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

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Summary

Background Entrectinib is a ROS1 inhibitor designed to effectively penetrate and remain in the central nervous system (CNS). We conducted an integrated analysis of three phase 1/2 entrectinib studies (ALKA-372-001, STARTRK-1, and STARTRK-2) in patients with locally advanced/metastatic *ROS1* fusion-positive non-small-cell lung cancer (NSCLC).

Methods The efficacy-evaluable population for the efficacy analysis included adult patients (≥18 years) with locally advanced/metastatic *ROS1* fusion-positive NSCLC who received entrectinib orally at ≥600 mg/day with ≥12 months of follow-up. All patients had an ECOG performance status ≤2; prior therapy (except for ROS1 inhibitors) was allowed. The safety-evaluable population for the safety analysis included all patients with *ROS1* fusion-positive NSCLC who received at least one dose of entrectinib. The primary endpoints - the proportion of patients achieving an objective response and duration of response (DoR) - were evaluated by blinded independent central review (BICR; Response Evaluation Criteria in Solid Tumors v1.1). ~~Secondary endpoints included progression-free survival, overall survival, intracranial response, intracranial DoR, and safety.~~ These ongoing studies are registered at ClinicalTrials.gov (NCT02097810 and NCT02568267) and EudraCT (2012-000148-88).

Findings Patients were first enrolled as follows: ALKA-372-001 October 26, 2012 to November XX, 2015; STARTRK-1 August 07, 2014 to February XX, 2016; STARTRK-2 November 19, 2015 (enrolment is ongoing). At the data cutoff date for this analysis, in the efficacy-evaluable population (n=53), the proportion of patients achieving a response was 77% (n=41; 95% CI 64–88). Median DoR was 24·6 months (95% CI 11·4–34·8). In the safety-evaluable population (n=134), 59% (n=79) of patients had grade 1/2 treatment-related adverse events (TRAEs). Dysgeusia (n=57, 43%), dizziness (n=44, 33%), and constipation (n=44, 33%) were most common. The most common grade 3/4 ~~treatment-related adverse events~~TRAEs were weight increase (n=10, 8%) and neutropenia (n=5, 4%). Serious TRAEs

were reported in 15 patients (11%); the most frequent were nervous system disorders (n=4, 3%) and cardiac disorders (n=3, 2%). There were no treatment-related deaths. Entrectinib discontinuation due to ~~treatment-related adverse events~~TRAEs was low (5%).

Interpretation Entrectinib is active in patients with *ROS1* fusion-positive NSCLC, including those with CNS disease. Entrectinib is well tolerated with a manageable safety profile~~.~~ making it amenable to long-term dosing in this population where durable disease control was observed. These data underscore the need to routinely test for *ROS1* fusions to broaden therapeutic options for patients with *ROS1* fusion-positive NSCLC.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and major congress abstracts for reports relating to the treatment of *ROS1* fusion-positive 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 is effective in patients with *ROS1* fusion-positive NSCLC. Unfortunately, about half of patients with *ROS1* fusion-positive NSCLC experience disease progression solely in the central nervous system (CNS), likely due to limited drug penetration. 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 achieving a response with entrectinib was high and disease control was durable (overall and in the CNS) in patients with ROS1 inhibitor-naïve, *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 TKI-naïve *ROS1* fusion-positive NSCLC. The intracranial activity of entrectinib is of particular importance, given the frequency of CNS involvement in *ROS1* fusion-positive NSCLC and the limited ability of crizotinib to penetrate the CNS.

Introduction

Recurrent gene fusions are oncogenic drivers of various cancers.[1] *ROS1* (ROS proto-oncogene 1, receptor tyrosine kinase) fusions include the kinase domain-containing 3' region of *ROS1* fused to a variety of 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% to 2% of cases.[4] Typically, *ROS1* fusions do not overlap with other canonical drivers, including *NTRK* (neurotrophic receptor tyrosine kinase 1) fusions, in NSCLCs.[5]

Targeted therapy for patients with *ROS1* fusion-positive NSCLC requires effective coverage of the central nervous system (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; many others will subsequently develop intracranial metastases.[6] The 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 occurs in almost half of patients with *ROS1* fusion-positive NSCLC who are treated with crizotinib.[6,10] This 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/C and anaplastic lymphoma kinase [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 0·43 to 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 to vehicle in orthotopic CNS xenografts of models that harbour established

fusion targets of the drug such as NCI-H228 (NSCLC),[13] BNN2/4 (glioblastoma),[16] and KM12SM (colorectal cancer).[17] In the NCI-H228 model, entrectinib resulted in increased survival compared to crizotinib. 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-naïve *ROS1* fusion-positive NSCLC was explored in three prospective phase 1/2 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 (≥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). Patients were enrolled in ALKA-372-001 between Oct 2012 and Nov 2015, STARTRK-1 between July 2014 and Feb 2016, and STARTRK-2 since Nov 2015 (recruitment ongoing). ALKA-372-001 was conducted at two sites in Italy. STARTRK-1 was conducted at ten sites in the United States, Spain, and South Korea. STARTRK-2 is ongoing at over 150 sites in 15 countries. Patients included in this pre-specified integrated efficacy analysis met the following criteria: (1) locally advanced or metastatic NSCLC harbouring a *ROS1* fusion; (2) ROS1 TKI-naïve; (3) measurable disease (investigator assessed, Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1); and (4) received at least one dose of entrectinib.[11] The safety analysis set included NSCLC patients who were not ROS1 TKI-naïve. Patients were enrolled using either local molecular profiling or central RNA-based next-generation sequencing (NGS; Trailblaze Pharos™). Local testing could include fluorescence in situ hybridisation (FISH) tests, quantitative polymerase chain reaction (qPCR), or DNA-/RNA-based NGS (see appendix p6). In ALKA and STARTRK-1, patients were enrolled based on 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 NGS testing following

enrolment. Patients had an Eastern Cooperative Oncology Group Performance Status of ≤2, a life expectancy of ≥3 months (ALKA-372-001 and STARTRK-1) or ≥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, prior cancer therapy was allowed (excluding prior ROS1 inhibitors); in STARTRK-1, prior cancer therapy was allowed, including crizotinib, ceritinib, and investigational drugs; and in STARTRK-2, prior anticancer therapy was allowed (excluding approved or investigational ROS1 inhibitors). All patients, regardless of line of therapy, had measurable disease as assessed locally using RECIST v1.1. 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 tyrosine kinase inhibitor-induced pneumonitis; peripheral neuropathy grade ≥2. Full g~~G~~eneral and study-specific eligibility criteria~~, including comorbidities that were not permitted~~ are provided in the online appendix, pp 11–12. All studies were conducted 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 and/or ethics committees.

Procedures

~~Patients were enrolled using either local molecular profiling or central RNA-based next-generation sequencing (NGS; Trailblaze Pharos™). Local testing could include fluorescence in situ hybridisation (FISH) tests, quantitative polymerase chain reaction (qPCR), or DNA-/RNA-based NGS (see appendix p6). In ALKA and STARTRK-1, patients were enrolled based on 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 NGS testing following enrolment.~~

Patients continued study treatment (entrectinib orally at ≥600 mg/day) until documented radiographic progression, unacceptable toxicity, or withdrawal of consent. Imaging assessments of

all known disease sites (including the brain, as applicable) were conducted via computed tomography (CT) or magnetic resonance imaging (MRI) scanning at screening at the end of cycle 1 (4 weeks), and every two cycles (8 weeks) thereafter. Serial CNS imaging was only required 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 (BICR) using 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 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 (Cycle 1, day 1; Cycle 1, day 15; Cycle 2, day 1; Cycle 2, day 15; Cycle 3, day 1; Cycle 3, day 15; day 1 of Cycle 4 and each subsequent cycle thereafter). If needed, dose reductions could occur in decrements of 200mg; no more than 2 dose reductions were allowed.

Outcomes

For this integrated analysis, the co-primary endpoints were the proportion of patients achieving an objective response to measure direct anti-tumour activity (defined as the proportion of responders with a confirmed complete response [CR] or partial response [PR]) and duration of response (DoR) to measure durability of anti-tumour activity (measured from the date of first objective response [either CR or PR] to first documentation of radiographic disease progression or the date of death due to any cause, whichever was earlier); both were measured by BICR. ~~Objective response was defined as the proportion of responders with a confirmed complete response (CR) or partial response (PR)~~. Key secondary endpoints were progression-free survival (PFS; defined as time from first dose of

entrectinib to first documentation of radiographic disease progression or death due to any cause ~~defined as the number of patients with documented progression~~ at the time of data cutoff) and overall survival (OS; defined as the time from the first dose of entrectinib to the date of death due to any cause ~~defined as the number of patients who had died~~ at the time of data cutoff) per BICR, and safety. Additional pre-specified endpoints evaluated in patients with baseline CNS disease per BICR were intracranial response, intracranial DoR, and intracranial PFS by BICR.

Statistical analysis

For response data, the number, percentage, and corresponding two-sided 95% Clopper–Pearson exact CI were summarised. The sample size was calculated based on the objective response endpoint, with assumptions based on the clinically meaningful response threshold and target response. Assuming the true objective response by BICR was 70%, a sample size of ≥50 patients would yield a 95% two-sided 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 rate excluding 50% or higher is considered clinically meaningful. There was no formal hypothesis testing and significance tests were not performed; there was no alpha spending for objective response and DoR endpoints. The Kaplan–Meier method was used to estimate the time-to-event endpoints (DoR, PFS, and OS), 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 naïve, had measurable disease at baseline, and ≥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 NSCLCs from all three studies who had received at least one dose of entrectinib, regardless of dose. Entrectinib was administered on intermittent or continuous dose schedules. Safety data were summarised descriptively. The

statistical evaluation was performed with the software package SAS version 9.3 or higher (SAS Institute Inc., Cary, NC, USA). 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, NCT02097810; STARTRK-2, NCT02568267.

Role of the funding source

The studies were funded by Ignyta Inc./F. Hoffmann-La Roche Ltd. and 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 access to the raw data. All authors contributed to the writing and approval of this report, and the lead and corresponding authors had full access to the data and the final responsibility for the decision to submit for publication. Professional medical writing assistance was funded by the sponsor.

Results

Fifty-three ROS1 inhibitor-naïve patients with *ROS1* fusion-positive NSCLC were included in the integrated efficacy analysis population (appendix p7). The first patients were enrolled in ALKA-372-001 on October 26, 2012 to November XX, 2015; in STARTRK-1 on August 07, 2014 to February XX, 2016; and in STARTRK-2 on November 19, 2015 (enrolment is ongoing). All three studies were ongoing on May 31, 2018, which was the data cutoff date for this integrated analysis. Table 1 summarises the clinical characteristics of all patients. The median age was 53 years (range, 27–73 years). The majority were female (n=34, 64%), never smokers (n=31, 59%), with lung adenocarcinoma (n=52, 76%). The majority of patients were treated with one or more prior chemotherapy and/or immunotherapy regimens (n=36, 68%).

The upstream *ROS1* fusion partner was known for 41 patients (77%). The most frequently detected fusions were *CD74–ROS1* (n=21, 40%), *SLC34A2–ROS1* (n=7, 13%), *SDC4–ROS1* (n=6, 11%), and *EZR–ROS1* (n=5, 9%). The remaining 12 (23%) patients were enrolled by FISH, with no (n=11,

21%) or insufficient (n=1, 2%) tissue for central NGS testing for fusion partner determination. Twenty patients (38%) had baseline CNS metastases as assessed by BICR; of the 12 patients with measurable CNS disease (the eight patients without measurable CNS disease had lesions <1 cm in size), six had no prior brain radiotherapy and one received radiotherapy >2 months before starting entrectinib. The median duration of follow-up was 15·5 months (95% CI 14·8–19·0; IQR 6·84 months).

The proportion of patients achieving a response was 77% (n=41; 95% CI 64–88; data cutoff May 31, 2018). Among the 53 patients, three (6%) had a CR, 38 (72%) had a PR, and one (2%) had stable disease as their best objective response to entrectinib (table 2). Disease regression in target lesions was achieved in most patients treated with entrectinib (figure 1A), including those with baseline CNS metastases (figure 1B). Response to entrectinib did not differ by upstream gene partner type (Appendix, p8). The proportion of patients achieving a response was 86% (18/21 patients) for *CD74–ROS1* versus 65% (13/20 patients) for non-*CD74–ROS1* fusions and 83% (10/12 patients) for unknown fusions. Responses occurred early; most responses occurred at the first follow-up imaging assessment (Appendix, p9). Time on therapy did not differ by upstream gene partner (Appendix, p10). The median treatment duration was 14·6 months for *CD74–ROS1* versus 14·2 months for non-*CD74–ROS1,* compared with 21·5 months for unknown fusions.

Of the 20 patients with baseline CNS metastases by BICR, the proportion of patients with an intracranial response was 55% (n=11; 95% CI 32–77) (table 2). Disease regression was achieved in the majority of patients with measurable intracranial disease (figure 1C). In patients with measurable CNS disease at baseline who had no previous radiotherapy or had received radiotherapy >2 months before starting entrectinib, the proportion of patients with an intracranial response was 71% (n=5 out of 7). In patients who had received radiotherapy within 2 months prior to entrectinib treatment, the proportion of patients with an intracranial response was 80% (n=4 out of 5).

The median DoR by BICR was 24·6 months (95% CI 11·40–34·8; figure 2A). The median PFS by BICR was 19·0 months (95% CI 12·2–36·6; n=25 patients with an event; figure 2B). The median overall PFS for patients with baseline CNS metastases (n=23) was 13·6 months (95% CI 4·5–NE; n=11

patients with an event) compared with 26·3 months (95% CI 15·7–36·6; n=14 patients with an event) in patients without baseline brain metastases (table 2). In both groups, the presence of CNS metastases at baseline was by investigator assessment. The median OS was not evaluable (NE; figure 2C). At the time of data cutoff, nine (17%) patients had died. The percentage who were alive at 12 and 18 months was 85% (n=45; 95% CI 74–95) and 82% (n=43; 95% CI 70–93), respectively. The median intracranial DoR was 12·9 months (95% CI 5·6–NE), and the median intracranial PFS was 7·7 months (range, 3·8–19·3; n=13 patients with an event; table 2).

The median time to CNS progression (time to first documentation of radiographic CNS disease progression or death from any cause) was NE (95% CI 15·1–NE; n=18 patients with an event; figure 2D), with a median follow-up for progression or death of 15·5 months.

In the safety-evaluable population of 134 patients with *ROS1* fusion-positive NSCLCs, the median duration of treatment was 8·3 months (range, 0·1–42·1). 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 >10% of patients can be found in the online appendix, p13. We observed on-target treatment-emergent adverse events, presumed to be secondary to the concurrent inhibition of TRKA/B/C by entrectinib: 2% (n=3) had a dose reduction for adverse events including confusion, depression, and mental status change, and 15% (n=20) had a dose reduction for a broader range of nervous system disorders, the most common being dizziness (n=8, 6%) and paraesthesia (n=3, 2%).

The most common treatment-related adverse events of any grade (table 3) were dysgeusia (n=57, 43%), dizziness (n=44, 33%), constipation (n=44, 33%), diarrhoea (n=38, 28%), weight increase (n=36, 27%), fatigue (n=32, 24%), and paraesthesia (n=23, 17%). The majority (n=79, 59%) of treatment-related adverse events were grade 1 or 2. Grade 3 and 4 treatment-related adverse events occurred in 31% (n=41) and 4% (n=5) of patients, respectively. No grade 5 treatment-related adverse events occurred. There were serious treatment-related adverse events reported in 15 patients (11%). The most frequent were nervous system disorders (n=4, 3%) and cardiac disorders

(n=3, 2%). Treatment-related adverse events led to dose reduction in 34% (n=46) of patients, and discontinuation in 5% (n=7) of patients. At the time of data cutoff, there were nine (7%) deaths in the *ROS1* fusion-positive NSCLC safety population—all deemed unrelated to treatment.

Discussion

In this integrated analysis of a prospective, global, multicentre dataset, we demonstrate that entrectinib is active both systemically and in the CNS in patients with advanced, ROS1 inhibitor-naïve, *ROS1* fusion-positive NSCLC. The proportion of patients achieving a response was 77%. Response to therapy was brisk (response occurred at the first follow-up imaging assessment in most patients) and did not differ by upstream partner (*CD74 vs* non-*CD74*). Disease control was durable, with a median PFS of 19·0 months and a median DoR of 24·6 months. These outcomes clearly exceed the activity of first-line chemotherapy and/or 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. Based on these data, entrectinib was granted approval by the United States Food and Drug Administration in August of 2019 for the treatment of patients with metastatic *ROS1* fusion-positive NSCLC.

This dataset had the highest 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-naïve *ROS1* fusion-positive NSCLCs. Notably, the PROFILE 1001 study did not report data on whether enrolled patients had evidence of brain metastases.[19,20] In phase 2 studies of crizotinib performed in East Asian TKI-naïve patients (OxOnc study) and of ceritinib in Korean patients, the frequency of patients with brain metastases at baseline were 18% and 25%, respectively.[21,22] Patients with intracranial metastases represent a subpopulation historically known to suffer from a shorter overall duration of disease control relative to patients without intracranial disease.[23]

Despite the pronounced enrichment for a population of patients with poorer outcomes, the response and median PFS with entrectinib remained comparable to the outcomes achieved with crizotinib (response 71·7%, median PFS of 15·9 months) and ceritinib (response 67%, median PFS of 19·3 months) in ROS1 TKI-naïve patients.[21,22] The median DoR of entrectinib (24·6 months) was highly durable, surpassing 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 crizotinib-naïve patients in the same setting (21·0 months).[22] It was comparable to the median DoR (24·7 months) from the PROFILE 1001 study.[23] Notably, whereas the activity of lorlatinib has also been explored in ROS1 TKI-naïve patients, the clinical outcomes achieved with this agent in a smaller series (n=13, response 62%, median DoR of 19·6 months) were also comparable to the outcomes achieved with entrectinib.[24] While the limitations of these cross-trial comparisons should be recognised, it should also be acknowledged that running a randomised, controlled trial of entrectinib versus crizotinib in this population would be challenging to perform given the low frequency of this genomic alteration.

These favourable overall outcomes in a population enriched for brain metastases also underscore the CNS activity of entrectinib. While a good estimate of the intracranial response of crizotinib is not available, the intracranial response of 55% with entrectinib was higher than that of ceritinib (25%).[22]In addition, the median overall PFS of entrectinib in patients with baseline brain metastases was longer than that of crizotinib in the OxOnc study (13·6 *vs* 10·2 months); this was similarly longer than crizotinib in patients without brain metastases in the same study (26·3 *vs* 18·8 months).[21] It is important to point out that this integrated entrectinib dataset arguably features the most well-characterised CNS-specific outcomes of any early-generation ROS1 TKI in *ROS1* fusion-positive NSCLCs. The median intracranial DoR was 12·9 months and the median intracranial PFS was 7·7 months. Moreover, this includes, to our knowledge, the first prospective analysis of time to CNS progression on any ROS1 TKI in *ROS1* fusion-positive NSCLCs. 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. Higher 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 secondary to entrectinib. As entrectinib is also a potent TRKA/B/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 were consistent with the drug's profile in the larger safety dataset, which includes patients whose cancers did not harbour *ROS1* fusions (appendix p13).[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% to 53% of patients, suggesting that next-generation ROS1 inhibition may benefit patients who progress on crizotinib or entrectinib.[10,26] ROS1 TKIs that can potentially re-establish disease control after progression on a prior ROS1 inhibitor are currently under clinical evaluation, including lorlatinib (listed in the NCCN Guidelines for ROS1 TKI pre-treated patients), repotrectinib, and cabozantinib.[27,28] In patients who previously received a ROS1 TKI, the proportion of patients achieving a response for lorlatinib and repotrectinib was 27% and 39%, respectively,[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 has yet to be reported.

In conclusion, entrectinib is a promising therapy for ROS1 TKI-naïve patients with advanced *ROS1* fusion-positive NSCLCs. The drug has demonstrable intracranial activity. The safety profile of entrectinib is favourable, making it amenable to long-term dosing in this population where 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]

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Ignyta, Inc. (a wholly owned subsidiary of F. Hoffmann-La Roche Ltd)

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Contributors

AD, ECM and RD contributed to study conception and design. AD, SS, RCD, FB, MGK, ATS, FdB, CR, JW, TS, BCC, MRP, CHC, TJ, KG, CSK, HTA, SWK, YO, LYC, YK, CHCho, GAO, HM, CCL, DSWT, HP and RD contributed to patient recruitment. AD, SS, RCD, FB, MGK, ATS, FdB, CR, MJA, JW, TS, BCC, MRP, CHC, TJ, KG, CSK, HTA, SWK, YO, LYC, YKC, CHC, GAO, HM, CCL, DSWT, RD were principal investigators at contributing sites. AD, RCD, MGK, ECM, LYC, CCL, DSWT, NC and RD were involved in data collection. AD, CHC, GAO, DSWT, HP, TR, ECM, 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/consulting fees for advisory boards for 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;

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TABLES

***Table 1*: Baseline characteristics**

Summary of the clinicopathologic features of all 53 ROS1 inhibitor-naïve *ROS1* fusion-positive patients included in the integrated efficacy analysis population. Baseline CNS disease featured in the table was as per investigator assessment, for which 23 patients with CNS disease were identified. By blinded independent central review, the number of patients with CNS disease was 20. *Percentage calculated out of 46 patients with available histological data. †Carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1 patient). ‡Percentage calculated out of the 23 patients with CNS disease at baseline. §Patients enrolled via a *ROS1* FISH assay, which does not provide information on fusion partner. CNS=central nervous system. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in situ hybridisation. NSCLC=non-small-cell lung cancer.

Characteristic	**Patients, n (N=53)**
Median age, years (range)	53 (27–73)
Sex, n	
Female	34 (64%)
Male	19 (36%)
Ethnicity, n	
White	31 (59%)
Asian	19 (36%)
Black/African American	3 (6%)
ECOG performance status, n	
0	20 (38%)
1	27 (51%)
2	6 (11%)
Smoking status, n	
Never smoker	31 (59%)
Former/current smoker	22 (42%)

Histology, n*	
Adenocarcinoma	52 (98%)
Other†	1 (2%)
CNS disease present at baseline, n	23 (43%)
Measurable	5 (9%)
Non-measurable	18 (34%)
Prior CNS disease treatment, n (%)‡	8 (35%)
Stereotactic radiotherapy	3 (13%)
Whole brain ± stereotactic radiotherapy	5 (22%)
No prior CNS disease treatment, n‡	15 (65%)
Number of prior systemic therapies, n	
0	17 (32%)
1	23 (43%)
2 or more	13 (25%)
Gene fusion, n	
CD74–ROS1	21 (40%)
SLC34A2–ROS1	7 (13%)
SDC4–ROS1	6 (11%)
EZR–ROS1	5 (9%)
TPM3–ROS1	2 (4%)
Unknown§	12 (23%)

Table 2: **Efficacy**

Summary of clinical activity of entrectinib in ROS1 inhibitor-naïve patients with *ROS1* fusion-positive lung cancers. Outcomes by the presence or absence of baseline brain metastases are featured. Shown are the proportion of patients achieving a response, duration of response, and progression-free survival (PFS; Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 by blinded independent central review [BICR]) in the integrated efficacy population (*ROS1* fusion-positive, ROS1 inhibitor-naïve non-small-cell lung cancer) and intracranial response, duration of response, and PFS in patients with central nervous system (CNS) disease at baseline (RECIST version 1.1 by BICR). *CNS disease status determined by investigator. †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. ‡CNS disease status determined by BICR. §These percentages do not equal 77% due to rounding. NE=not evaluable.

Efficacy parameter	**Integrated efficacy-evaluable**	**Baseline CNS disease***	**No baseline CNS disease***
Systemic efficacy	(n=53)	(n=23)	(n=30)
Objective response, % (95% CI)	77 (64–88)	74 (52–90)	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-CR/non-PD, 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 efficacy		(n=20)‡	
Overall response, % (95% CI)		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-CR/non-PD, n (%)		4 (20)	
Missing or unevaluable‡, n (%)		2 (10)	
Duration of response			
Median, months (95% CI)		12·9 (5·6–NE)	
Progression-free survival			
Median, months (95% CI)		7·7 (3·8–19·3)	

Table 3: **Treatment-related adverse events**

Summary of treatment-related adverse events observed in >10% of 134 patients with *ROS1* fusion-positive lung cancers treated with entrectinib. Data are n (%) of patients. Adverse events were encoded using Medical Dictionary for Regulatory Activities (version 21.0). *All patients who received at least one dose of entrectinib regardless of tumour type and fusion. NSCLC=non-small-cell lung cancer. TRAE=treatment-related adverse event.

~~Safety outcomes, n~~				
~~TRAEs in >10% of patients~~Treatment-related adverse events, n	Grade 1-2	Grade 3	Grade 4	Grade 5
Dysgeusia	56 (42%)	1 (<1%)	0	0
Dizziness	43 (32%)	1 (<1%)	0	0
Constipation	44 (33%)	0	0	0
Diarrhoea	35 (26%)	3 (2%)	0	0
Weight increase	26 (19%)	10 (8%)	0	0
Fatigue	32 (24%)	0	0	0
Paraesthesia	23 (17%)	0	0	0
Nausea	23 (17%)	0	0	0
Peripheral oedema	22 (16%)	0	0	0
Myalgia	19 (14%)	2 (2%)	0	0
Vomiting	19 (14%)	0	0	0
Blood creatinine increased	17 (13%)	1 (1%)	0	0
Aspartate aminotransferase increased	14 (10%)	2 (2%)	0	0
Alanine aminotransferase increased	13 (10%)	3 (2%)	0	0
~~Grade 3, 4 TRAEs in any patient, n~~				
Hyperaesthesia	12 (9%)	1 (<1%)	0	0
Arthralgia	12 (9%)	1 (<1%)	0	0
Anaemia	11 (8%)	1 (<1%)	0	0
Hyperuricaemia	11 (8%)	0	1 (<1%)	0

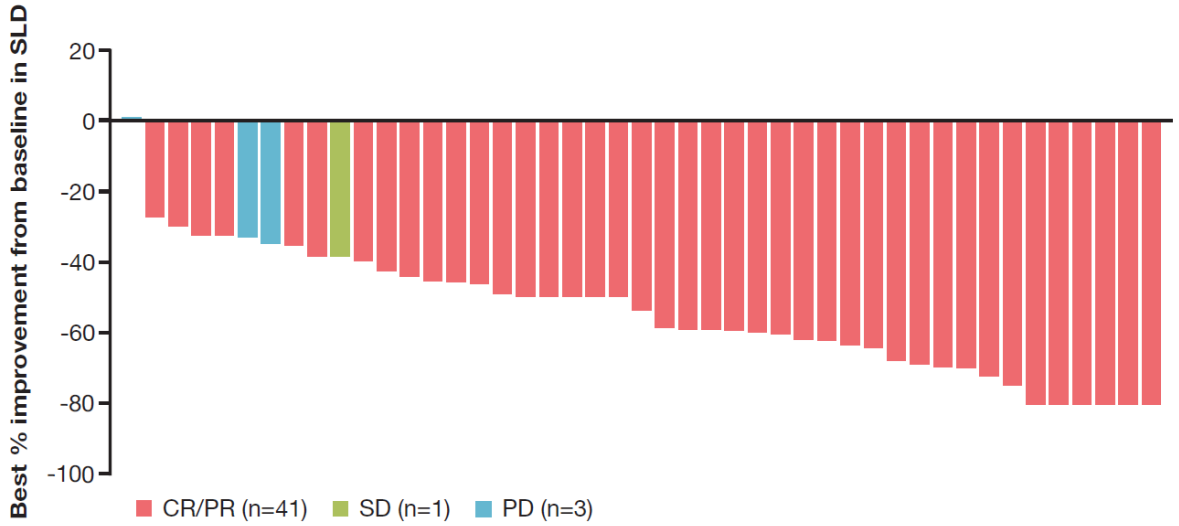
Rash	9 (7%)	2 (1%)	0	0
Pruritus	9 (7%)	1 (<1%)	0	0
Peripheral sensory neuropathy	8 (6%)	1 (<1%)	0	0
Cognitive disorder	8 (6%)	1 (<1%)	0	0
Muscular weakness	6 (4%)	1 (<1%)	0	0
Hypotension	6 (4%)	1 (<1%)	0	0
Neutropenia	5 (4%)	5 (4%)	0	0
Neutrophil count decreased	5 (4%)	3 (2%)	0	0
Ataxia	5 (4%)	1 (<1%)	0	0
Pyrexia	5 (4%)	1 (<1%)	0	0
Dysarthria	4 (3%)	1 (<1%)	0	0
Pain of skin	4 (3%)	1 (<1%)	0	0
Lymphocyte count decreased	2 (1%)	1 (<1%)	0	0
Blood creatine phosphokinase increased	2 (1%)	1 (<1%)	1 (<1%)	0
Hypophosphataemia	2 (1%)	1 (<1%)	0	0
Orthostatic hypotension	2 (1%)	1 (<1%)	0	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0	0
Amylase increased	1 (<1%)	1 (<1%)	0	0
Dehydration	0	2 (1%)	0	0
Limbic encephalitis	0	0	1 (<1%)	0
Anorectal disorder	0	0	1 (<1%)	0
Myocarditis	0	0	1 (<1%)	0
Myoclonus	0	1 (<1%)	0	0
Hypoxia	0	1 (<1%)	0	0
Hypertension	0	1 (<1%)	0	0

Cardiac failure	0	1 (<1%)	0	0

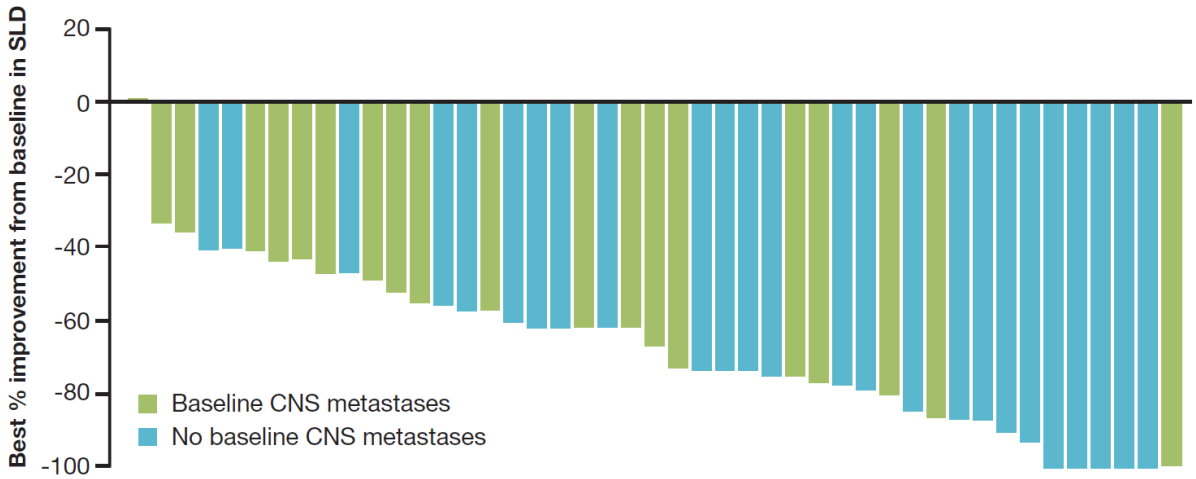
FIGURES

Figure 1: Response and time on treatment

The best response to entrectinib in ROS1 inhibitor-naïve 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 to baseline. Patients without measureable disease were excluded, as such, 45 patients are shown in each plot. All assessments shown were based on BICR. Waterfall plots are colour coded by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 response (A) and the presence or absence of baseline CNS disease (B). A waterfall plot of best intracranial response is shown (C). Patients with non-measurable intracranial disease were excluded from the plot, as such 11 patients are shown. CNS=central nervous system. BICR=blinded independent central review. NSCLC=non-small-cell lung cancer. SLD=sum of longest diameter.


Best % improvement from baseline in SLD
20
0
-20
-40
-60
-80
-100
CR/PR (n=41)
SD (n=1)
PD (n=3)

B


Best % improvement from baseline in SLD
20
0
-20
-40
-60
-80
-100
Baseline CNS metastases
No baseline CNS metastases

C

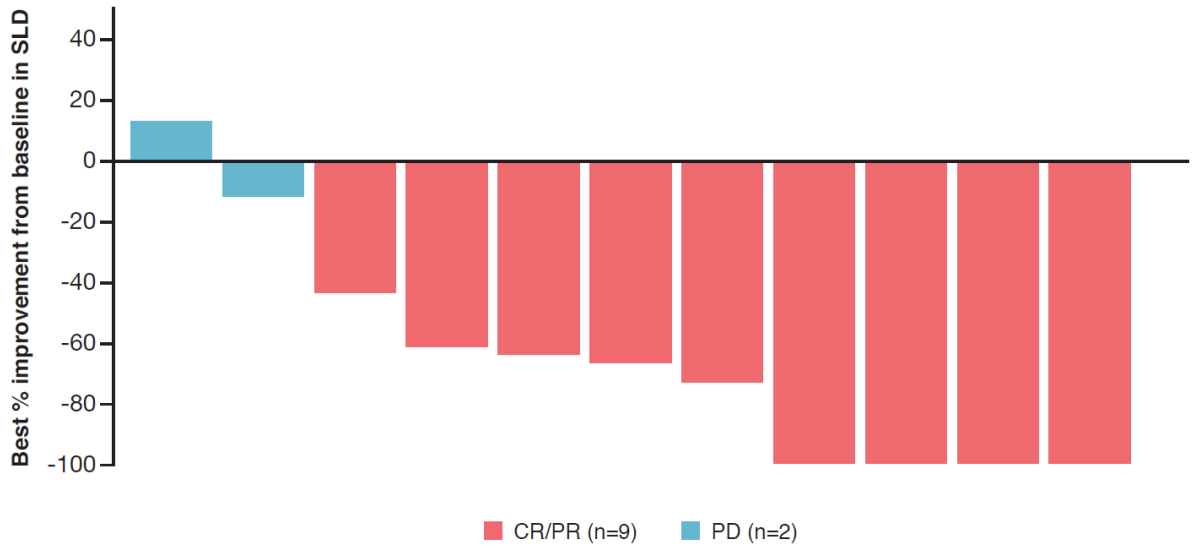
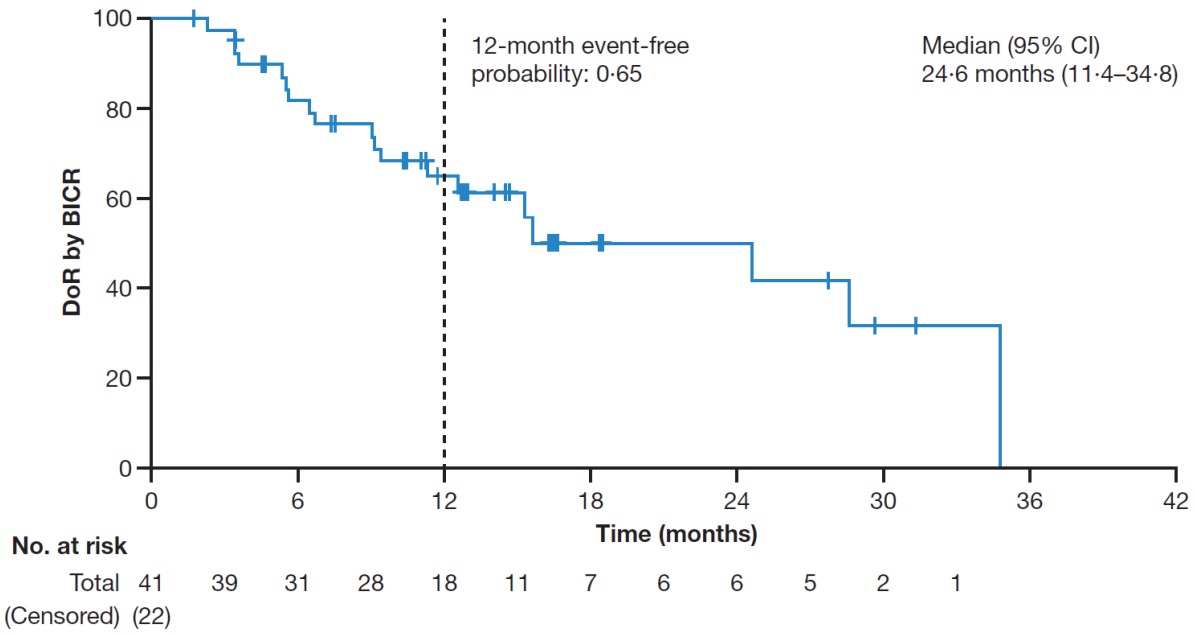

Best % improvement from baseline in SLD
40
20
0
-20
-40
-60
-80
-100
CR/PR (n=9)
PD (n=2)

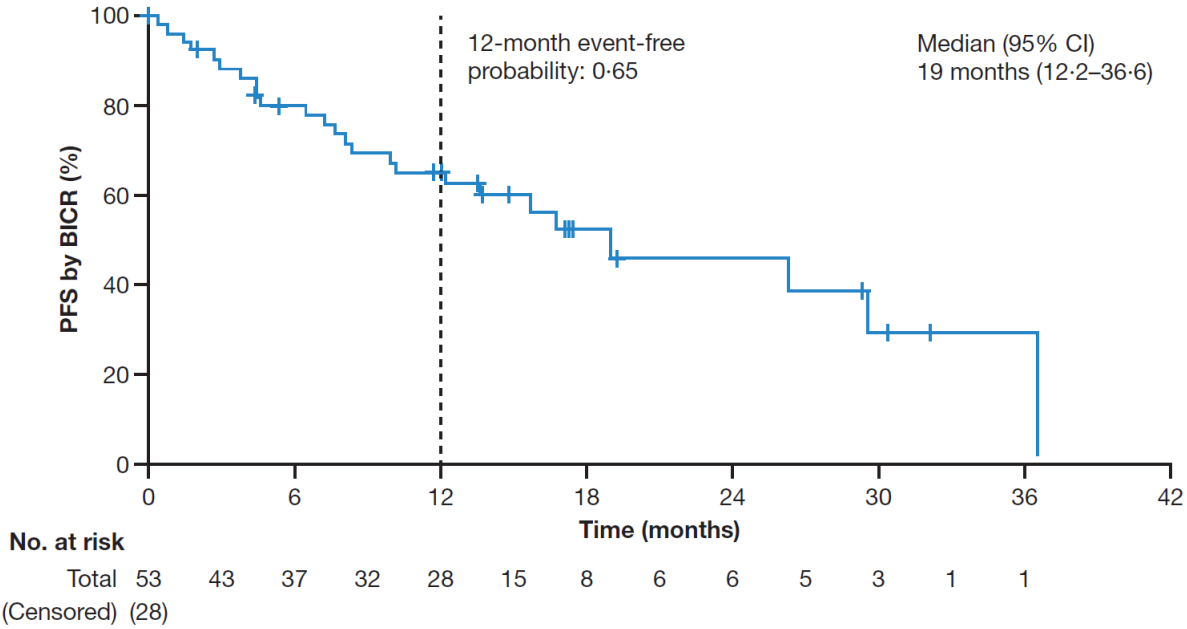
***Figure 2*: Time-to-event analyses**

Kaplan–Meier curves of the duration of response (A), progression-free survival (B), and overall survival (C) in patients with ROS1 inhibitor-naïve *ROS1* fusion-positive lung cancers. A Kaplan–Meier curve is shown for the time to CNS progression in patients with ROS1 inhibitor-naïve *ROS1* fusion-positive lung cancers (D). All assessments shown were based on blinded independent central review (BICR). CNS=central nervous system. DoR=duration of response. NE=not evaluable. NSCLC=non-small-cell lung cancer.

A

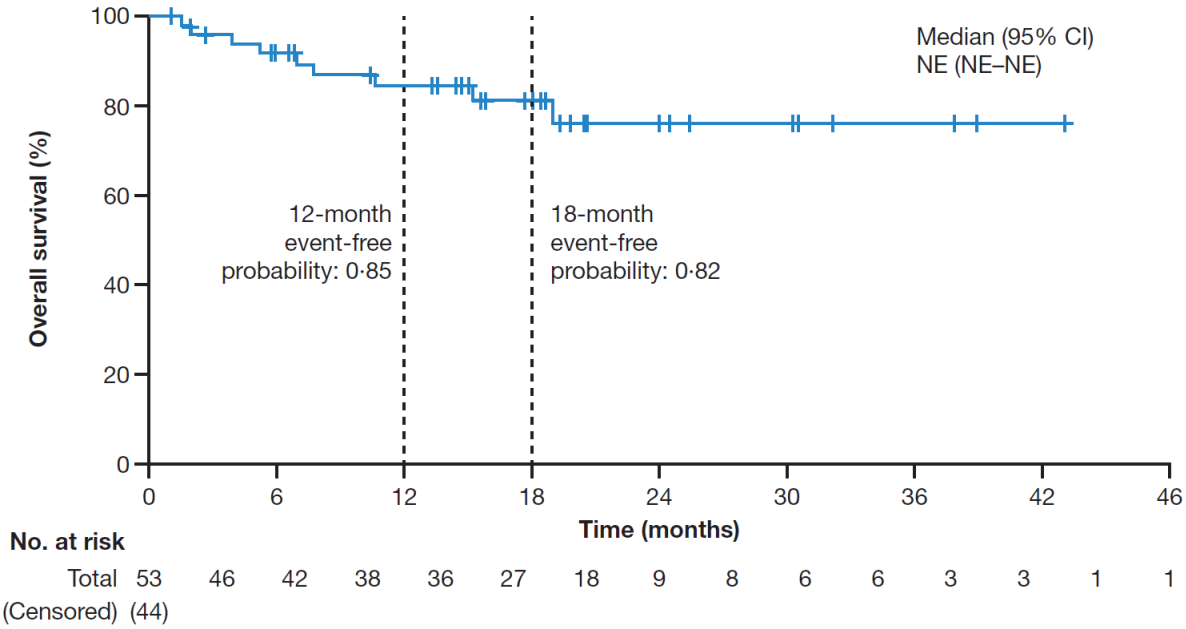


B

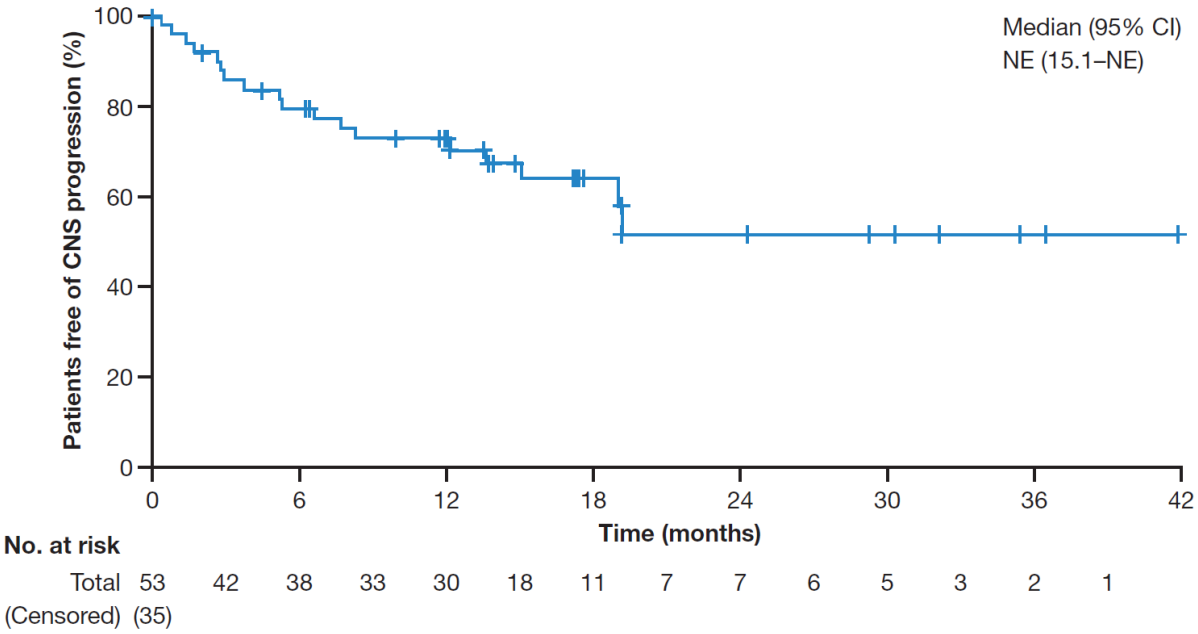


No. at risk													
Total	53	43	37	32	28	15	8	6	6	5	3	1	1
(Censored)	(28)												

C



No. at risk														
Total	53	46	42	38	36	27	18	9	8	6	6	3	3	1	1
(Censored)	(44)														



No. at risk

Total	53	42	38	33	30	18	11	7	7	6	5	3	2	1
(Censored)	(35)													