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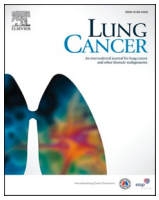

Updated efficacy and safety of entrectinib in *NTRK* fusion-positive non-small cell lung cancer

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A R T I C L E I N F O

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A B S T R A C T

Objectives: NTRK fusions result in constitutively active oncogenic TRK proteins responsible for ~ 0.2 % of non-small cell lung cancer (NSCLC) cases. Approximately 40 % of patients with advanced NSCLC develop CNS metastases; therefore, treatments with intracranial (IC) efficacy are needed. In an integrated analysis of three phase I/II studies (ALKA-372–001: EudraCT 2012–000148–88; STARTRK-1: NCT02097810; STARTRK-2: NCT02568267), entrectinib, a potent, CNS-active, TRK inhibitor, demonstrated efficacy in patients with *NTRK* fusion-positive (fp) NSCLC (objective response rate [ORR]: 64.5 %; 2 August 2021 data cut-off). We present updated data for this cohort.

Materials and methods: Eligible patients were ≥ 18 years with locally advanced/metastatic, *NTRK*-fp NSCLC with ≥ 12 months of follow-up. Tumor responses were assessed by blinded independent central review (BICR) per RECIST v1.1 at Week 4 and every eight weeks thereafter. Co-primary endpoints: ORR; duration of response (DoR). Secondary endpoints included progression-free survival (PFS); overall survival (OS); IC efficacy; safety. Enrolment cut-off: 2 July 2021; data cut-off: 2 August 2022.

List of non standard Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; fp, fusion positive; IC, intracranial; MedDRA, Medical Dictionary for Regulatory Activities; ND, not determined; NE, not estimable; NGS, next-generation sequencing; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tropomyosin receptor kinase; MASC, mammary analogue secretory carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SLD, sum of lesion diameters; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase.

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Results: The efficacy-evaluable population included 51 patients with *NTRK*-fp NSCLC. Median age was 60.0 years (range 22–88); 20 patients (39.2 %) had investigator-assessed baseline CNS metastases. Median survival follow–up was 26.3 months (95 % CI 21.0–34.1). ORR was 62.7 % (95 % CI 48.1–75.9), with six complete and 26 partial responses. Median DoR and PFS were 27.3 months (95 % CI 19.9–30.9) and 28.0 months (95 % CI 15.7–30.4), respectively. Median OS was 41.5 months. In patients with BICR-assessed baseline CNS metastases, IC-ORR was 64.3 % (n = 9/14; 95 % CI 35.1–87.2), including seven complete responders, and IC-DoR was 55.7 months. In the safety–evaluable population (n = 55), most treatment-related adverse events were grade 1/2; no treatment-related deaths were reported.
Conclusion: Entrectinib has continued to demonstrate deep and durable systemic and IC responses in patients with *NTRK*-fp NSCLC.

1. Introduction

Small-molecule inhibitors of altered tyrosine kinase proteins, including ALK, EGFR, ROS1 and TRK, have demonstrated efficacy in the treatment of patients with non-small cell lung cancer (NSCLC) [1–4]. Approximately 0.2 % of patients with NSCLC harbor fusions in the neurotrophic tyrosine receptor kinase (*NTRK1/2/3*) genes, resulting in the constitutive activation of oncogenic TRK proteins [5,6]. Furthermore, up to 40 % of patients with advanced, oncogenic driven NSCLC develop central nervous system (CNS) metastases, but there is no clear indication to the relationship between *NTRK* fusions and the likelihood of developing CNS metastases [7]. Consequently, there is a need for a treatment with proven overall and intracranial (IC) efficacy for patients with *NTRK* fusion-positive (fp) NSCLC.

Larotrectinib and entrectinib were the first TRK inhibitors to be approved in the USA and Europe for the treatment of patients with *NTRK*-fp solid tumors, including NSCLC [8–11]. However, data from preclinical studies suggest that larotrectinib has limited exposure in the CNS, resulting from mechanisms that export it out of the brain [12,13]. IC efficacy was not a pre-defined endpoint in the clinical studies of larotrectinib [14]. Conversely, entrectinib is a potent tyrosine kinase inhibitor (TKI) that was specifically designed to penetrate the blood–brain barrier with demonstrated activity within the CNS [4,12,15–17].

In an integrated analysis of three phase I/II studies (ALKA-372–001: EudraCT 2012–000148–88; STARTRK-1: NCT02097810; STARTRK-2: NCT02568267), entrectinib was associated with deep and durable overall and IC responses in patients with *NTRK*-fp solid tumors [4,18,19]. At the clinical cut-off of 2 August 2021, entrectinib was associated with an ORR of 61.3 % (n = 92/150; 95 % CI 53.1–69.2) and a median duration of response (DoR) of 20.0 months (95 % CI 13.2–31.1) in the overall population of patients with *NTRK*-fp solid tumors [19]. Additionally, 69.2 % of patients with measurable CNS metastases at baseline assessed by blinded independent central review (BICR), had an IC response. Entrectinib was also well tolerated with a manageable safety profile. At the same cut-off efficacy and safety was also assessed in a subgroup of patients with *NTRK*-fp NSCLC. In these patients, entrectinib yielded an objective response rate (ORR) of 64.5 % (n = 20/31, 95 % confidence interval [CI] 45.4–80.8) [20]. Altogether, these data show that entrectinib consistently yields deep and durable systemic and IC responses in patients with *NTRK*-fp solid tumors, and suggest that this efficacy is also seen in patients with *NTRK*-fp NSCLC. Here we present updated efficacy and safety data from this integrated analysis of entrectinib, with a longer follow-up and a larger patient cohort than previously, focusing on the subset of patients with *NTRK*-fp NSCLC.

2. Materials and methods

2.1. Study design and patients

The enrolment cut-off for this analysis was 2 July 2021 and the clinical cut-off was 2 August 2022. No patients from ALKA-372–001 had NSCLC, thus, efficacy and safety data for the entrectinib *NTRK*-fp NSCLC population were analyzed from STARTRK-1 (phase I) and STARTRK-2 (phase II global basket study) only. The study designs of the STARTRK-1 and STARTRK-2 trials have been described previously [18,21,22].

Briefly, eligible patients included in this analysis were aged ≥ 18 years with measurable *NTRK1*, *NTRK2* or *NTRK3*-fp NSCLC, as per the investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), had an Eastern Cooperative Oncology Group performance status 0–2 and no prior treatment with TKIs [23]. The efficacy-evaluable population included patients with ≥ 12 months follow-up from first on-study scan (i.e. ≥ 13 months from enrolment). Safety analyses included all patients with *NTRK*-fp NSCLC who were treated with ≥ 1 dose of entrectinib.

NTRK gene fusions were confirmed in patients' tumors using local or central assay methods such as Sanger sequencing, DNA- or RNA-based next-generation sequencing (NGS), or reverse transcription polymerase chain reaction. Patients who were asymptomatic by local testing were required to provide additional tumor tissue for testing by independent NGS, given that there were no medical contraindications. Lastly, patients with CNS metastases, who were asymptomatic or previously treated and controlled, were included in the analysis.

The studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was collected from all enrolled patients. All protocols for these studies were approved by relevant institutional review boards and/or ethics committees.

2.2. Treatment and assessments

Patients received oral entrectinib (600 mg) once daily until radiographic progression per BICR assessment (RECIST v1.1), unacceptable toxicity, or consent withdrawal. Patients with documented radiological disease progression could continue treatment if there was still a clinical benefit according to the investigator.

Tumor screenings, evaluated by BICR, included computed tomography and magnetic resonance imaging scanning, and were undertaken ≤ 30 days before patients received their first dose of entrectinib. Subsequent tumor assessments occurred at the end of Cycle 1 (Week 4), then every eight weeks until the end of treatment. Furthermore, patients with investigator-assessed CNS metastases at baseline underwent brain scans at each tumor assessment. In patients without baseline CNS metastases as determined by the investigator, brain scans were undertaken as clinically indicated or as part of routine clinical practice.

Safety assessments were undertaken by physical examination, laboratory tests and monitoring patients' adverse events (AEs). AEs were coded using the Medical Dictionary for Regulatory Activities (version 24.0) and graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Patients were permitted up to two dose reductions in decrements of 200 mg.

2.3. Study endpoints

The co-primary endpoints were ORR and DoR. The ORR was defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR). DoR was defined as the time from the first objective response to the first documentation of radiographic disease or death. Both endpoints were assessed by BICR (RECIST v1.1). For patients without disease progression or death, DoR was censored at the last tumor assessment.

Secondary endpoints included progression-free survival (PFS) and overall survival (OS). PFS was assessed by BICR and defined as the time from the first dose to the first documented disease progression or death due to any cause, and OS was defined as the time from first dose to death due to any cause.

Other pre-specified secondary endpoints included overall efficacy (ORR, DoR and PFS) per BICR in patients with investigator-assessed baseline CNS disease, and IC efficacy outcomes (IC-ORR, IC-DoR and IC-PFS) per BICR, in patients with baseline CNS metastases confirmed by BICR. Per RECIST v1.1, radiographic CNS metastases progression was defined as the occurrence of a new CNS lesion or progression in pre-existing CNS lesions; non-measurable CNS disease could only be classified as CR, non-CR/non-progressive disease (PD), or PD. Time to CNS progression (deaths censored; only CNS disease progression was counted as an event), was an exploratory endpoint assessed by BICR in the efficacy-evaluable population and in patients with and without investigator-assessed CNS metastases at baseline.

Safety and tolerability were assessed in the safety analysis set. Safety endpoints included adverse events and serious adverse events (all-cause or treatment-related), laboratory tests, dose exposure, and physical observations and measurements.

2.4. Statistical analyses

Patient demographic data and safety data were summarized descriptively. For response data, the number, percentage and two-sided exact 95 % CIs, calculated by the Clopper–Pearson method, were summarized. Median time-to-event endpoints (DoR, PFS, OS) were estimated using the Kaplan-Meier method, with corresponding 95 % CIs. SAS software (version 9.3 or higher; SAS Institute Inc., Cary, NC) was used for all statistical analyses.

3. Results

3.1. Demographics

At clinical cut-off (2 August 2022), a total of 51 patients were included in the efficacy-evaluable population; the median survival follow-up time was 26.3 months (95 % CI 21.0–34.1). Baseline demographics and disease characteristics of the efficacy-evaluable population are presented in Table 1.

The median age was 60.0 years, and 51.0 % (n = 26) of patients were male. A total of 27.5 % (n = 14) of patients had received ≥ 2 prior lines of therapy in the metastatic setting; 39.2 % (n = 20) of patients had investigator-assessed baseline CNS disease, and 27.5 % (n = 14) of patients had baseline CNS metastases confirmed by BICR. In patients with investigator-assessed baseline CNS disease, 50.0 % (n = 10/20) had received prior radiotherapy to the brain. In total, 21 *NTRK* fusion partners were identified, the most frequent of which was *TPM3*.

3.2. Efficacy

In the efficacy-evaluable population, the ORR was 62.7 % (n = 32/51; 95 % CI 48.1–75.9); six patients (11.8 %) had a CR, and 26 patients (51.0 %) had a PR (Table 2). Responses were seen in patients with and those without investigator-assessed CNS metastases at baseline, with ORRs of 60.0 % (n = 12/20; 95 % CI 36.1–80.9) and 64.5 % (n = 20/31;

Table 1
Patient demographics and baseline characteristics of the *NTRK*-fp NSCLC population.

Characteristic		Efficacy-evaluable population (N = 51)
Age, years	Median (range)	60.0 (22–88)
Sex, n (%)	Female	25 (49.0)
	Male	26 (51.0)
Race, n (%)	Asian	27 (52.9)
	Black/African American	1 (2.0)
	White	20 (39.2)
	Not reported	3 (5.9)
ECOG PS, n (%)	0	18 (35.3)
	1	30 (58.8)
	2	3 (5.9)
Smoking status	Never smoker	28 (54.9)
	Former/current smoker	23 (45.1)
Histology	Adenocarcinoma	44 (86.3)
	Large cell carcinoma	1 (2.0)
	NOS	1 (2.0)
	NSCLC – NOS	3 (5.9)
	Squamous cell carcinoma	2 (3.9)
Prior lines of systemic therapy, n (%)	0	18 (35.3)
	1	19 (37.3)
	2	7 (13.7)
	3	4 (7.8)
	4	1 (2.0)
	> 4	2 (3.9)
Any previous therapy, n (%)	Chemotherapy	37 (72.5)
	Immunotherapy	14 (27.5)
	Targeted therapy	6 (11.8)
	Hormonal therapy	1 (2.0)
CNS metastases at baseline*, n (%)	Yes	20 (39.2)
	No	31 (60.8)
Prior radiotherapy of the brain†, n (%)	Yes	10 (50.0)
	No	10 (50.0)
Time from end of prior radiotherapy of the brain to first dose‡, n (%)	< 2 months	3 (30.0)
	2–< 6 months	2 (20.0)
	≥ 6 months	5 (50.0)
NTRK fusion, n (%)	*NTRK1*	30 (58.8)
	NTRK2	5 (9.8)
	NTRK3	16 (31.4)
NTRK fusion partner, n (%)	*ARHGEF2–NTRK1*	1 (2.0)
	BCR-NTRK2	1 (2.0)
	CD74–NTRK1	2 (3.9)
	CDC42BPA–NTRK1	1 (2.0)
	EML4–NTRK3	4 (7.8)
	EPS15–NTRK1	2 (3.9)
	EPS15L1–NTRK1	1 (2.0)
	ETV6–NTRK3	8 (15.7)
	GP2–NTRK1	1 (2.0)
	IRF2BP2–NTRK1	2 (3.9)
	LMNA-NTRK1	1 (2.0)
	RIMKLA-NTRK1	1 (2.0)
	SQSTM1–NTRK1	5 (9.8)
	SQSTM1–NTRK2	4 (7.8)
	SQSTM1–NTRK3	2 (3.9)
	STK32C-NTRK1	1 (2.0)
	THSD4-NTRK3	1 (2.0)
	TPM3–NTRK1	10 (19.6)
	TPR–NTRK1	1 (2.0)
	TRIM24–NTRK3	1 (2.0)
	TRIM33-NTRK1	1 (2.0)

*CNS disease status as assessed by investigator (RECIST v1.1). 14 patients had baseline CNS metastases confirmed by BICR.
†Among patients with baseline CNS metastases by investigator.
‡Among patients with baseline CNS metastases and prior radiotherapy of the brain.
BICR, blinded independent central review; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; fp, fusion positive; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tropomyosin receptor kinase.

Table 2
Efficacy outcomes in the efficacy-evaluable *NTRK*-fp NSCLC population and in patients with and without baseline CNS metastases per investigator assessment.

Efficacy parameter	Efficacy-evaluable population (N = 51)	Baseline CNS metastases‡ (n = 20)	No baseline CNS metastases‡ (n = 31)
Objective response rate*, n (%, 95 % CI)	32 (62.7, 48.1–75.9)	12 (60.0, 36.1–80.9)	20 (64.5, 45.4–80.8)
Best overall response, n (%)			
Complete response	6 (11.8)	2 (10.0)	4 (12.9)
Partial response	26 (51.0)	10 (50.0)	16 (51.6)
Stable disease	5 (9.8)	3 (15.0)	2 (6.5)
Progressive disease	3 (5.9)	2 (10.0)	1 (3.2)
Non-CR/non-PD	3 (5.9)	0	3 (9.7)
Missing or unevaluable†	8 (15.7)	3 (15.0)	5 (16.1)
Duration of confirmed response*	n = 32	n = 12	n = 20
Median, months (95 % CI)	27.3 (19.9–)	29.4 (27.3–NE)	27.1 (18.4–NE)
Patients with event, n (%)	30.9)	6 (50.0)	9 (45.0)
12-month event-free rate, % (95 % CI)	15 (46.9) 82.4 (68.2–96.5)	91.7 (76.0–100.0)	78.1 (59.0–97.2)
Progression-free survival*			
Median, months (95 % CI)	28.0 (15.7–30.4)	28.3 (6.5–30.4)	28.0 (15.7–NE)
Patients with event, n (%)	25 (49.0)	11 (55.0)	14 (45.2)
12-month event-free rate, % (95 % CI)	71.6 (58.4–84.7)	65.5 (43.0–87.9)	75.8 (60.1–91.4)
Overall survival			
Median, months (95 % CI)	41.5 (30.9–NE)	41.5 (28.3–NE)	NE (30.9–NE)
Patients with event, n (%)	18 (35.3)	9 (45.0)	9 (29.0)
12-month event-free rate, % (95 % CI)	81.3 (70.3–92.3)	71.6 (50.4–92.8)	86.8 (74.7–98.9)

*As assessed by BICR.
†Missing or unevaluable included patients with on-study scans that could not be evaluated or who discontinued prior to obtaining adequate scans to evaluate or confirm response.
‡CNS disease status determined by the investigator.
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; *NTRK,* neurotrophic tropomyosin receptor kinase; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

95 % CI 45.4–80.8), respectively (Table 2; Fig. 1**A**). ORR by histology is presented in **Table A1**; ORR in patients with adenocarcinoma (n = 44/51) was 65.9 % (n = 29/44; 95 % CI 50.1–79.5). Median time to response was 1.0 month (95 % CI 0.9–1.0) and patients with non-CR/non-PD were on treatment for ≥ 10 months (Fig. 1**B**). In patients who responded to entrectinib treatment, the median DoR was 27.3 months (95 % CI 19.9–30.9) and the 12-month DoR rate was 82.4 % (95 % CI 68.2–96.5; Table 2; Fig. 1**C**).

At clinical cut-off, 25 patients (49.0 %) had experienced disease progression or died; the median PFS was 28.0 months (95 % CI 15.7–30.4) and the 12-month PFS rate was 71.6 % (95 % CI 58.4–84.7; Table 2; Fig. 2**A**). In patients with investigator-assessed baseline CNS metastases, median PFS was 28.3 months (95 % CI 6.5–30.4) compared with 28.0 months (95 % CI 15.7–not estimable [NE]) in patients without (Table 2; Fig. 2**A**). Median OS was 41.5 months (95 % CI 30.9–NE); 18 patients (35.3 %) died during follow-up and the 12-month OS rate was 81.3 % (95 % CI 70.3–92.3; Table 2; Fig. 2**B**).

Eighteen patients (35.3 %) had received no prior systemic treatment in the metastatic setting; in these patients the ORR was 66.7 % (n = 12/18; 95 % CI 41.0–86.7), the median DoR was 30.9 months (95 % CI 14.8–NE), and the median PFS was 19.4 months (95 % CI 10.2–41.5).

3.3. Intracranial efficacy

Median time to CNS progression (deaths censored) was NE in the efficacy-evaluable population and only three events occurred overall (one new CNS lesion in a patient with investigator-assessed baseline CNS metastases; two patients with disease progression; Fig. 2**C**). In 14 patients with measurable or non-measurable baseline CNS metastases by BICR, IC-ORR was 64.3 % (n = 9/14; 95 % CI 35.1–87.2), which includes seven patients (50 %) who had an IC-CR. IC-DoR was 55.7 months (95 % CI 8.0–NE) and IC-PFS was 32.7 months (95 % CI 5.9–NE; Table 3).

3.4. Safety

The safety-evaluable population comprised 55 patients with NSCLC who had received ≥ 1 dose of entrectinib. The median treatment duration was 14.7 months (range: 0.0–72.0 months) and the median dose intensity was 97.7 % (range: 14.2–105.3). Most patients (n = 52; 94.5 %) experienced a treatment-related adverse event (TRAE); however, the majority of these were grade 1/2 and non-serious (serious TRAEs were reported in eight [14.5 %] patients). The most frequent TRAEs in the safety-evaluable population are summarized by grade in Table 4. No grade 4 TRAEs and no treatment-related deaths occurred in this population.

The most commonly reported grade 1/2 TRAE was dysgeusia and blood creatinine increase, both reported by 24 patients (43.6 %); 24 patients (43.6 %) reported grade 3 TRAEs, the most frequent of which was weight gain (n = 6; 10.9 %). TRAEs led to treatment discontinuation in three patients (5.5 %), dose reduction in 13 patients (23.6 %) and dose interruption in 18 patients (32.7 %).

4. Discussion

In this updated analysis, entrectinib was associated with a high ORR (62.7 %) in patients with *NTRK*-fp NSCLC. After a median follow-up of 26.3 months, patients treated with entrectinib showed durable responses, with long median PFS and OS, regardless of the presence of CNS metastases at baseline.

The updated data from the *NTRK*-fp NSCLC cohort presented in this report (clinical cut-off: 2 August 2022) align with those previously reported (clinical cut-off: 2 August 2021) for this population and for the overall *NTRK*-fp study population (all patients with *NTRK*-fp solid tumors; N = 150) [19,20]. The ORR in this updated analysis (N = 51 patients with *NTRK*-fp NSCLC) was 62.7 %, compared with a previously reported ORR of 61.3 % in the overall *NTRK*-fp study population (N = 150 patients with *NTRK*-fp solid tumors); median DoR was 27.3 months and 20.0 months in these two populations, respectively. Conversely, PFS did not align between the two populations: median PFS was 28.0 months in patients with *NTRK*-fp NSCLC (12-month event-free rate: 71.6 %) and 13.8 months in the overall *NTRK*-fp study population. Finally, entrectinib was associated with long survival in both cohorts of patients: median OS was 41.5 months (12-month event-free rate: 81.3 %) in patients with *NTRK*-fp NSCLC and 37.1 months in the overall *NTRK*-fp study population.

Treatment with entrectinib was also associated with IC efficacy: in patients with BICR-assessed baseline CNS metastases, the IC-ORR was high at 64.3 %, including seven IC-CRs, and IC responses were durable, with a 12-month IC-DoR rate of 64.8 %. Interestingly, in patients with investigator-assessed CNS metastases at baseline, overall ORR was high at 60.0 % and responses were durable (12-month event-free DoR rate: 91.7 %), despite patients with CNS disease often having a poor prognosis [24,25]. These results were consistent with those seen in patients without baseline CNS disease. Taken together with the observed IC

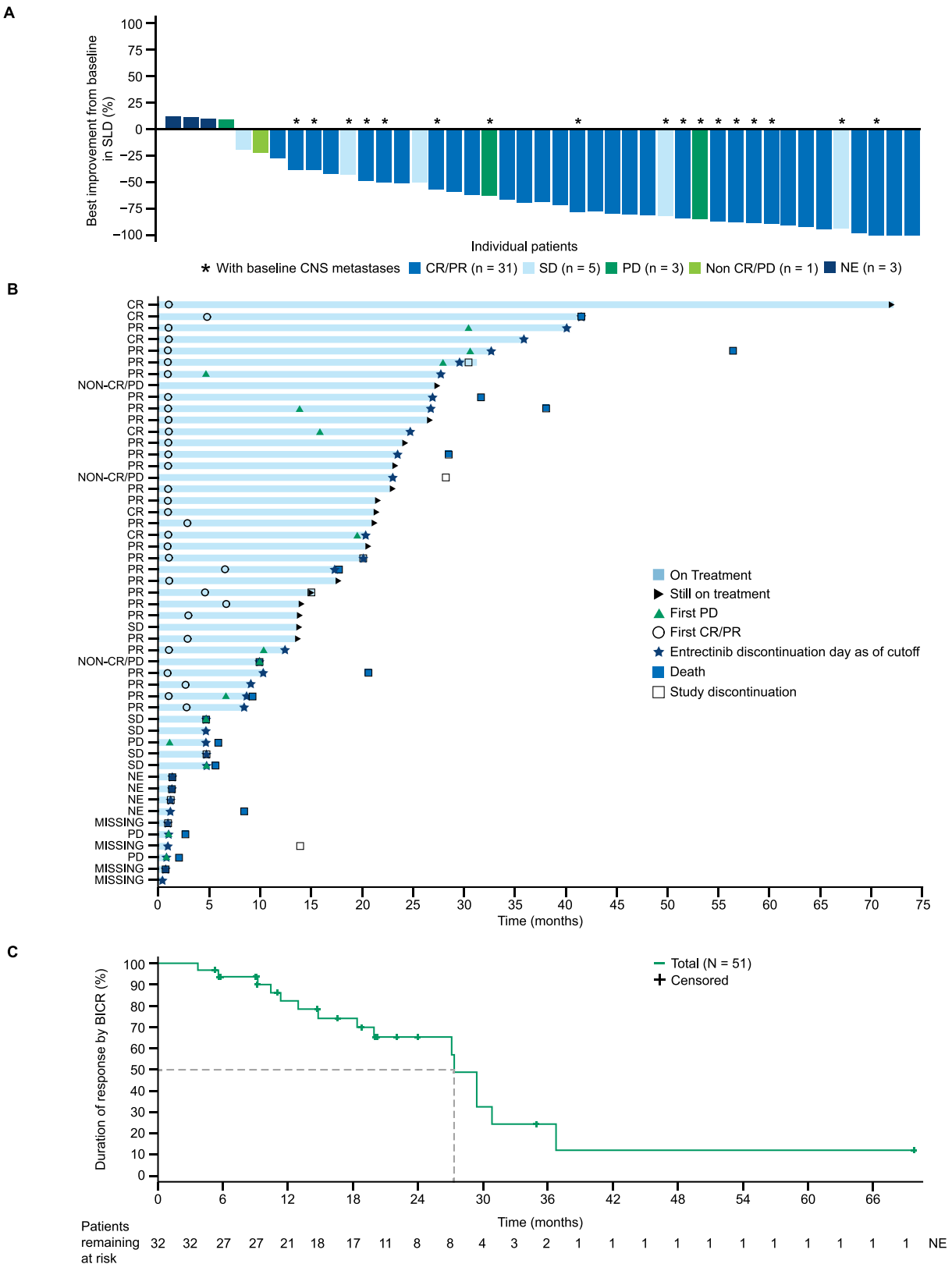

Fig. 1. Responses (BICR assessed) and time on entrectinib treatment in the efficacy-evaluable *NTRK*-fp NSCLC population. (A) Best individual patient responses in target lesions; (B) Time on entrectinib treatment and best overall response; (C) Duration of response. Eight patients without matched pre/post therapy scans or without measurable disease at baseline were excluded from the waterfall plot. BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; fp, fusion positive; ND, not determined; NE, not estimable; NSCLC, non-small cell lunger; *NTRK*, neurotrophic tropomyosin receptor kinase; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of lesion diameters.

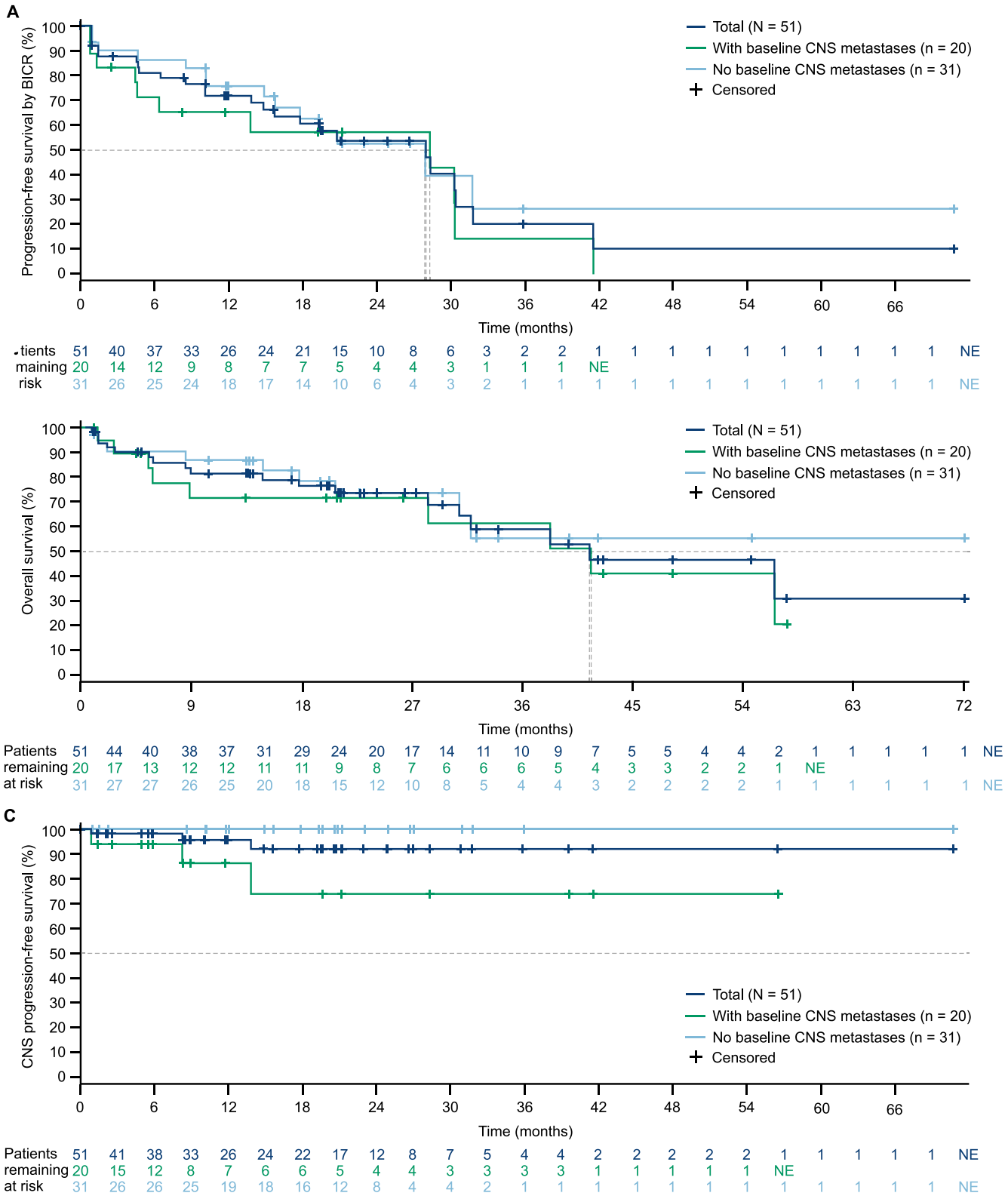

Fig. 2. Time-to-event analyses in the efficacy-evaluable *NTRK*-fp NSCLC population. (A) Progression-free survival per BICR in all patients and in patients with and without investigator-assessed baseline CNS metastases; (B) Overall survival in all patients and in patients with and without investigator-assessed baseline CNS metastases; (C) Time to CNS progression (deaths censored) in all patients and in patients with and without investigator-assessed baseline CNS metastases. BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; NE, not estimable.

Table 3
Intracranial efficacy outcomes in the efficacy-evaluable *NTRK*-fp NSCLC population with CNS metastases at baseline per BICR.

	Efficacy-evaluable population Baseline CNS metastases* (n = 14)
Intracranial objective response rate*, n (%, 95 % CI)	9 (64.3, 35.1–87.2)
Best overall response, n (%)	
Complete response	7 (50.0)
Partial response	2 (14.3)
Stable disease	2 (14.3)
Progressive disease	1 (7.1)
Non-CR/non-PD	1 (7.1)
Missing or unevaluable	1 (7.1)
Intracranial duration of response*	
Median, months (95 % CI)	55.7 (8.0–NE)
Patients with event, n (%)	4 (44.4)
12-month event-free rate, % (95 % CI)	64.8 (32.4–97.2)
Intracranial progression-free survival*	
Median, months (95 % CI)	32.7 (5.9–NE)
Patients with event, n (%)	7 (50.0)
12-month event-free rate, % (95 % CI)	50.0 (20.9–79.1)

*Assessed by BICR (RECIST v1.1).
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; fp, fusion positive; NE, not estimable; NSCLC, non–small-cell lung cancer; *NTRK*, neurotrophic tropomyosin receptor kinase; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

efficacy, these data confirm previous findings that entrectinib has high activity in the brain.

Furthermore, patients without baseline CNS metastases did not develop symptomatic CNS lesions (of note, brain scans were not mandated at each tumor assessment visit for these patients), and only one patient (5 %) with baseline CNS metastases developed a new CNS lesion, following treatment with entrectinib. These results are in line with previously reported data from patients with *ROS1*-fp NSCLC and patients with *NTRK*-fp solid tumors treated with entrectinib, and provide further evidence that, in addition to having clinical efficacy against existing lesions, entrectinib may also provide protection against the development of new CNS lesions [4,26].

Previous studies have investigated the efficacy of other TRK inhibitors in patients with *NTRK*-fp solid tumors. In an updated analysis of two phase I/II studies of larotrectinib, patients with *NTRK*-fp NSCLC had an ORR of 74 %, durable responses (median DoR: 33.9 months) and long survival (median PFS: 33.0 months; median OS: 39.3 months) [27]. In the 12 patients with baseline CNS metastases, the ORR was 67 % (all PRs); however, the responses in these patients were not durable (median DoR: 9.5 months) and survival was short (median PFS: 9.9 months; median OS: 19.4 months) [27]. The shorter time-to-event endpoints in patients with CNS metastases at baseline compared with the overall population of patients highlights the lower efficacy of larotrectinib in patients with CNS metastases, which is in contrast to what we have observed with entrectinib. IC efficacy was not a pre-specified endpoint in the larotrectinib studies and was not reported. The patient populations in the entrectinib and larotrectinib trials differ in several ways (e.g., the population in the entrectinib trial was older and included more patients with non-adenocarcinoma histology) and the single-arm clinical trials have different designs. Therefore, cross-trial comparisons should be viewed with caution and it is difficult to draw meaningful conclusions.

The safety profile of entrectinib in patients with *NTRK*-fp NSCLC was consistent with that previously reported in the overall *NTRK*-fp study population [19]. Patients treated with entrectinib reported mostly grade 1/2 TRAEs and a low occurrence of grade 3 TRAEs, that were manageable through dose modifications. Finally, the clinical profile of entrectinib in patients with *NTRK*-fp NSCLC was in line with that of entrectinib in patients with *ROS1*-fp NSCLC as reported in two independent studies, demonstrating that entrectinib is effective in different subtypes of NSCLC [28,29].

Table 4
Treatment-related adverse events reported in ≥ 5 % of patients or with at least one grade 3 event.

Treatment-related adverse event	Safety-evaluable *NTRK*-fp NSCLC population (N = 55)		
Patients, n (%)	Grade 1	Grade 2	Grade 3
Dysgeusia	18 (32.7)	6 (10.9)	0
Blood creatinine increased	13 (23.6)	11 (20.0)	0
Diarrhea	13 (23.6)	3 (5.5)	1 (1.8)
AST increased	11 (20.0)	3 (5.5)	0
ALT increased	11 (20.0)	2 (3.6)	0
Constipation	11 (20.0)	3 (5.5)	0
Anemia	10 (18.2)	4 (7.3)	0
Fatigue	8 (14.5)	6 (10.9)	0
Dizziness	8 (14.5)	5 (9.1)	0
Vomiting	7 (12.7)	1 (1.8)	1 (1.8)
Hyperuricemia	7 (12.7)	1 (1.8)	1 (1.8)
Edema peripheral	6 (10.9)	3 (5.5)	0
Nausea	5 (9.1)	0	0
Weight increased	4 (7.3)	5 (9.1)	6 (10.9)
Blood CPK increased	4 (7.3)	0	0
Headache	4 (7.3)	0	0
Hypotension	4 (7.3)	0	1 (1.8)
Vertigo	4 (7.3)	0	0
White blood cell count decreased	3 (5.5)	4 (7.3)	0
Blood LDH increased	3 (5.5)	0	0
Taste disorder	3 (5.5)	1 (1.8)	0
Hyperesthesia	3 (5.5)	0	0
Peripheral sensory neuropathy	3 (5.5)	0	0
Abdominal pain	3 (5.5)	1 (1.8)	0
Asthenia	3 (5.5)	0	1 (1.8)
Hyponatremia	3 (5.5)	0	0
Myalgia	3 (5.5)	0	0
Vision blurred	3 (5.5)	0	0
Hematuria	3 (5.5)	0	0
Pain of skin	3 (5.5)	0	0
Neutrophil count decreased	2 (3.6)	2 (3.6)	4 (7.3)
Paresthesia	2 (3.6)	2 (3.6)	0
Neuropathy peripheral	2 (3.6)	1 (1.8)	0
Malaise	2 (3.6)	0	1 (1.8)
Hypertriglyceridemia	2 (3.6)	2 (3.6)	2 (3.6)
Decreased appetite	2 (3.6)	0	1 (1.8)
Neutropenia	2 (3.6)	0	1 (1.8)
Insomnia	2 (3.6)	1 (1.8)	0
Cough	2 (3.6)	1 (1.8)	0
Pain in extremity	2 (3.6)	1 (1.8)	0
Renal failure	2 (3.6)	1 (1.8)	0
GFR decreased	1 (1.8)	2 (3.6)	0
Gait disturbance	1 (1.8)	2 (3.6)	0
Ejection fraction decreased	0	3 (5.5)	0
Syncope	0	0	1 (1.8)
Hepatic failure	0	0	1 (1.8)
Renal impairment	0	0	1 (1.8)
Diplopia	0	0	1 (1.8)
Anxiety	0	0	1 (1.8)
Anaphylactic reaction	0	0	1 (1.8)

Adverse events were encoded using MedDRA (version 24.0). No grade 4/5 treatment-related adverse events were reported.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; fp, fusion positive; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; *NTRK,* neurotrophic tropomyosin receptor kinase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate.

5. Conclusions

Entrectinib demonstrated clinically meaningful overall and IC efficacy and a manageable safety profile in patients with *NTRK*-fp NSCLC. The data described in this analysis support the use of entrectinib as a first-line treatment for patients with *NTRK*-fp NSCLC, including

those with baseline CNS disease. Further investigation is needed to increase our understanding of the prognosis of patients in this rare population, and their long-term outcomes with entrectinib.

CRediT authorship contribution statement

Byoung Chul Cho: Investigation, Writing – original draft, Writing – review & editing. **Chao-Hua Chiu:** Investigation, Writing – original draft, Writing – review & editing. **Erminia Massarelli:** Investigation, Writing – original draft, Writing – review & editing. **Gary L. Buchschacher Jr:** Investigation, Writing – original draft, Writing – review & editing. **Koichi Goto:** Investigation, Writing – original draft, Writing – review & editing. **Tobias R. Overbeck:** Investigation, Writing – original draft, Writing – review & editing. **Herbert H.F. Loong:** Investigation, Writing – original draft, Writing – review & editing. **Cheng E. Chee:** Investigation, Writing – original draft, Writing – review & editing. **Pilar Garrido:** Investigation, Writing – original draft, Writing – review & editing. **Xiaorong Dong:** Investigation, Writing – original draft, Writing – review & editing. **Yun Fan:** Investigation, Writing – original draft, Writing – review & editing. **Shun Lu:** Investigation, Writing – original draft, Writing – review & editing. **Sven Schwemmers:** Supervision, Writing – original draft, Writing – review & editing. **Walter Bordogna:** Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Harald Zeuner:** Investigation, Writing – original draft, Writing – review & editing. **Stuart Osborne:** Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Thomas John:** Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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N, Imnewrun, Janssen, Takeda, MSD, Medpacto, Blueprint Medicines, RandBio, and Hanmi Pharm. Invited speaker for ASCO, AstraZeneca, Guardant Health, F. Hoffmann-La Roche Ltd, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, and Pfizer. Advisory role for Kanaph Therapeutics, Bridge Biotherapeutics, Cyrus, Guardant Health, and Oscotec. Member of the board of directors for Interpark Bio Convergence Corp and J INTS Bio. Stock ownership for TheraCanVac, Gencurix, Bridge Biotherapeutics, Kanaph Therapeutics, Cyrus, Interpark Bio Convergence Corp, and J INTS Bio. Employment with Yonsei University Health System. 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Data Sharing Statement

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked because of a potential increase in the risk of patient re-identification.

Appendix A. Supplementary data

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