

6 Final Efficacy and Safety Data From the Phase I/II ARROW Study of Pralsetinib in Patients With Advanced *RET* Fusion–Positive Non–Small Cell Lung Cancer

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ABSTRACT

RET fusions appear in 1%–2% of non–small cell lung cancers (NSCLCs). The results from the ARROW study (ClinicalTrials.gov identifier: [NCT03037385](https://clinicaltrials.gov/ct2/show/study/NCT03037385)) supported US Food and Drug Administration approval of pralsetinib, an oral selective *RET* inhibitor, for metastatic *RET*-altered NSCLC and *RET* fusion–positive thyroid cancers. ARROW was a phase I/II open-label study of pralsetinib 400 mg once daily in *RET* fusion–positive NSCLCs. Coprimary end points were overall response rate (ORR) and safety. Key secondary end points included duration of response, progression-free survival, and overall survival (OS). At data lock (May 20, 2024), 281 patients initiated pralsetinib (median treatment duration, 15.0 months). ORR (measurable disease patients; n = 259) was 78% (95% CI, 69 to 86) for treatment-naïve patients and 63% (95% CI, 54 to 71) for prior platinum-based chemotherapy patients. Median OS was 44.3 months (95% CI, 30.9 to 53.1), 50.1 months (95% CI, 28.3 to not reached) in treatment-naïve patients, and 39.7 months (95% CI, 27.8 to 53.2) in prior platinum patients. Common grade ≥3 treatment-related adverse events were anemia (21%), hypertension (15%), and decreased neutrophils (13%). Three treatment-related deaths occurred (pneumonia, n = 2; interstitial lung disease and rhabdomyolysis, n = 1 each). Safety was consistent with previous ARROW reports; no hypersensitivity was reported in patients receiving prior immunotherapies. Pralsetinib produced robust, durable responses with manageable safety in treatment-naïve and previously treated patients with *RET* fusion–positive NSCLCs, confirming previous findings with longer follow-up.

ACCOMPANYING CONTENT

-  Appendix
-  Data Sharing Statement
-  Protocol

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INTRODUCTION

RET fusions are targetable alterations in non–small cell lung cancer (NSCLC).¹ Next-generation selective *RET* inhibitors pralsetinib and selpercatinib have demonstrated superior efficacy and reduced toxicity compared with earlier therapies.^{1–6}

Pralsetinib, an oral tyrosine kinase inhibitor selectively targeting oncogenic *RET* fusions and mutations, exhibits activity against V804 gatekeeper mutations, which confer resistance to multikinase inhibitors.⁷ Interim analyses of the phase I/II registrational ARROW trial (ClinicalTrials.gov identifier: [NCT03037385](https://clinicaltrials.gov/ct2/show/study/NCT03037385)) demonstrated pralsetinib's tolerability and efficacy at 400 mg once daily, supporting US Food and Drug Administration approval for treatment of metastatic *RET* fusion–positive NSCLC in adults and metastatic *RET* fusion–positive thyroid cancer.^{5,7–9} Herein, we

present final data in patients with *RET* fusion–positive NSCLC, adding 42 months of follow-up to the previously published analyses.

MATERIALS AND METHODS

Study Design

ARROW was an open-label, phase I/II study evaluating pralsetinib in adults with advanced *RET*-altered malignancies.^{7,8} Detailed methods were previously published.^{5,7,8} Study protocol and methodological details are provided in [Appendix 1](#) (online only).

Patients with *RET* fusion–positive, locally advanced, or metastatic NSCLC were enrolled. After a July 11, 2019, protocol amendment, both treatment-naïve and previously treated patients were enrolled regardless of eligibility for

TABLE 1. Baseline Characteristics in *RET* Fusion–Positive NSCLC (efficacy population)

Characteristic	Overall (N = 281) ^a	Treatment-Naïve (n = 116) ^b	Prior Platinum (n = 141)
Age, years, median (range)	60.0 (26-87)	62.5 (31-87)	59.0 (26-85)
Sex, male, No. (%)	129 (46)	55 (47)	67 (48)
Race			
White	130 (46)	57 (49)	57 (40)
Asian	128 (46)	52 (45)	71 (50)
Other ^c	5 (2)	1 (<1)	3 (2)
Smoking history, No. (%)			
Current/former	100 (36)	45 (39)	50 (35)
Never	176 (63)	68 (59)	89 (63)
Unknown	5 (2)	3 (3)	2 (1)
ECOG PS, No. (%)			
0	83 (30)	35 (30)	37 (26)
1	191 (68)	80 (69)	98 (70)
2 ^d	6 (2)	1 (<1)	5 (4)
NSCLC histologic type, No. (%)			
Adenocarcinoma	272 (97)	115 (99)	136 (96)
Squamous	3 (1)	1 (<1)	1 (<1)
Other ^e	6 (2)	0	4 (3)
Metastases identified at baseline, No. (%)			
History of brain metastases	97 (35)	34 (29)	55 (39)
Liver metastases	61 (22)	22 (19)	33 (23)
Previous lines of therapy, median (range)	2 (1-8)	0	2 (1-8)
Previous therapy type, No. (%)			
Platinum-based	141 (50)	0	141 (100)
Multikinase inhibitor	45 (16)	0	39 (28)
PD-(L)1 inhibitor	73 (26)	0	57 (40)
<i>RET</i> fusion partner, No. (%)			
<i>KIF5B</i>	197 (70)	81 (70)	98 (70)
<i>CCDC6</i>	50 (18)	19 (16)	27 (19)
<i>NCOA4</i>	2 (<1)	1 (<1)	1 (<1)
Other	32 (11)	15 (13)	15 (11)

Abbreviations: BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer.

^aData not shown for patients receiving prior nonplatinum systemic treatment (n = 24).

^bOne patient was deemed not to have measurable disease per the latest BICR data.

^cIncludes American Indian or Alaska Native, Black or African American, and Native Hawaiian or Other Pacific Islander. Race unknown for 18 patients.

^dECOG PS of 2 was permitted before protocol amendment in July 2018. ECOG PS not reported for one patient.

^eIncludes undifferentiated tumors.

platinum–based chemotherapy.⁵ Patients with eligible CNS metastases without progressive neurologic symptoms or need for corticosteroid increase for disease control were permitted. Participants received pralsetinib 400 mg orally once daily until disease progression, unacceptable toxicity, or consent withdrawal.

Efficacy and Safety Measures

Primary end points were overall response rate (ORR; assessed by blinded independent central review [BICR] per RECIST v1.1) and safety.^{5,10} Key secondary end points

included duration of response (DOR), clinical benefit rate (CBR; confirmed complete response, partial response, or stable disease for ≥16 weeks), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Intracranial response rate (CNS ORR) was assessed in patients with measurable CNS metastases.

Statistical Analyses

Final database lock was May 20, 2024, adding 42 months of follow-up beyond previously published analyses.⁵ PFS and OS were evaluated in the intention-to-treat/efficacy

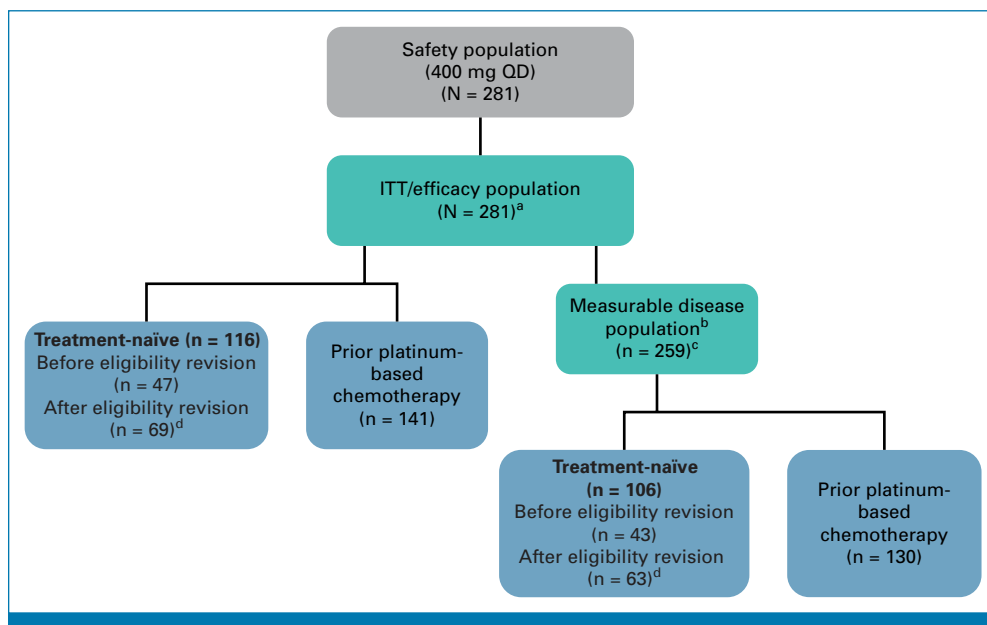


FIG 1. Patient disposition. ^aData not shown for patients receiving prior nonplatinum systemic treatment (n = 24). ^bSubset of ITT population with sufficient evidence of a *RET* fusion and centrally adjudicated baseline measurable disease (BICR per RECIST v1.1). ^cData not shown for patients receiving prior non-platinum systemic treatment (n = 23). ^dProtocol amendment in July 2019 expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted. BICR, blinded independent central review; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; QD, once daily.

population (identical to safety population), and ORR, DCR, CBR, and DOR were evaluated in the measurable disease population. Statistical analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

Ethics

Institutional review boards at each center approved the protocol; all participants provided written informed consent.

RESULTS

Patients

At database lock, 281 patients with *RET* fusion–positive NSCLC had enrolled and initiated pralsetinib 400 mg once daily (efficacy population; [Table 1](#), [Fig 1](#), [Appendix Table A1](#)). Forty-seven treatment-naïve patients enrolled before the eligibility revision (not candidates for platinum-based chemotherapy) and 69 treatment-naïve patients enrolled after the eligibility revision ([Appendix Table A1](#)). The measurable disease population included 259 patients with centrally adjudicated measurable disease at baseline ([Fig 1](#)).

Efficacy

ORR among treatment-naïve patients was 78% (95% CI, 69 to 86) and 63% (95% CI, 54 to 71) among patients receiving prior platinum-based chemotherapy ([Table 2](#)). CBR, DCR,

and DOR for treatment-naïve and prior platinum-based chemotherapy patients are shown in [Table 2](#), including by geographical region. Outcomes for treatment-naïve patients before and after eligibility revision are shown in [Appendix Table A2](#). ORR remained generally high in subgroups bearing the *RET* fusion partners *KIF5B* and *CCDC6* among both treatment-naïve and prior platinum-based chemotherapy patients ([Figs 2B](#) and [2C](#)). Among all patients, median DOR was reported to be longer in *CCDC6* (47.9 months; n = 36) versus *KIF5B* (13.1 months; n = 132).

Overall median OS was 44.3 months (95% CI, 30.9 to 53.1). Median OS was 62.4 months (95% CI, 44.3 to not reached) for patients in the United States, 29.6 months (95% CI, 21.1 to 46.0) in Europe, and 44.5 months (95% CI, 24.2 to 53.2) in Asia ([Table 2](#), [Fig 2A](#)). Overall median PFS was 13.1 months (95% CI, 11.4 to 16.8). Median PFS for patients in the United States was 25.9 months (95% CI, 14.7 to 43.3), 12.8 months (95% CI, 8.8 to 16.6) in Europe, and 12.6 months (95% CI, 9.2 to 15.2) in Asia ([Table 2](#)).

Fifteen patients had measurable CNS/brain metastases at baseline. Intracranial response rate (CNS ORR) was 53% (8/15; 95% CI, 27 to 79). In the 11 response-evaluable patients, CNS ORR was 73% (8/11; 95% CI, 39 to 94; [Appendix Table A3](#)).

Safety

In the safety population (N = 281), median treatment duration was 15.0 months. Common grade ≥ 3 treatment-related

TABLE 2. Efficacy Summary in *RET* Fusion–Positive NSCLC

Outcome	Overall	Treatment-Naïve ^a	Prior Platinum
Measurable disease population, No.	259 ^b	106	130
ORR, % (95% CI)	70 (64 to 76)	78 (69 to 86)	63 (54 to 71)
CR, No. (%)	18 (7)	8 (8)	9 (7)
PR, No. (%)	164 (63)	75 (71)	73 (56)
Regional ORR, % (95% CI)			
United States	n = 58	n = 19	n = 31
	78 (65 to 88)	100 (82 to 100)	65 (45 to 81)
Europe	n = 89	n = 43	n = 36
	65 (54 to 75)	65 (49 to 79)	64 (46 to 79)
Asia	n = 112	n = 44	n = 63
	71 (61 to 79)	82 (67 to 92)	62 (49 to 74)
CBR, % (95% CI)	77 (72 to 82)	80 (71 to 87)	75 (66 to 82)
DCR, % (95% CI)	91 (87 to 94)	90 (82 to 95)	92 (85 to 96)
DOR, median, months (95% CI) ^c	n = 182	n = 83	n = 82
	19.1 (14.5 to 27.9)	13.4 (9.4 to 21.7)	31.8 (15.1 to 40.4)
Follow-up, median, months (95% CI)	46.8 (42.3 to 50.2)	42.3 (37.4 to 44.2)	50.3 (46.9 to 56.8)
Efficacy population, No.	281 ^b	116	141
OS, median, months (95% CI)	44.3 (30.9 to 53.1)	50.1 (28.3 to NR)	39.7 (27.8 to 53.2)
Follow-up, median, months (95% CI)	47.6 (44.8 to 49.2)	43.7 (41.8 to 47.4)	49.7 (48.8 to 52.7)
Regional OS, median, months (95% CI)			
United States	n = 64	n = 22	n = 34
	62.4 (44.3 to NR)	NR (31.9 to NR)	47.7 (17.2 to NR)
Europe	n = 95	n = 46	n = 38
	29.6 (21.1 to 46.0)	28.3 (13.2 to NR)	36.9 (17.1 to NR)
Asia	n = 122	n = 48	n = 69
	44.5 (24.2 to 53.2)	NR (20.1 to NR)	35.3 (19.2 to 53.1)
PFS, median, months (95% CI) ^c	13.1 (11.4 to 16.8)	12.1 (9.2 to 16.6)	16.4 (11.4 to 23.5)
Follow-up, median, months (95% CI)	48.4 (44.1 to 49.2)	42.3 (39.6 to 48.2)	51.1 (49.0 to 56.4)
Regional PFS, median, months (95% CI)			
United States	n = 64	n = 22	n = 34
	25.9 (14.7 to 43.3)	42.5 (10.9 to NR)	22.1 (7.7 to 42.4)
Europe	n = 95	n = 46	n = 38
	12.8 (8.8 to 16.6)	11.6 (7.3 to 21.1)	16.4 (7.4 to 33.1)
Asia	n = 122	n = 48	n = 69
	12.6 (9.2 to 15.2)	9.2 (7.4 to 13.5)	12.8 (8.7 to 28.6)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; FDA, US Food and Drug Administration; NSCLC, non–small cell lung cancer; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

^aProtocol amendment in July 2019 expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

^bData not shown for patients receiving prior nonplatinum systemic treatment (n = 23). Similar responses were observed in these patients.

^cPer FDA censoring rule.

adverse events (TRAEs) were anemia (21%), hypertension (15%), and decreased neutrophils (13%; Appendix Table A4). Twenty-one (7%) patients experienced grade ≥ 3 severe infection TRAEs, including pneumonia (5%) and sepsis (1%). Two serious QT prolongation events occurred (<1%). No hypersensitivity reactions were noted in patients with prior immunotherapies.

Twenty-nine (10%) patients discontinued pralsetinib, and 144 (51%) experienced dose reductions due to TRAEs. Anemia and decreased neutrophil count were the most common AEs (any cause) leading to dose reductions, in 35 (12%) and 26 (9%) of patients, respectively. There were three treatment-related deaths associated with four TRAEs (all prior treatment-naïve patients in Asia), including

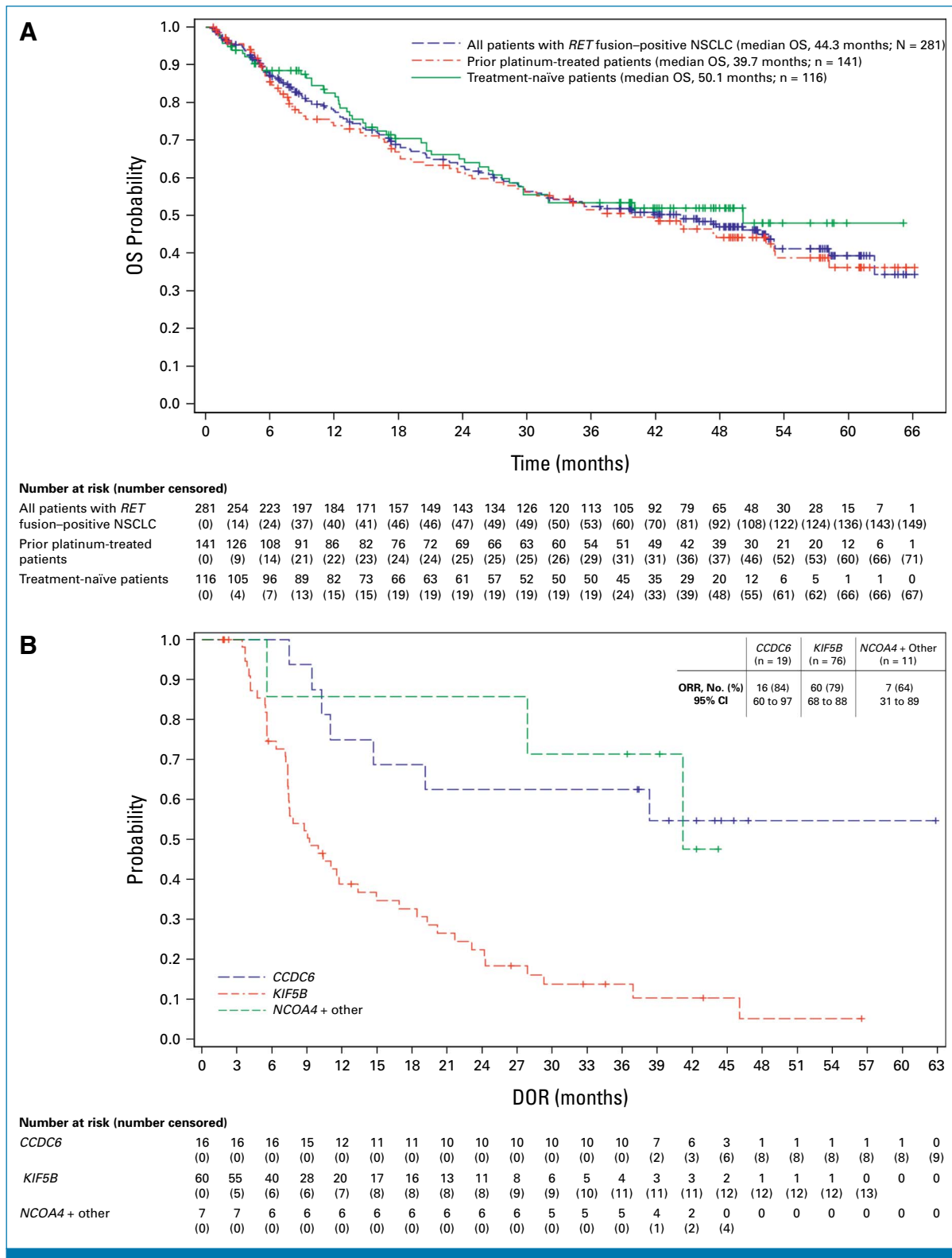


FIG 2. (A) OS in treatment-naïve and prior platinum-treated patients, and DOR by *RET* fusion partner in (B) treatment-naïve patients and (C) prior platinum-treated patients, with ORR shown in insets. (A) OS is shown for the measurable disease population. (B) ORR and DOR are shown for treatment-naïve patients in the measurable disease population; DOR is shown for responders only. (C) ORR and DOR are shown for prior platinum-treated patients in the measurable disease population; DOR shown for responders only. DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival. (continued on following page)

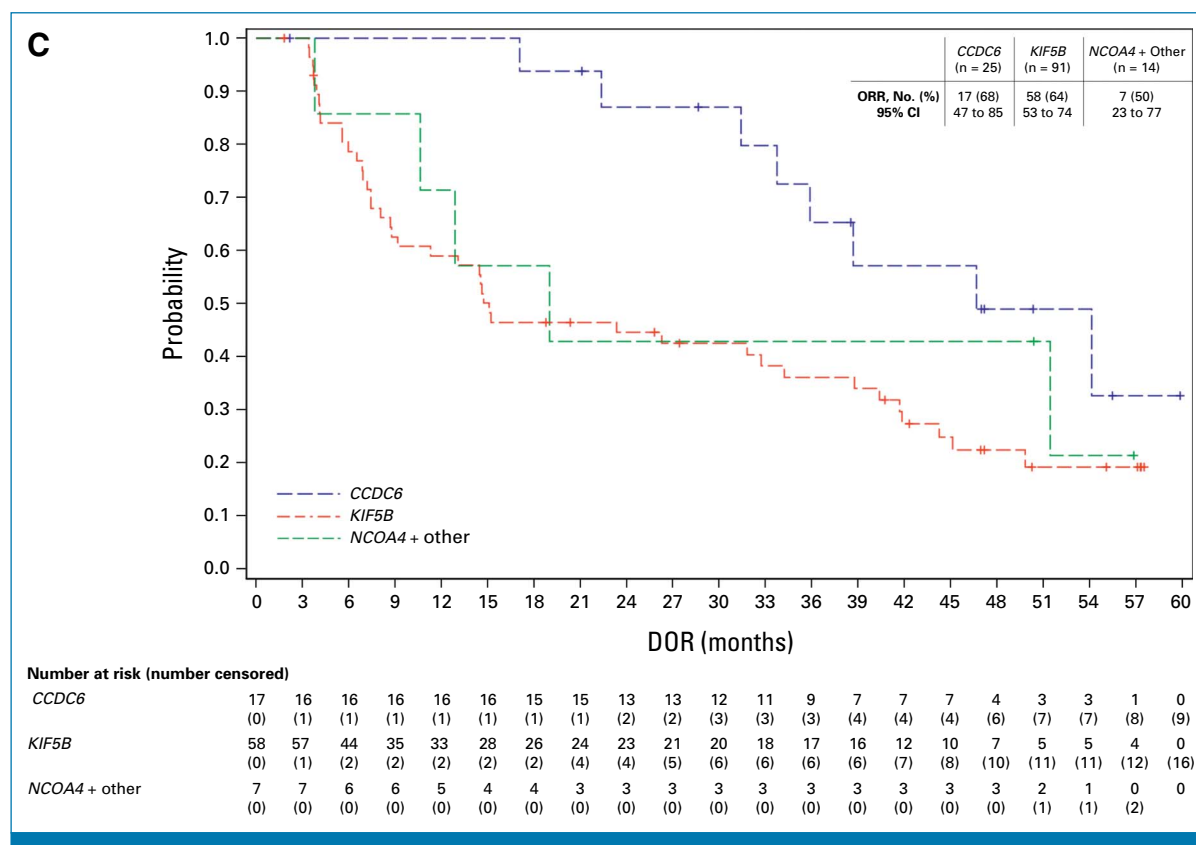


FIG 2. (Continued).

pneumonia (n = 2), interstitial lung disease (n = 1), and rhabdomyolysis (n = 1; Appendix Table A5).

DISCUSSION

We report final ARROW efficacy and safety analyses in patients with *RET* fusion–positive NSCLC. Consistent with previous ARROW reports,^{5,7} pralsetinib 400 mg once daily produced robust responses, including CNS activity, across treatment groups and a manageable toxicity profile, with no hypersensitivity reactions observed in patients receiving prior immunotherapies. Updated results demonstrate a median OS of 44.3 months overall, 50.1 months in treatment-naïve patients, and 39.7 months in prior platinum patients, with median follow-ups of 47.6, 43.7, and 49.7 months, respectively.

Before selective *RET* inhibitors were introduced, real-world studies reported median OS of 4.1–11.1 months in advanced/metastatic NSCLC.^{11–13} Improvements observed with ARROW extended follow-up reinforce the value of selective *RET* inhibition in this setting. NCCN guidelines now recommend selective *RET* inhibitors, including pralsetinib, as preferred first-line treatments for patients with advanced *RET* fusion–positive NSCLC.¹⁴

This analysis revealed regional differences, with patients in the United States (compared with Europe or Asia)

experiencing longer median PFS and OS, and a lower rate of deaths due to AEs (any cause) than European or Asian patients. Regional differences in site start-up timing, standards for supportive care or monitoring, and regulatory approvals may have influenced outcomes, but additional studies are needed to clarify driving factors.

The clinical relevance of *RET* fusion partners is unknown, although they influence prognosis and therapeutic efficacy. Among *RET* fusion–positive NSCLC patients treated with *RET* inhibitors, such as pralsetinib and selpercatinib, *KIF5B-RET* was associated with poorer survival and response outcomes than non-*KIF5B* partners, particularly *CCDC6*,^{15–18} which is consistent with shorter DOR in our cohort. One hypothesis is that *KIF5B-RET* yields higher *RET* expression than other partners, increasing *RET* oncoprotein burden.¹⁸

After additional follow-up, pralsetinib's safety profile remains characterized by toxicities that are manageable by dose modifications and standard supportive care. Although dose reductions occurred in approximately 50% of patients, most commonly to manage AEs of neutropenia and anemia, only 10% discontinued treatment for TRAEs.^{5,7} Some safety differences from selpercatinib have emerged, although cross-trial comparisons should be interpreted cautiously.^{6,19} Selpercatinib trials have shown lower rates of hematologic events but higher rates of liver enzyme elevations and QT

prolongation.^{9,19–22} No hypersensitivity was observed in patients exposed to prior immunotherapies; seliprecitinib has reported an incidence of 7% and higher (approximately 12%) in patients previously receiving immune checkpoint inhibitors.^{22,23}

Although the ARROW trial demonstrates pralsetinib's efficacy in *RET* fusion–positive NSCLC, the single-arm design limits interpretation and comparisons with other treatments. Small sample sizes, such as in the CCDC6 fusion partner subgroups, further limit the reliability of specific

conclusions. Interpretation is also limited by unavailability of data for comutations, including *TP53*.

In this final ARROW update, with an additional 42 months of follow-up, pralsetinib's safety profile remained consistent with previous ARROW reports. The selective oral *RET* inhibitor continues to deliver durable responses, intracranial activity, and manageable safety in advanced *RET* fusion–positive NSCLC.^{5,7} Our findings reinforce the importance of early biomarker testing, including gene fusions, in all patients with metastatic NSCLC to guide treatment.

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DISCLAIMER

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EQUAL CONTRIBUTION

B.B., V.S., and G.C. contributed equally to this work.

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CLINICAL TRIAL INFORMATION

[NCT03037385](https://clinicaltrials.gov/ct2/show/study/NCT03037385)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO-25-01489>.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-25-01489>.

For deidentified data, requests may be sent to datasharing@rigel.com at least 24 months after clinical trial completion, provided a scientifically valid research proposal is made by qualified, academic researchers for data associated with interventions that have received regulatory approval in the United States and Europe.

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APPENDIX 1. SUPPLEMENTAL METHODS

Patients and Study Design

ARROW was a multiple-cohort, multicenter, open-label, phase I/II study (ClinicalTrials.gov identifier: [NCT03037385](https://clinicaltrials.gov/ct2/show/study/NCT03037385)) designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of pralsetinib in patients with advanced nonresectable *RET*-altered tumors.^{7,8} Phase II evaluated pralsetinib 400 mg once daily in several cohorts defined by disease type and treatment history.⁷

In the *RET* fusion–positive non–small cell lung cancer (NSCLC) cohort, patients were age 18 years and older with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2 (limited to 0–1 after protocol amendment) and had pathologically documented, definitively diagnosed, locally advanced or metastatic nonresectable NSCLC, with an identified *RET* fusion and baseline measurable disease as per RECIST (version 1.1) guidelines.²⁴ Using local testing methods, including next-generation sequencing of tumor tissue or circulating tumor DNA in the blood, or via fluorescence in situ hybridization of tumor tissue, *RET* alterations were detected. Patients who presented with CNS metastases were eligible if they did not have progressive neurologic symptoms or the need for an increase of corticosteroids to control the disease. As of July 11, 2019, treatment-naïve patients were eligible for enrollment regardless of their eligibility for standard platinum-based chemotherapy. Before the amendment, only patients deemed ineligible for platinum-based chemotherapy by the investigator were eligible for the study.

Pralsetinib 400 mg once daily was continued until disease progression, unacceptable toxicity, consent withdrawal, or investigator's decision. Dose reductions below 100 mg once daily or interruptions lasting >28 days due to AEs were not permitted.

Ethics

The study adhered to the ethical standards outlined in the Declaration of Helsinki and followed Good Clinical Practice guidelines, as specified by International Council for Harmonisation E6.

Assessments

All disease sites were assessed by computerized tomography or magnetic resonance imaging at screening. Imaging was subsequently performed approximately every 8 weeks during study treatment. For patients who discontinued therapy in the absence of disease progression, assessments were conducted every 3–4 months after the last administered dose.

AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, and monitored through 30 days after the final dose of study medication. Safety laboratory evaluations were performed locally according to the protocol-defined schedule.

End Points

The primary end points in the phase II study were overall response rate (ORR, defined as complete response [CR] or partial response [PR] assessed by blinded independent central review [BICR] according to RECIST v1.1) and safety.^{5,10} Key secondary end points included duration of response (DOR, defined as the time from first response until disease progression or death), clinical benefit rate (CBR, defined as confirmed CR, PR, or stable disease maintained for at least 16 weeks), disease control rate (DCR, defined as CR, PR, or stable disease), progression-free survival (PFS, defined as the time from first dose to disease progression or death, whichever occurred first), and overall survival (OS, defined as the time from first dose to death from any cause). Intracranial response rate (CNS ORR) was assessed among patients with measurable (per RECIST v1.1) CNS metastases, with patients considered evaluable for response if they had a postbaseline assessment for target lesions. Dose intensity (mg/d) was calculated as cumulative dose divided by treatment duration. Relative dose intensity was the ratio of dose intensity to the planned dose intensity.

Statistical Analyses

Efficacy analyses were conducted on patients in the intention-to-treat/efficacy population treated at 400 mg once daily, including patients who had received prior platinum-based chemotherapy or were treatment-naïve (regardless of eligibility for standard platinum-based therapy).⁵ The efficacy population was the primary population for analysis of PFS and OS. The measurable disease population, a subset of the efficacy population with sufficient evidence of *RET* fusion and centrally adjudicated baseline measurable disease (BICR per RECIST v1.1), served as the primary population for analysis of ORR, DCR, CBR, and DOR. For this analysis, the safety and efficacy populations were identical.

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%, a sample size of approximately 170 was required for the *RET* fusion–positive, NSCLC, treatment-naïve cohort. For patients receiving prior platinum-based chemotherapy, a sample size of approximately 80 was estimated to provide >95% power at the two-sided significance level of .05 for testing the null hypothesis ORR of 23% versus the alternative ORR of 50%.

Two-sided 95% CIs were calculated using the exact binomial approach with the Clopper-Pearson method. DOR, PFS, and OS were calculated using Kaplan-Meier (K-M) methodology. Median durations of follow-up for these end points were determined using the reverse K-M method, and 95% CIs were derived using the Greenwood formula. Subgroup analyses were conducted for geographic region, *RET* fusion partner, and CNS/brain metastases. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

TABLE A1. Baseline Characteristics in Treatment-Naïve Patients With *RET* Fusion–Positive NSCLC

Characteristic	Efficacy Population Treatment-Naïve Patients		Measurable Disease Population Treatment-Naïve Patients	
	Before Eligibility Revision ^a (n = 47)	After Eligibility Revision (n = 69)	Before Eligibility Revision ^a (n = 43)	After Eligibility Revision (n = 63)
Age, years, median (range)	65.0 (31-87)	61.0 (31.0-87.0)	65.0 (31.0-87.0)	59 (31.0-83.0)
Sex, male, No. (%)	26 (55)	29 (42)	24 (56)	26 (41)
Race				
White	30 (64)	27 (39)	27 (63)	25 (40)
Asian	13 (28)	39 (57)	12 (28)	35 (56)
Other ^b	4 (9)	3 (4)	4 (9)	3 (5)
Smoking history, No. (%)				
Current/former	21 (45)	24 (35)	20 (47)	24 (38)
Never	25 (53)	43 (62)	22 (51)	38 (60)
Unknown	1 (2)	2 (3)	1 (2)	1 (2)
ECOG PS, No. (%)				
0	18 (38)	17 (25)	18 (42)	15 (24)
1	28 (60)	52 (75)	24 (56)	48 (76)
2 ^c	1 (2)	0 (0)	1 (2)	0 (0)
NSCLC histologic type, No. (%)				
Adenocarcinoma	46 (98)	69 (100)	42 (98)	63 (100)
Squamous	1 (2)	0	1 (2)	0
History of brain metastases, No. (%)	17 (36)	17 (25)	15 (35)	15 (24)
<i>RET</i> fusion partner, No. (%)				
<i>KIF5B</i>	33 (70)	48 (70)	31 (72)	45 (71)
<i>CCDC6</i>	5 (11)	14 (20)	5 (12)	14 (22)
<i>NCOA4</i>	0	1 (1)	—	—
Other	9 (19)	6 (9)	7 (16)	4 (6)

Abbreviations: BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer.

^aPublished previously in Griesinger et al (2022).⁵

^bIncludes American Indian or Alaska Native, Black or African American, and Native Hawaiian or Other Pacific Islander.

^cECOG PS of 2 was permitted before protocol amendment in July 2018.

TABLE A2. Efficacy in Treatment-Naïve Patients With *RET* Fusion–Positive NSCLC Before and After Eligibility Revision

Outcome	Before Eligibility Revision	After Eligibility Revision
Measurable disease population, No.	43	63 ^a
ORR, % (95% CI)	74 (59 to 87)	81 (69 to 90)
CR, No. (%)	5 (12)	3 (5)
PR, No. (%)	27 (63)	48 (76)
CBR, % (95% CI)	79 (64 to 90)	81 (69 to 90)
DCR, % (95% CI)	91 (78 to 97)	89 (78 to 95)
DOR, median, months (95% CI) ^b	n = 32 14.7 (7.3 to 27.9)	n = 51 12.6 (8.7 to 24.2)
Follow-up, median, months (95% CI)	42.9 (36.4 to NR)	42.4 (34.6 to 44.2)
Efficacy population, No.	47	69
OS, median, months (95% CI)	NR (26.4 to NR)	29.6 (23.7 to NR)
Follow-up, median, months (95% CI)	47.6 (17.1 to 52.5)	42.6 (40.1 to 46.4)
Median PFS, months (95% CI) ^b	9.9 (7.3 to 20.1)	12.7 (9.2 to 22.1)
Follow-up, median, months (95% CI)	41.9 (16.6 to 58.0)	44.1 (39.4 to 47.3)

NOTE. Protocol amendment in July 2019 expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

Abbreviations: BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; FDA, US Food and Drug Administration; NSCLC, non–small cell lung cancer; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

^aOne patient was deemed not to have measurable disease per the latest BICR data.

^bPer FDA censoring rule.

TABLE A3. Efficacy in Patients With *RET* Fusion–Positive Non–Small Cell Lung Cancer With CNS/Brain Metastases (measurable disease population)

Outcome	Patients With CNS/Brain Metastases (n = 15 ^a)	Response-Evaluable Patients With CNS/Brain Metastases (n = 11)
CNS ORR, % (95% CI)	53 (27 to 79)	73 (39 to 94)
CR, No. (%)	3 (20)	3 (27)
PR, No. (%)	5 (33)	5 (45)
CBR, % (95% CI)	60 (32 to 84)	82 (48 to 98)
DCR, % (95% CI)	73 (45 to 92)	100 (72 to 100)
Median DOR, months (95% CI) ^b	14.8 (10.5 to NR)	14.8 (10.5 to NR)
Follow-up, median, months (95% CI)	59.1 (15.5 to 59.1)	59.1 (15.5 to 59.1)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; FDA, US Food and Drug Administration; NR, not reached; NSCLC, non–small cell lung cancer; ORR, overall response rate; PR, partial response.

^aTreatment-naïve, n = 1; prior platinum, n = 13; prior nonplatinum systemic treatment, n = 1.

^bPer FDA censoring rule.

TABLE A4. Most Common TRAEs Occurring in Patients With *RET* Fusion–Positive Non–Small Cell Lung Cancer (any grade ≥20% overall; safety population)

TRAE	Any Grade, No. (%)			Grade ≥3, No. (%)		
	Overall (N = 281 ^a)	Treatment-Naïve (n = 116)	Prior Platinum (n = 141)	Overall (N = 281 ^a)	Treatment-Naïve (n = 116)	Prior Platinum (n = 141)
AST increased	128 (46)	52 (45)	68 (48)	11 (4)	3 (3)	6 (4)
Anemia	121 (43)	52 (45)	59 (42)	59 (21)	29 (25)	26 (18)
ALT increased	98 (35)	44 (38)	48 (34)	9 (3)	2 (2)	5 (4)
Neutrophils decreased	87 (31)	40 (34)	42 (30)	37 (13)	18 (16)	17 (12)
Hypertension	77 (27)	29 (25)	42 (30)	41 (15)	17 (15)	22 (16)
WBC decreased	77 (27)	35 (30)	39 (28)	15 (5)	8 (7)	7 (5)
Constipation	73 (26)	36 (31)	33 (23)	2 (<1)	0	2 (1)
Neutropenia	61 (22)	19 (16)	35 (25)	25 (9)	5 (4)	17 (12)

Abbreviation: TRAE, treatment-related adverse event.

^aData not shown for patients receiving prior nonplatinum systemic treatment (n = 24).

TABLE A5. Treatment Discontinuations Due to TRAEs and TEAEs Leading to Death in Patients With *RET* Fusion–Positive Non–Small Cell Lung Cancer by Region (safety population)

TRAE Outcome	United States (n = 64)	Europe (n = 95)	Asia (n = 122)
Discontinuations due to TRAEs, No. (%)	12 (19)	22 (23)	37 (30)
Deaths due to TRAEs, No. (%)	0	0	3 (2) ^a
Deaths due to TEAEs (any cause), No. (%)	8 (13)	16 (17)	25 (20)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

^aOne patient had two TRAEs leading to death.