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Published in:
Annals of Oncology

DOI:
10.1016/j.annonc.2022.08.002

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ORIGINAL ARTICLE

Safety and efficacy of pralsetinib in *RET* fusion—positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial☆

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Available online 13 August 2022

Background: *RET* fusions are present in 1%-2% of non-small-cell lung cancer (NSCLC). Pralsetinib, a highly potent, oral, central nervous system-penetrant, selective RET inhibitor, previously demonstrated clinical activity in patients with *RET* fusion—positive NSCLC in the phase I/II ARROW study, including among treatment-naive patients. We report an updated analysis from the ARROW study.

Patients and methods: ARROW is a multi-cohort, open-label, phase I/II study. Eligible patients were ≥18 years of age with locally advanced or metastatic solid tumours and an Eastern Cooperative Oncology Group performance status of 0-2 (later 0-1). Patients initiated pralsetinib at the recommended phase II dose of 400 mg once daily until disease progression, intolerance, consent withdrawal, or investigator's decision. The co-primary endpoints (phase II) were overall response rate (ORR) by blinded independent central review and safety.

Results: Between 17 March 2017 and 6 November 2020 (data cut-off), 281 patients with *RET* fusion—positive NSCLC were enrolled. The ORR was 72% [54/75; 95% confidence interval (CI) 60% to 82%] for treatment-naive patients and 59% (80/136; 95% CI 50% to 67%) for patients with prior platinum-based chemotherapy (enrolment cut-off for efficacy analysis: 22 May 2020); median duration of response was not reached for treatment-naive patients and 22.3 months for prior platinum-based chemotherapy patients. Tumour shrinkage was observed in all treatment-naive patients and in 97% of patients with prior platinum-based chemotherapy; median progression-free survival was 13.0 and 16.5 months, respectively. In patients with measurable intracranial metastases, the intracranial response rate was 70% (7/10; 95% CI 35% to 93%); all had received prior systemic treatment. In treatment-naive patients with *RET* fusion—positive NSCLC who initiated pralsetinib by the data cut-off ($n = 116$), the most common grade 3-4 treatment-related adverse events (TRAEs) were neutropenia (18%), hypertension (10%), increased blood creatine phosphokinase (9%), and lymphopenia (9%). Overall, 7% (20/281) discontinued due to TRAEs.

Conclusions: Pralsetinib treatment produced robust efficacy and was generally well tolerated in treatment-naive patients with advanced *RET* fusion—positive NSCLC. Results from the confirmatory phase III AcceleRET Lung study (NCT04222972) of pralsetinib versus standard of care in the first-line setting are pending.

Key words: RET fusion, non-small-cell lung cancer, RET inhibition, pralsetinib, frontline therapy, targeted therapy

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☆Note: A portion of these data were presented at the 2021 American Society of Clinical Oncology Annual Meeting (Poster number: 9089).

INTRODUCTION

RET proto-oncogene (*RET*) fusions are targetable oncogenic drivers in 1%-2% of non-small-cell lung cancer (NSCLC).[1-3] For treatment-naive patients without a driver gene alteration, treatment with platinum-doublet cytotoxic chemotherapy is associated with modest response rates and short progression-free survival (PFS).[4-10] Immune checkpoint inhibitors [targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1)] as monotherapy or in combination with platinum-based chemotherapy are an option for patients lacking actionable oncogenic alterations[11]; however, outcomes with immune checkpoint inhibitors remain poor in patients with *RET* fusion—positive NSCLC regardless of PD-L1 expression.[12-15] Given the modest overall clinical benefit of standard first-line chemotherapy with or without immune checkpoint inhibitors for patients with *RET* fusion—positive NSCLC, novel approaches which selectively target RET are needed.

Pralsetinib (formerly BLU-667) is a selective and highly potent small-molecule inhibitor of wild-type RET and mutated or rearranged RET, with activity against V804 gatekeeper mutations that confer resistance to multikinase inhibitors.[16] In an interim analysis of the phase I/II registrational ARROW study (NCT03037385), pralsetinib was generally well tolerated and demonstrated clinical activity in patients with *RET* fusion—positive NSCLC at a 400 mg once-daily (QD) starting dose, with an overall response rate (ORR) of 70% and 61% in treatment-naive patients and patients with prior platinum-based chemotherapy, respectively.[17,18] In this previous analysis (data cut-off: 22 May 2020; efficacy enrolment cut-off: 11 July 2019), the treatment-naive population was limited in number ($n = 29$) and represented patients who *were* not candidates for standard platinum-based chemotherapy as determined by the investigator. Following a protocol amendment in July 2019, the eligibility criteria were expanded to include treatment-naive patients who were candidates for standard platinum-based chemotherapy, allowing enrolment of a patient cohort more representative of the real-world, first-line population. The updated analysis of the ARROW study presented here includes treatment-naive patients enrolled before and after the protocol eligibility revision, as well as an update on the overall population with an extended follow-up.

METHODS

Patients and study design

ARROW is a multi-cohort, multicentre, open-label, phase I/II study (ClinicalTrials.gov, NCT03037385) designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of pralsetinib in patients with advanced *RET*-altered tumours. Phase I evaluated pralsetinib in dose escalation (30-600 mg), determining 400 mg QD as the recommended phase II dose.[19] Phase II evaluated pralsetinib 400 mg QD in multiple expansion groups defined by disease type and treatment history. The study design has been previously described.[17,20] Briefly, eligible patients were ≥18 years of age with unresectable, locally advanced or metastatic solid tumours, and a pathologically or genetically documented *RET* fusion or mutation, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (limited to 0-1 after protocol amendment), and baseline measurable disease as per RECIST version 1.1. Patients with central nervous system (CNS) metastases or a primary CNS tumour associated with progressive neurological symptoms or requiring increasing doses of corticosteroids to control the CNS disease were excluded. For the *RET* fusion—positive NSCLC cohorts, patients were required to have a documented *RET* fusion as determined by local testing of tumour or circulating tumour nucleic acid (ctDNA) in blood. Following a protocol amendment on 11 July 2019, treatment-naive patients with *RET* fusion—positive NSCLC were enrolled regardless of their eligibility for standard platinum-based chemotherapy. Before 11 July 2019, only treatment-naive patients who were not candidates for standard platinum-based chemotherapy as determined by the investigator were eligible for enrolment. The full eligibility criteria are described in the protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2022.08.002).

This study was conducted in compliance with the International Conference on Harmonization for Good Clinical Practice and the Declaration of Helsinki. All patients provided written, informed consent. The study protocol was approved by the institutional review boards/independent ethics committees at all sites. Safety was monitored by the safety review committee comprising investigators and sponsor representatives.

Assessments

Patients were initiated on pralsetinib 400 mg QD and continued therapy until disease progression, intolerance, consent withdrawal, or investigator's decision. Dose reductions due to adverse events (AEs) below 100 mg QD were not permitted, and dose interruptions due to AEs for >28 days were not permitted [full criteria for dose modifications are described in the protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2022.08.002)].

RET alterations were detected by local testing methods, including next-generation sequencing of tumour or ctDNA in blood, or fluorescence in situ hybridization of tumour tissue (Table 1). Pre-treatment tumour tissue (archived or new tissue) was analysed centrally for *RET* gene status. Centrally confirmed *RET* gene alteration was not required for study entry; however, in the event local *RET* testing was not available, enrolment was based on the central laboratory results. Computerized tomography or magnetic resonance imaging of all known disease sites was conducted at screening and every ∼8 weeks on treatment, and every 3-4 months after the last dose for patients who discontinued

Table 1. Baseline characteristics (ITT population)

	Treatment-naive			Prior treatment		*RET* fusion–positive NSCLC ($n = 233$)
	All ($n = 75$)	Before eligibility revision ($n = 47$)[a]	After eligibility revision ($n = 28$)[a]	Prior platinum-based chemotherapy ($n = 136$)	Prior non-platinum systemic therapy ($n = 22$)	
Median age (range), years	63 (30-87)	65 (30-87)	56 (35-87)	59 (26-85)	61 (47-84)	60 (26-87)
Male, *n* (%)	39 (52)	26 (55)	13 (46)	65 (48)	7 (32)	111 (48)
Race, *n* (%)						
White	52 (69)	30 (64)	22 (79)	55 (40)	14 (64)	121 (52)
Asian	17 (23)	13 (28)	4 (14)	70 (51)	5 (23)	92 (39)
Other/unknown	6 (8)	4 (9)	2 (7)	11 (8)	3 (14)	20 (9)
Smoking history, *n* (%)						
Current/former	32 (43)	21 (45)	11 (39)	48 (35)	4 (18)	84 (36)
Never	41 (55)	25 (53)	16 (57)	86 (63)	18 (82)	145 (62)
Unknown	2 (3)	1 (2)	1 (4)	2 (1)	0	4 (2)
ECOG PS, *n* (%)						
0	31 (41)	18 (38)	13 (46)	37 (27)	10 (45)	78 (33)
1	43 (57)	28 (60)	15 (54)	94 (69)	12 (55)	149 (64)
2[b]	1 (1)	1 (2)	0	5 (4)	0	6 (3)
Brain metastases, *n* (%)[c]	25 (33)	17 (36)	8 (29)	54 (40)	8 (36)	87 (37)
RET fusion partner, *n* (%)						
KIF5B	50 (67)	33 (70)	17 (61)	98 (72)	16 (73)	164 (70)
CCDC6	13 (17)	5 (11)	8 (29)	24 (18)	4 (18)	41 (18)
NCOA4	1 (1)	0	1 (4)	0	0	1 (<1)
Other	11 (15)	9 (19)	2 (7)	14 (10)	2 (9)	27 (12)
RET local testing method, *n* (%)						
NGS	54 (72)	—	—	112 (82)	19 (86)	185 (79)
Tissue	36 (48)	—	—	50 (37)	14 (64)	100 (43)
Plasma[d]	12 (16)	—	—	20 (15)	5 (23)	37 (16)
Unknown	6 (8)	—	—	42 (31)	0	48 (21)
FISH	20 (27)	—	—	19 (14)	3 (14)	42 (18)
Other	1 (1)	—	—	5 (4)	0	6 (3)
Prior therapy type, *n* (%)						
Platinum-based chemotherapy	0	0	0	136 (100)	0	136 (58)
Non-platinum-based chemotherapy	0	0	0	0	2 (9)	2 (1)
Multikinase inhibitor	0	0	0	38 (28)	6 (27)	44 (19)
PD-L1 inhibitor	0	0	0	55 (40)	14 (64)	69 (30)

ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; ITT, intent-to-treat; NSCLC, non-small-cell lung cancer; NGS, next-generation sequencing; PD-L1, programmed cell death/programmed cell death ligand-1.
[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.
[b]ECOG PS of 2 was permitted before protocol amendment in July 2018.
[c]History of or current.
[d]If local testing method is NGS but specimen type is missing, and ctDNA testing method is also NGS and specimen type is available, the specimen type used in ctDNA test is applied.

treatment without disease progression. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and monitored from the treatment initiation until 30 days after the last dose. Safety laboratory assessments were conducted at local laboratories according to the schedules provided in the protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2022.08.002).

Endpoints

The co-primary endpoints for the phase II portion were ORR [complete response (CR) or partial response (PR) as per RECIST version 1.1] as assessed by blinded independent central review, and safety. Secondary endpoints included duration of response (DOR; time from first response until disease progression or death, whichever occurred first), clinical benefit rate (CBR; confirmed CR, PR, stable disease for ≥16 weeks), disease control rate (DCR; CR, PR, or stable disease), PFS (time from first dose to disease progression or death, whichever occurred first), overall survival (OS; time from first dose to death), and correlation of *RET* gene alteration and efficacy.

Statistical analyses

A sample size of ∼170 patients with treatment-naive *RET* fusion–positive NSCLC was estimated to provide >90% power at the two-sided significance level of 0.05 for testing the null hypothesis ORR of 48% versus the alternative ORR of 61%. For patients with *RET* fusion–positive NSCLC who had previously received platinum-based chemotherapy, a sample size of ∼80 patients was estimated to provide >95% power at the two-sided significance level of 0.05 for testing the null hypothesis ORR of 23% versus the alternative ORR of 50%.

The interim data included in this article represent updated analyses conducted in the registrational population for

European Union (EU) regulatory filings. Efficacy analyses included all patients with *RET* fusion—positive NSCLC in the intent-to-treat (ITT) population who initiated pralsetinib at the recommended phase II dose of 400 mg QD by 22 May 2020 (enrolment cut-off), including patients who had received prior treatment (platinum-based chemotherapy or non-platinum systemic therapy) or were treatment-naive (regardless of eligibility for standard platinum-based chemotherapy). Efficacy data are also reported for the measurable disease population, comprising a subset of patients in the ITT population with sufficient evidence of a *RET* fusion and baseline measurable disease. Safety analyses included all patients with *RET*-altered tumours who had enrolled and initiated 400 mg QD pralsetinib by 6 November 2020 (data cut-off); an additional safety analysis was conducted for all patients with *RET* fusion—positive NSCLC by treatment history (treatment-naive or pre-treated).

Two-sided 95% confidence intervals (CIs) were based on exact binomial distributions using the Clopper—Pearson method. DOR, PFS, and OS were determined using Kaplan—Meier (K—M) analyses; estimates for duration of follow-up for these outcomes were determined using the inverse K—M method, with 95% CIs based on the Greenwood formula. ORR subgroup analyses were conducted for patient subgroups, defined by sex, ECOG performance status, smoking, CNS/brain metastases, treatment history, and *RET* fusion partner. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

Between 17 March 2017 and 6 November 2020 (data cut-off), 528 patients with *RET*-altered tumours had enrolled in dose escalation and dose expansion and initiated 400 mg QD pralsetinib (safety population), of whom 281 had *RET* fusion—positive NSCLC (Figure 1). In total, 233 patients with *RET* fusion—positive NSCLC had enrolled by 22 May 2020 (ITT population), comprising 75 treatment-naive patients and 158 patients who had received prior treatment (136 patients with prior platinum-based chemotherapy and 22 patients with prior non-platinum systemic therapy). Among the 75 treatment-naive patients, 47 patients had enrolled before the eligibility revision (not candidates for standard platinum-based chemotherapy as determined by the investigator) and 28 patients had enrolled after the eligibility revision (enrolled regardless of their eligibility for standard platinum-based chemotherapy). By the 6 November 2020 data cut-off (median follow-up: 17.1 months), 110 patients in the *RET* fusion—positive NSCLC ITT population were still on treatment; the most common reasons for treatment discontinuation were disease progression ($n = 74$) and AEs ($n = 34$) (Figure 1).

In the treatment-naive ITT population ($n = 75$), median age was 63 years (range 30-87 years), 52% were male, 43% were current/former smokers, 59% had an ECOG performance status of 1-2, and 33% had history of or active CNS/

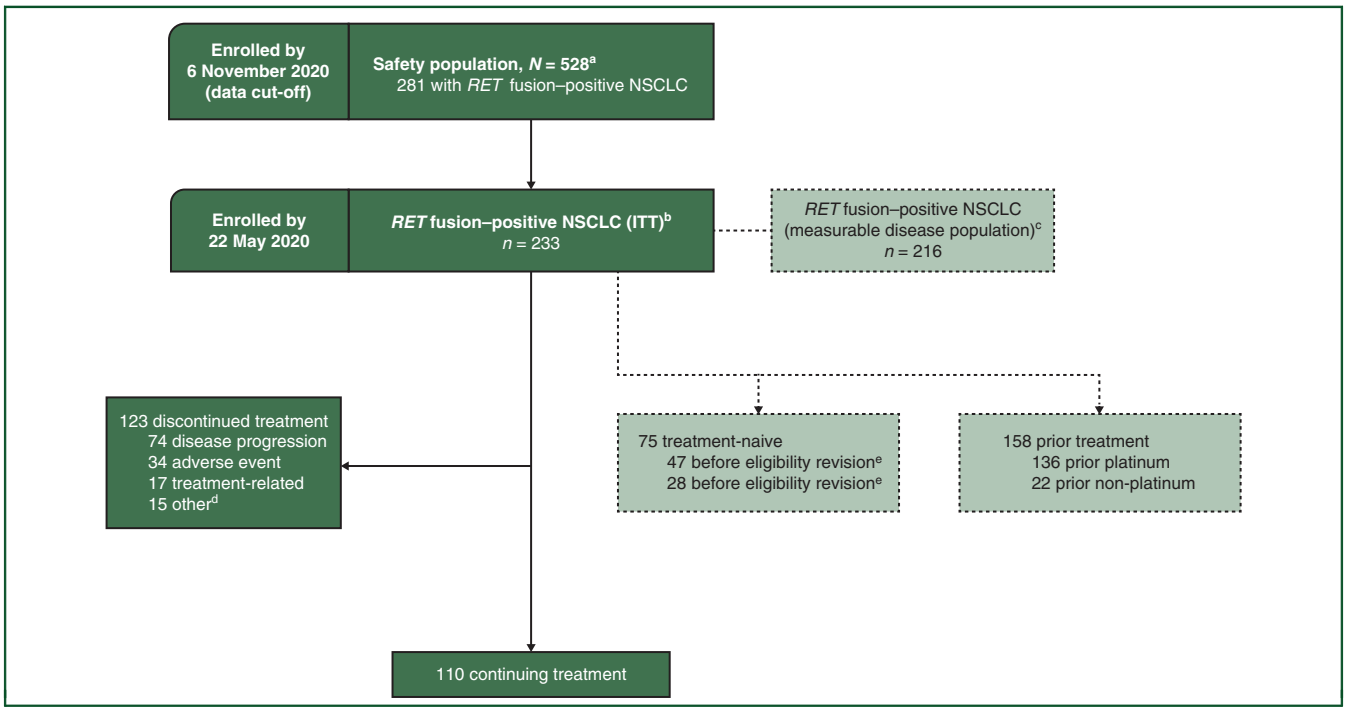

Figure 1. Patient disposition.
[a]Safety analysis includes all patients enrolled by 6 November 2020 (data cut-off), in dose escalation (phase I) and dose expansion (phase II). [b]Efficacy analysis includes all patients with *RET* fusion—positive NSCLC in the ITT population enrolled by 22 May 2020. [c]Patients with sufficient evidence of a *RET* fusion and baseline measurable disease. [d]Other reasons for discontinuation were withdrawn consent ($n = 10$), investigator's decision ($n = 3$), and administrative reason/other ($n = 2$). [e]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.
ITT, intent-to-treat; NSCLC, non-small-cell lung cancer.

brain metastases (Table 1). The baseline characteristics were generally similar between treatment-naive patients and patients who had received prior treatment. Of note, treatment-naive patients who had enrolled after eligibility revision ($n = 28$) had a lower median age, proportionally higher ECOG performance status of 0, and proportionally lower brain metastases than those enrolled before the eligibility revision, consistent with the more favourable prognostic factors expected from this population.

Efficacy

Among treatment-naive patients with *RET* fusion–positive NSCLC in the ITT population ($n = 75$), the ORR was 72% (95% CI 60% to 82%) with a median time to first response of 1.8 months (range 0.9-6.1 months) (Table 2). Four (5%) patients had a CR, 50 (67%) had a PR, 14 (19%) had stable disease, 5 (7%) had progressive disease, and 2 (3%) were not assessable. The DCR was 91% (95% CI 82% to 96%) and CBR was 80% (95% CI 69% to 88%). Median DOR was not reached (NR; 95% CI 9.0 months-NR) after a median follow-up of 7.4 months (95% CI 6.4-9.5 months), with 84% (95% CI 73% to 95%) and 54% (95% CI 34% to 74%) of patients still responding at 6 months and 12 months, respectively (Table 2 and Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2022.08.002). For treatment-naive patients who enrolled before the eligibility revision, the ORR was 68% (95% CI 53% to 81%) and for patients who had enrolled after the eligibility revision, ORR was 79% (95% CI 59% to 92%) (Table 2); median DOR was 11.0 months [95% CI 7.4 months-NR; median follow-up: 11.1 months (95% CI 9.5-13.6 months)] and NR [95% CI not estimable; median follow-up: 5.6 months (95% CI 4.3-6.5 months)], respectively. The ORR remained generally high in all reported subgroups, including those defined by sex (female or male), ECOG performance status (0, 1, or 2), CNS/brain metastases history (yes or no), *RET* fusion partner (*KIF5B*, *CCDC6*, *NCOA4,* or others), or smoking history (never [smoked <100 cigarettes in their lifetime] or former/current) (Supplementary Figure S2A, available at https://doi.org/10.1016/j.annonc.2022.08.002). Tumour shrinkage was observed in all treatment-naive patients with baseline and post-baseline assessments (67/67) (Figure 2A). Median PFS was 13.0 months (95% CI 9.1 months-NR) after a median follow-up of 9.2 months (95% CI 8.6-11.0 months; Figure 3A and Table 2); 27 (36%) patients had progression events or died. The estimated 6- and 12-month PFS rates were 80% (95% CI 71% to 90%) and 53% (95% CI 38% to 68%), respectively. Median PFS for treatment-naive patients who enrolled before the eligibility revision was 10.9 months [95% CI 7.7 months-NR; median follow-up: 13.2 months (95% CI 11.0-14.8 months)] and median PFS was NR [95% CI not estimable; median follow-up: 8.2 months (95% CI 7.3-9.1 months)] for patients who enrolled after the eligibility revision. In all treatment-naive patients, OS was NR after a

Table 2. Efficacy summary (ITT population)

	Treatment-naive			Prior treatment		*RET* fusion–positive NSCLC ($n = 233$)
	All ($n = 75$)	Before eligibility revision ($n = 47$)[a]	After eligibility revision ($n = 28$)[a]	Prior platinum-based chemotherapy ($n = 136$)	Prior non-platinum systemic therapy ($n = 22$)	
ORR, % (95% CI)	72 (60-82)	68 (53-81)	79 (59-92)	59 (50-67)	73 (50-89)	64 (58-71)
Best overall response, *n* (%)						
CR	4 (5)	4 (9)	0	7 (5)	0	11 (5)
PR	50 (67)	28 (60)	22 (79)	73 (54)	16 (73)	139 (60)
SD	14 (19)	9 (19)	5 (18)	43 (32)	4 (18)	61 (26)
PD	5 (7)	5 (11)	0	6 (4)	2 (9)	13 (6)
NE	2 (3)	1 (2)	1 (4)	7 (5)	0	9 (4)
DCR, % (95% CI)[b]	91 (82-96)	87 (74-95)	96 (82-100)	90 (84-95)	91 (71-99)	91 (86-94)
CBR, % (95% CI)[c]	80 (69-88)	74 (60-86)	89 (72-98)	74 (66-81)	77 (55-92)	76 (70-82)
Median time to first response (range), months	1.8 (0.9-6.1)	1.8 (0.9-5.6)	1.8 (1.7-6.1)	1.8 (1.3-11.4)	1.8 (1.6-5.5)	1.8 (0.9-11.4)
Median DOR (95% CI), months	NR (9.0-NR)	11.0 (7.4-NR)	NR (NR-NR)	22.3 (15.1-NR)	NR (9.2-NR)	22.3 (14.7-NR)
DOR rate, % (95% CI)						
6-month	84 (73-95)	79 (63-94)	93 (81-100)	83 (74-91)	93 (81-100)	84 (78-91)
12-month	54 (34-74)	49 (29-69)	NR (NR-NR)	68 (57-80)	56 (25-87)	64 (55-73)
Median follow-up (95% CI), months	7.4 (6.4-9.5)	11.1 (9.5-13.6)	5.6 (4.3-6.5)	16.7 (12.9-18.5)	18.5 (7.7-22.0)	12.4 (9.3-16.6)
Median PFS (95% CI), months[d]	13.0 (9.1-NR)	10.9 (7.7-NR)	NR (NR-NR)	16.5 (10.5-24.1)	12.8 (9.1-NR)	16.4 (11.0-24.1)
PFS rate, % (95% CI)						
6-month	80 (71-90)	75 (62-88)	89 (78-100)	72 (64-80)	76 (58-94)	75 (69-81)
12-month	53 (38-68)	44 (28-60)	84 (70-99)	57 (48-66)	52 (29-76)	56 (49-63)
Median follow-up (95% CI), months	9.2 (8.6-11.0)	13.2 (11.0-14.8)	8.2 (7.3-9.1)	18.4 (13.2-19.8)	20.2 (9.3-23.8)	12.9 (11.1-17.5)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ITT, intent-to-treat; NSCLC, non-small-cell lung cancer; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease, PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease.

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.

[b]Confirmed CR or PR or SD.

[c]CR or PR or SD of ≥16 weeks.

[d]Evaluated in all patients with *RET* fusion–positive NSCLC who initiated 400 mg QD pralsetinib by 22 May 2020.

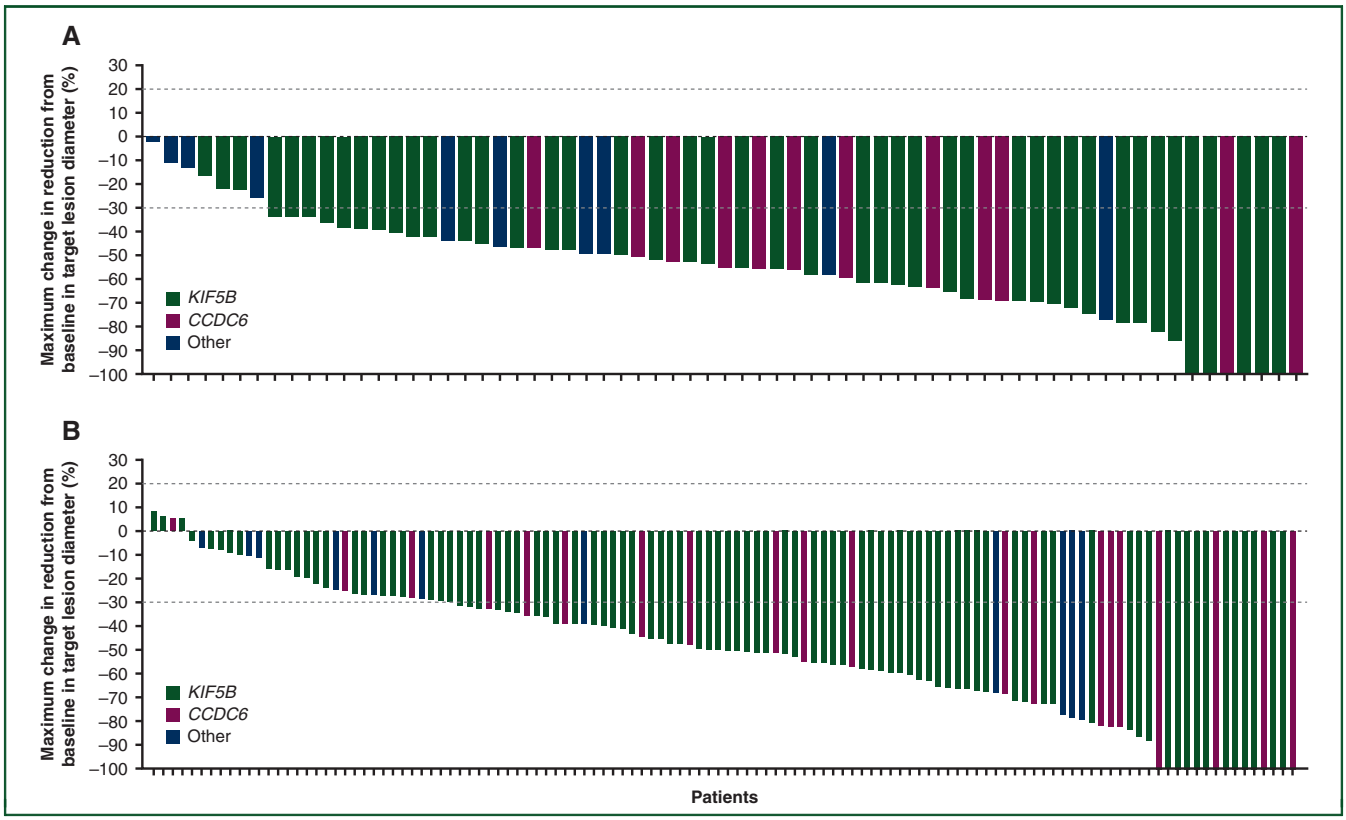

Figure 2. Tumour shrinkage in patients with *RET* fusion—positive NSCLC. Maximum reduction in target lesion diameter in (A) treatment-naive patients ($n = 67$) and (B) patients with prior platinum-based chemotherapy ($n = 120$) with baseline and post-baseline measurable disease. The dotted lines represent the thresholds for progressive disease (+20%), partial response (−30%), and complete response (−100%) as per RECIST.
NSCLC, non-small-cell lung cancer.

median follow-up of 12.8 months (95% CI 11.1-15.0 months); 12 (16%) patients died. The estimated 6- and 12-month OS rates were 92% (95% CI 85% to 98%) and 82% (95% CI 72% to 93%), respectively.

In patients with *RET* fusion—positive NSCLC who had previously received platinum-based chemotherapy ($n = 136$), the ORR was 59% (95% CI 50% to 67%), with a median time to first response of 1.8 months (95% CI 1.3-11.4 months) (Table 2). The ORR remained high in most reported patient subgroups (Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2022.08.002) and median DOR was 22.3 months (95% CI 15.1 months-NR) after a median follow-up of 16.7 months (95% CI 12.9-18.5 months) (Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2022.08.002). Tumour shrinkage was observed in 97% (116/120) of patients (Figure 2B). Median PFS was 16.5 months (95% CI 10.5-24.1 months) after a median follow-up of 18.4 months (95% CI 13.2-19.8 months; Figure 3B and Table 2). Median OS was NR after a median follow-up of 20.1 months (95% CI 19.4-21.5 months), with estimated 6- and 12-month OS rates of 85% (95% CI 79% to 91%) and 72% (95% CI 64% to 81%), respectively.

In patients with *RET* fusion—positive NSCLC who had previously received non-platinum systemic therapy ($n = 22$), the ORR was 73% (95% CI 50% to 89%), with a median time to first response of 1.8 months (95% CI 1.6-5.5 months) (Table 2). Median DOR was NR [95% CI 9.2 months-NR; median follow-up: 18.5 months (95% CI 7.7-22.0 months)] and median PFS was 12.8 months [95% CI 9.1 months-NR; median follow-up: 20.2 months (95% CI 9.3-23.8 months)].

Shrinkage of brain metastases was observed in all assessable patients with measurable intracranial metastases (10/10; Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.08.002). All of these patients had received prior systemic treatment, including nine patients with prior platinum-based chemotherapy and one patient with prior non-platinum systemic therapy. Four patients had received prior brain radiotherapy. The intracranial response rate was 70% (7/10; 95% CI 35% to 93%), including three patients (30%) with intracranial CRs, with a median time to response of 1.7 months (range 1.6-11.4 months). Median duration of intracranial response was 10.5 months (95% CI 5.5-12.6 months), with 71% (95% CI 38% to 100%) and 36% (95% CI 0% to 75%) of responses ongoing at 6 and 12 months, respectively. Among patients without baseline CNS metastases (223/233), only two patients had scan-confirmed CNS progressive disease at data cut-off.

Efficacy findings in the ITT population were consistent with the measurable disease population ($n = 216$) for both treatment-naive and previously treated cohorts (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.08.002).

Safety

In patients with *RET* fusion—positive NSCLC who initiated 400 mg QD pralsetinib and enrolled by 6 November 2020

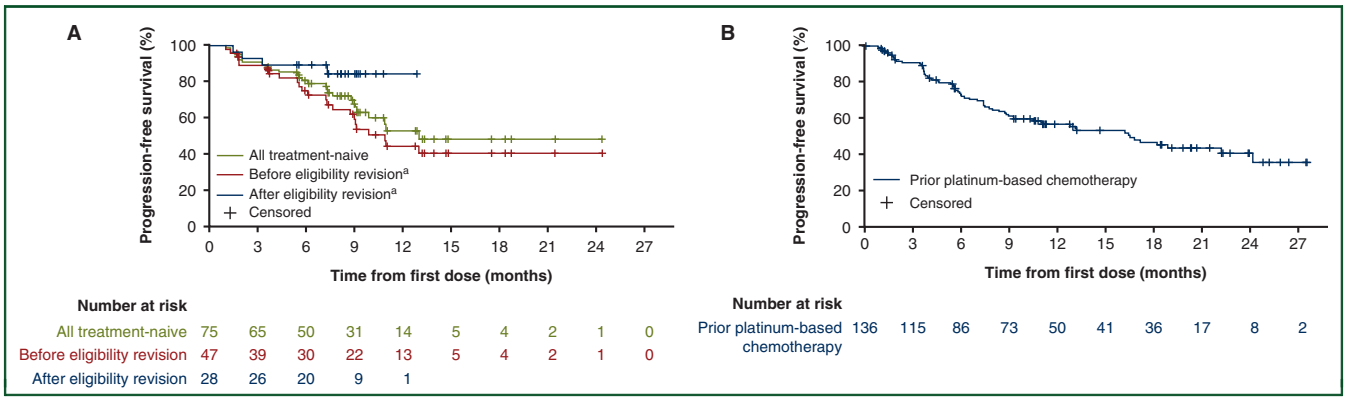

Figure 3. Progression-free survival in patients with *RET* fusion—positive NSCLC. Progression-free survival in (A) treatment-naive patients and (B) patients with prior platinum-based chemotherapy.
[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.
NSCLC, non-small-cell lung cancer.

($n = 281$), median duration of treatment was 7.9 months (range 0.3-28.4 months) with a median relative dose intensity of 92% (range 27%-100%); 7% (20/281) discontinued due to treatment-related adverse events (TRAEs). In the treatment-naive population ($n = 116$), 108 (93%) patients experienced a TRAE, including 60 (52%) patients who experienced a grade 3-4 TRAE (Table 3). In the pre-treated population ($n = 165$), 156 (95%) patients experienced a TRAE, including 93 (56%) patients who experienced a grade 3-4 TRAE. The most common TRAEs in the treatment-naive population (occurring in ≥30% of patients) were neutropenia (43%; febrile neutropenia in 2%), leukopenia (39%), increased aspartate aminotransferase (39%), increased alanine aminotransferase (32%), anaemia (32%), and constipation (30%); the most common grade 3-4 TRAEs (occurring in ≥10% of patients) were neutropenia (18%) and hypertension (10%). In the pre-treated population, the most common TRAEs were neutropenia (47%; febrile neutropenia in 2%), anaemia (43%), increased aspartate aminotransferase (42%), and leukopenia (31%); the most common grade 3-4 TRAEs were neutropenia (22%), anaemia (18%), and hypertension (13%). The most common treatment-related serious AEs for treatment-naive and pre-treated populations were pneumonitis [six (5%) and eight (5%) patients, respectively] and pneumonia [seven (6%) and six (4%) patients, respectively]. In both treatment-naive and pre-treated patients, neutropenia was the most common TRAE leading to dose reduction [17 (15%) and 23 (14%) patients, respectively] and dose interruption [19 (16%) and 27 (16%) patients, respectively] (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.08.002). Pneumonitis was the most common TRAE leading to permanent treatment discontinuation for both treatment-naive [four (3%)] and pre-treated [three (2%)] populations. Grade 3-4 treatment-related pneumonia and treatment-related pneumonitis were reported in seven (6%) and three (3%) patients, respectively, in the treatment-naive population, and in four (2%) and three (2%) patients, respectively, in the pre-treated population. Most treatment-related pneumonitis events were grade 1-2 in severity. As per protocol, high-dose intravenous and/or oral corticosteroids ($n = 7$) or oral corticosteroids only ($n = 15$) were used to treat pneumonitis. Overall, 45% (5/11) of treatment-naive patients had resolved their treatment-emergent pneumonitis, with a median time of onset and resolution of 66 days (range 16-225 days) and 16 days (range 9-41 days), respectively; 64% (16/25) of pre-treated patients had resolved their treatment-emergent pneumonitis, with a median time of onset and resolution of 146 days (range 19-673 days) and 37 days (range 5-137 days), respectively. There was no treatment-related hypersensitivity. There was one (<1%) TRAE leading to death in the treatment-naive group (pneumonia).

The safety profile of patients irrespective of tumour type who initiated 400 mg QD pralsetinib and enrolled by 6 November 2020 ($N = 528$) is shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.08.002.

DISCUSSION

In this updated analysis of patients with *RET* fusion—positive NSCLC from the ARROW study, pralsetinib administered at a 400 mg QD starting dose was generally well tolerated and demonstrated clinical activity in all reported treatment groups, consistent with previous findings.[17] The ORR in the treatment-naive population was high (72%), including among patients who enrolled before (68%) and after (79%) the eligibility revision. Tumour shrinkage was observed in all assessable treatment-naive patients. Of note, treatment-naive patients who enrolled after the eligibility revision presented with a numerically lower proportion of unfavourable prognostic factors at baseline compared with patients who enrolled beforehand, including age (median 56 years versus 65 years), current/former smoking status (39% versus 45%), ECOG performance status 1-2 (54% versus 62%), and brain metastases (29% versus 36%). The response rate for the treatment-naive population was comparable to other oncogene-targeted therapies, such as osimertinib in *EGFR*-mutant NSCLC (80%); alectinib (83%), brigatinib (74%), and lorlatinib (76%) in *ALK*-positive NSCLC; and entrectinib (77%)

Table 3. Treatment-related adverse events by grouped preferred term in patients with *RET* fusion—positive NSCLC (safety population)

Treatment-related AE, *n* (%)	Treatment-naive patients (*n* = 116)		Pre-treated patients (*n* = 165)		All (*n* = 281)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Neutropenia	50 (43)	21 (18)	78 (47)	36 (22)	128 (46)	57 (20)
Leukopenia	45 (39)	8 (7)	51 (31)	14 (8)	96 (34)	22 (8)
Increased aspartate aminotransferase	45 (39)	2 (2)	69 (42)	6 (4)	114 (41)	8 (3)
Anaemia	37 (32)	5 (4)	71 (43)	30 (18)	108 (38)	35 (12)
Increased alanine aminotransferase	37 (32)	1 (1)	47 (28)	5 (3)	84 (30)	6 (2)
Constipation	35 (30)	0	38 (23)	2 (1)	73 (26)	2 (1)
Fatigue	29 (25)	1 (1)	41 (25)	4 (2)	70 (25)	5 (2)
Increased blood creatine phosphokinase	27 (23)	10 (9)	22 (13)	8 (5)	49 (17)	18 (6)
Hypertension	24 (21)	12 (10)	47 (28)	22 (13)	71 (25)	34 (12)
Taste disorder	19 (16)	0	20 (12)	0	39 (14)	0
Lymphopenia	17 (15)	10 (9)	25 (15)	14 (8)	42 (15)	24 (9)
Hyperbilirubinaemia	17 (15)	0	17 (10)	2 (1)	34 (12)	2 (1)
Thrombocytopenia	14 (12)	3 (3)	31 (19)	8 (5)	45 (16)	11 (4)
Oedema	14 (12)	0	35 (21)	0	49 (17)	0
Increased blood creatinine	14 (12)	1 (1)	27 (16)	0	41 (15)	1 (<1)
Diarrhoea	13 (11)	1 (1)	26 (16)	1 (1)	39 (14)	2 (1)
Dry mouth	13 (11)	0	22 (13)	0	35 (12)	0
Hyperphosphataemia	13 (11)	0	17 (10)	0	30 (11)	0
Pneumonitis	10 (9)	3 (3)	24 (15)	3 (2)	34 (12)	6 (2)
Increased blood alkaline phosphatase	5 (4)	0	20 (12)	3 (2)	25 (9)	3 (1)

Treatment-related AEs of any grade reported in ≥10% of patients in the treatment-naive (*n* = 116), pre-treated (*n* = 165), or all *RET* fusion—positive (*n* = 281) populations who initiated 400 mg QD pralsetinib by the 6 November 2020 data cut-off.
AE, adverse event; NSCLC, non-small-cell lung cancer; QD, once daily.

and crizotinib (72%) in *ROS1* fusion—positive NSCLC.[21-26] While PFS data were immature for treatment-naive patients, median PFS was estimable (13.0 months); median PFS was not yet reached for treatment-naive patients who enrolled after the eligibility revision. Median OS was NR at the time of data cut-off for all reported treatment subgroups (median follow-up 17.1 months for overall population), and the estimated 6- and 12-month OS rates for the overall NSCLC population (*n* = 233) were ≥75%.

The estimated lifetime risk of brain metastases is high and prognosis is poor among patients with *RET* fusion—positive NSCLC.[27,28] Here, we report shrinkage of brain metastases in all 10 assessable patients with measurable intracranial metastases (all of whom received prior systemic treatment and four of whom had received prior radiotherapy), with an intracranial response rate of 70% and duration of intracranial response of 10.5 months. Additionally, there were only two incidences of scan-confirmed CNS progressive disease among patients without CNS metastases at baseline. This number may be an underestimation due to the fact that serial surveillance brain magnetic resonance imaging was not required for those patients not known to have brain metastases at baseline (and so would have been done as per investigator discretion or triggered by symptoms). The intracranial activity seen with pralsetinib allows consideration of systemic therapy as a preferred first-line approach over historically favoured interventions such as surgery and/or radiotherapy for brain metastases if deemed clinically appropriate.

Until recently, there were no specific guidelines for the frontline treatment of *RET* fusion—positive NSCLC. First-line use of standard platinum-based chemotherapy in NSCLC is associated with moderate response rates (15%-41%) and short PFS (median 4.5-6.5 months).[4-10] Immune checkpoint inhibitors with or without platinum-based chemotherapy improve the ORR in patients lacking actionable oncogenic mutations (e.g. *EGFR*, *ALK*, and *RET*)[11,29]; however, outcomes with immune checkpoint inhibitors remain poor for patients with *RET* fusion—positive NSCLC (ORR of 0%-7% and median PFS of 2.2-3.4 months), including those positive for PD-L1 expression (≥1% PD-L1).[12-15] Along with data reported for selpercatinib,[30] the clinical activity observed with pralsetinib in treatment-naive patients with *RET* fusion—positive NSCLC further supports first-line use of selective RET inhibitors in this patient population. Furthermore, use of a once daily oral treatment offers a marked improvement in quality of life due to fewer hospital trips for previous intravenous therapies in this patient population.[31]

In this updated analysis with longer follow-up, pralsetinib remained well tolerated at the 400 mg QD starting dose in patients with *RET* fusion—positive NSCLC (median relative dose intensity >90% for both treatment-naive and pre-treated population). The safety profile was consistent with that observed in the overall *RET*-altered tumour population, and there were no new safety signals. While cross-trial comparisons should be avoided due to differences between study populations and other factors, the incidence of grade 3-4 TRAEs with pralsetinib is comparable to patients receiving chemotherapy with or without an immune checkpoint inhibitor.[4-10] Furthermore, ≤20% of patients experienced grade 3-4 treatment-related neutropenia or anaemia, and grade 3-4 treatment-related pneumonia and pneumonitis were rare. Finally, AEs were manageable and response rates remained high at the 400 mg QD starting dose despite dose reductions and interruptions due to AEs.

The updated analysis of the ARROW study presented here supports the approval of pralsetinib as the first and only RET

inhibitor for the first-line treatment of patients with *RET* fusion—positive NSCLC in the EU.[32] Pralsetinib is currently approved in the United States[18] and Canada[33] for the treatment of metastatic *RET* fusion—positive NSCLC and advanced or metastatic *RET*-altered thyroid cancers, in Switzerland[34] for *RET* fusion—positive NSCLC and advanced or metastatic *RET*-altered thyroid cancers in the second-line setting, and in China[35] for locally advanced or metastatic *RET* fusion—positive NSCLC after platinum-based chemotherapy. The ongoing phase III AcceleRET Lung (NCT04222972) and LIBRETTO-431 (NCT04194944) studies will evaluate the efficacy and safety of pralsetinib and selpercatinib, respectively, versus standard of care in treatment-naive advanced/metastatic *RET* fusion—positive NSCLC.

In conclusion, we show that orally administered once daily pralsetinib produces a robust ORR, including intracranial activity and durable PFS, in patients with advanced *RET* fusion—positive NSCLC who are treatment-naive or refractory to standard-of-care chemotherapy. These results show the importance of early comprehensive biomarker testing that includes fusions for all patients with metastatic NSCLC before treatment initiation to inform optimal health care decisions. Results from the phase III AcceleRET Lung study may further support the use of pralsetinib for *RET* fusion—positive NSCLC in the first-line setting.

ACKNOWLEDGEMENTS

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support, including assisting authors with the development of the outline and initial draft and incorporation of comments, was provided by Kenny Tran, MSc; and editorial support, including fact checking, referencing, figure preparation, formatting, proofreading, and submission, was provided by Travis Taylor, all of Paragon, Knutsford, supported by Blueprint Medicines Corporation and F. Hoffmann-La Roche, Ltd., according to Good Publication Practice guidelines (https://doi.org/10.7326/M22-1460). The sponsor was involved in the study design, collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

FUNDING

This work was supported by Blueprint Medicines Corporation and F. Hoffmann-La Roche, Ltd, Switzerland (no grant number).

DISCLOSURE

FG has consulted or provided expert opinion for Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Celgene, GSK, Lilly, MSD, Novartis, Pfizer, Roche, Siemens, and Takeda; has received fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Celgene, GSK, Lilly, MSD, Novartis, Pfizer, Roche, Siemens, and Takeda; and has received funding for scientific research from Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Celgene, GSK, Lilly, MSD, Novartis, Pfizer, Roche, Siemens, and Takeda. GC has consulted and/or had advisory roles for AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Foundation Medicine, GlaxoSmithKline, Lilly, Novartis, Pfizer, Roche/Genentech, Samsung, and Seattle Genetics; served on speakers' bureaus for Daiichi Sankyo, Foundation Medicine, Lilly, Novartis, Pfizer, Roche/Genentech, and Samsung; received travel, accommodations, and expenses from Pfizer, Roche/Genentech; received honoraria from Ellipses Pharma and research funding from Merck; and is supported by the OPTIMA [grant number 101034347]. MT has received honoraria for scientific meetings (self) from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Novartis, Pfizer, Roche, and Takeda; advisory-board honoraria (self) from AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Novartis, Pfizer, Roche, and Takeda; travelling support (self) from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Novartis, Pfizer, Roche, and Takeda; and has received research funding (institution) from AstraZeneca, BMS, Roche, and Takeda. VS reports research funding/grant support for clinical trials from AbbVie, Agensys, Alfa-sigma, Altum, Amgen, Bayer, Berg Health, Biotherapeutics, Blueprint Medicines Corporation, Boston Biomedical, Boston Pharmaceuticals, Celgene, D3, Dragonfly Therapeutics, Exelixis, Fujifilm, GSK, Idera Pharma, Incyte, Inhibrx, Loxo Oncology, MedImmune, MultiVir, Nanocarrier, National Comprehensive Cancer Network, NCI-CTEP, Novartis, Northwest Biotherapeutics, Pfizer, PharmaMar, Roche/Genentech, Takeda, Turning Point Therapeutics, UT MD Anderson Cancer Center, and Vegenics; travel support from ASCO, ESMO, Helsinn, Incyte, Novartis, and PharmaMar; consultancy/advisory board participation for Helsinn, Incyte, Loxo Oncology/Eli Lilly, MedImmune, Novartis, R-Pharma US, QED Pharma; and other relationship with Medscape. CSB has received consulting fees from AstraZeneca, Blueprint Medicines Corporation, Daiichi Sankyo, Turning Point Therapeutics, Guardant, Regeneron, Silverback, and Takeda; and has received research funding to their institution from AbbVie, AstraZeneca, Blueprint Medicines Corporation, Daiichi Sankyo, Genentech Inc., Janssen, Lilly, Loxo Oncology, Novartis, Pfizer, Rain Therapeutics, Spectrum Pharmaceuticals, and Turning Point Therapeutics. DSWT has consulted and/or had advisory roles for AstraZeneca, Bayer, Lilly, Loxo Oncology, Merrimack, Novartis, Pfizer, and Takeda; received honoraria from Boehringer Ingelheim, Merck, and Roche; and research funding to their institution from AstraZeneca, Bayer, GSK, and Novartis. DHL has received personal fees from AbbVie, AstraZeneca, Boehringer Ingelheim, BMS, Chong Keun Dang, CJ Healthcare, Genexine, Janssen, Lilly, Merck, Menarini, MSD, Mundipharma, Novartis, Ono, Pfizer, Roche, Samyang Biopharm, ST Cube, and Takeda; and non-financial support from Blueprint Medicines Corporation and Takeda. DM has consulted and/or had advisory roles at scientific meetings for AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Novartis, Roche, Sanofi, and Takeda (institution, no personal honoraria). EG has consulted and/or had advisory roles for

Alkermes, BMS, Boehringer Ingelheim, Ellipses Pharma, Janssen, NeoMed, Roche, Seattle Genetics, TFS, Thermo Fisher Scientific; served on speakers' bureaus for MSD, Roche, and Thermo Fisher Scientific; received travel and accommodation expenses from BMS, Glycotope GmbH, Menarini, and MSD; research funding to their institution from Novartis, Roche, and Thermo Fisher Scientific; and is supported by a grant from the 'la Caixa' Foundation [grant number LCF/PR/CE07/50610001]. DWK has received travel and accommodation expenses from Amgen and Daiichi Sankyo; and research funding to their institution from Alpha Biopharma, Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, Daiichi Sankyo, Hanmi, Janssen, Merus, Mirati Therapeutics, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan. AJvdW reports research funding/grant support for clinical trials from AstraZeneca [grant number ESR-16-12212], Boehringer Ingelheim, Pfizer, Roche, and Takeda [grant number 2019N0853/2020N0366]; and consultancy/advisory board participation for AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck, Pfizer, Roche, and Takeda. JFG has an immediate family member who is an employee of Ironwood Pharmaceuticals; has consulted and/or had advisory roles for Agios, Amgen, Array BioPharma, Blueprint Medicines Corporation, BMS, Genentech, Gilead Sciences, Jounce Therapeutics, Lilly, Loxo Oncology, Merck, Mirati, Silverback Therapeutics, GlydeBio, Moderna Therapeutics, Oncorus, Regeneron, Takeda, and Theravance; has stock and ownership in Ironwood Pharmaceuticals; has received honoraria from ARIAD, Incyte, Merck, Novartis, Pfizer, and Takeda; and research funding from Adaptimmune, ALX Oncology, ARIAD, Array BioPharma, AstraZeneca, Blueprint Medicines Corporation, BMS, Genentech, Jounce Therapeutics, Merck, Novartis, and Tesaro. LPA has a leadership role in ALTUM Sequencing and Genomica; served on speakers' bureaus for AstraZeneca, BMS, Lilly, MSD Oncology, Merck Serono, Pfizer, Roche/Genentech; received travel, accommodation, and expenses from AstraZeneca, BMS, MSD, Pfizer, Roche, and Takeda; honoraria from Amgen, AstraZeneca, Bayer, Blueprint Medicines Corporation, BMS, Celgene, Ipsen, Lilly, Merck Serono, Mirati Therapeutics, MSD, Novartis, Pfizer, PharmaMar, Roche/Genentech, Sanofi, Servier, and Takeda; research funding to their institution from AstraZeneca, BMS, Kura Oncology, MSD, and PharmaMar; other relationships with Roche; and an immediate family member has other relationships with Amgen, Ipsen, Merck Novartis, Pfizer, Sanofi, Servier, and Roche. SVL served as a consultant or advisory board member to Amgen, AstraZeneca, Bayer, BeiGene, Blueprint Medicines Corporation, BMS, Daiichi Sankyo, Eisai, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Lilly, Merck/MSD, Novartis, Regeneron, Sanofi, Takeda, and Turning Point Therapeutics; received research funding (to institution) from Alkermes, Bayer, Blueprint Medicines Corporation, BMS, Elevation Oncology, Genentech, Lilly, Merck, Merus, Pfizer, Rain Therapeutics, RAPT Therapeutics, Turning Point Therapeutics; and is supported by the National Cancer Institute [grant number UM1CA186691]. GPK received research grants from Blueprint Medicines Corporation, Merck, AbbVie, Takeda, Daiichi, and Cullinan. DWB served on an advisory board for Blueprint Medicines Corporation. ASM received research funding from DoD, Mark Foundation, NIH, Novartis, and Verily; honoraria to institution for participation in advisory boards: AbbVie, BeiGene, BMS, Genentech, Inc., Janssen; travel support from: Roche; is a non-remunerated member of the Mesothelioma Applied Research Foundation Board of Directors; and is supported by the Mark Foundation for Cancer Research ASPIRE Award, the National Cancer Institute [grant number R21 CA251923], and Department of Defense Concept Award [grant number W81XWH-22-1-0021]. JJL served as a compensated consultant or advisory board member for Genentech, C4 Therapeutics, Blueprint Medicines Corporation, Nuvalent, Bayer, Elevation Oncology, Novartis, Mirati Therapeutics, and Turning Point Therapeutics; received honorarium and travel support from Pfizer; received institutional research funding from Hengrui Therapeutics, Turning Point Therapeutics, Neon Therapeutics, Relay Therapeutics, Bayer, Elevation Oncology, Roche, Linnaeus Therapeutics, Nuvalent, and Novartis; and received CME funding from OncLive, MedStar Health, and Northwell Health. VSm is an employee and/or equity holder of F. Hoffmann-La Roche, Ltd. AR is an employee and/or equity holder of F. Hoffmann-La Roche, Ltd and equity holder of Merck/MSD. SK is a former employee and/or equity holder of F. Hoffmann-La Roche, Ltd. AZ, MLG and ALB are employees and/or equity holders of Blueprint Medicines Corporation. JM has provided expertise for Amgen, AstraZeneca, Blueprint Medicines Corporation, BMS, Daiichi Sankyo, Hengrui, MSD, Novartis, Pierre Fabre, Roche, and Takeda; and received research funding from AstraZeneca, BMS, Pierre Fabre, and Roche. YH has declared no conflicts of interest.

DATA SHARING

The anonymized derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years after this article's publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to medinfo@blueprintmedicines.com. The trial protocol will also be made available, as will a data fields dictionary.

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