16. DOI:10.1200/PO.17.00063.

11 Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I Ttials (ALKA-372–001 and STARTRK-1). *Cancer Discov* 2017; **7:** 400–09.

12 Rolfo C, Ruiz R, Giovannetti E, et al. Entrectinib: a potent new TRK, ROS1, and ALK inhibitor. *Expert Opin Investig Drugs* 2015; **24:** 1493–500.

13 Ardini E, Menichincheri M, Banfi P, et al. Entrectinib, a pan-TRK, ROS1, and ALK inhibitor with activity in multiple molecularly defined cancer indications. *Mol Cancer Ther* 2016; **15:** 628–39.

14 Menichincheri M, Ardini E, Magnaghi P, et al. Discovery of entrectinib: a new 3-aminoindazole as a potent anaplastic lymphoma kinase (ALK), c-ros oncogene 1 kinase (ROS1), and pan-tropomyosin receptor kinases (Pan-TRKs) inhibitor. *J Med Chem* 2016; **59:** 3392–408.

15 US Food and Drug Administration. Ignyta entrectinib briefing document. Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee. 2016. https://www.fda.gov/media/99207/download (accessed April 29, 2019).

16 Cook PJ, Thomas R, Kannan R, et al. Somatic chromosomal engineering identifies BCAN-NTRK1 as a potent glioma driver and therapeutic target. *Nat Commun* 2017; **8:** 15987.

17 Nishiyama A, Yamada T, Kita K, et al. Foretinib overcomes entrectinib resistance associated with the *NTRK1* G667C mutation in *NTRK1* fusion-positive tumor cells in a brain metastasis model. *Clin Cancer Res* 2018; **24:** 2357–69.

18 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.

19 Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in *ROS1*-rearranged non-small-cell lung cancer. *N Engl J Med* 2014; **371:** 1963–71.

20 Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol* 2019; **30:** 1121–26.

21 Wu YL, Yang JC, Kim DW, et al. Phase II study of crizotinib in east Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J Clin Oncol* 2018; **36:** 1405–11.

22 Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol* 2017; **35:** 2613–18.

23 Rodrigus P, de Brouwer P, Raaymakers E. Brain metastases and non-small cell lung cancer. Prognostic factors and correlation with survival after irradiation. *Lung Cancer* 2001; **32:** 129–36.

24 Ou S, Shaw A, Riely G, et al. OA02·03 clinical activity of lorlatinib in patients with ROS1+ advanced non-small cell lung cancer: phase 2 study cohort EXP-6. *J Thorac Oncol* 2018; **13:** S322–23.

25 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. *Lancet Oncol* 2019; published online Dec 11. https://doi.org/10.1016/S1470-2045(19)30691-6.

26 McCoach CE, Le AT, Gowan K, et al. Resistance mechanisms to targeted therapies in *ROS1*+ and *ALK*+ non-small cell lung cancer. *Clin Cancer Res* 2018; **24:** 3334–47.

27 Katayama R, Kobayashi Y, Friboulet L, et al. Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. *Clin Cancer Res* 2015; **21:** 166–74.

28 Drilon A, Ou SI, Cho BC, et al. Repotrectinib (TPX-0005) is a next-generation ROS1/TRK/ALK inhibitor that potently inhibits ROS1/TRK/ALK solvent- front mutations. *Cancer Discov* 2018; **8:** 1227–36.

29 Cho BC, Drilon AE, Doebele RC, et al. Safety and preliminary clinical activity of repotrectinib in patients with advanced ROS1 fusion-positive non-small cell lung cancer (TRIDENT-1 study). *J Clin Oncol* 2019; **37:** 9011.

30 Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Mol Diagn* 2018; **20:** 129–59.