Safety and efficacy of pralsetinib in patients with advanced *RET* fusion–positive non-small cell lung cancer: update from the ARROW trial

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Background and methods

- Rearranged during transfection (*RET*) fusions are targetable oncogenic drivers in 1–2% of non-small cell lung cancer (NSCLC)[1–4]
- The phase 1/2 registrational ARROW study (NCT03037385) supported FDA approval of pralsetinib, a highly potent, oral, selective RET inhibitor, in patients with metastatic *RET* fusion–positive NSCLC and advanced/metastatic *RET*-altered thyroid cancers[5]
- Findings from the registrational dataset for patients with advanced *RET* fusion–positive NSCLC enrolled in ARROW were presented at ASCO 2020[6]
- Initially, all treatment-naïve patients with advanced *RET* fusion–positive NSCLC were required per-protocol to not be candidates for standard platinum-based therapy, generally due to age, comorbidities, or other poor prognostic factors
  - Eligibility criteria were expanded by a protocol amendment in July 2019, allowing enrollment of treatment-naïve patients who were candidates for standard platinum-based therapy, to provide a study population more representative of the real-world population
- In this update we provide longer follow-up with a focus on treatment-naïve patients with *RET* fusion–positive NSCLC enrolled in the ARROW study before and after the eligibility revision

ARROW study design

Eligibility criteria
- Age ≥18 years
- Advanced or metastatic solid tumor
- *RET* alteration per local assessment
- Measurable disease (RECIST v1.1)
- ECOG PS 0–1

Protocol amendment (July 19, 2019)
Eligibility criteria were expanded to allow treatment-naïve patients with NSCLC who were candidates for platinum-based therapy

Phase 1 dose escalation (Completed)
Phase 2 dose determined: 400 mg QD

Phase 2 dose expansion (Ongoing)
Treated at 400 mg QD

RET fusion–positive NSCLC

Medullary thyroid cancer[a]

Other *RET*-altered tumors

1º endpoints:
- ORR (BICR per RECIST v1.1)
- Safety

Key 2º endpoints:
- DOR
- CBR
- DCR
- PFS
- OS

[a]Patients with medullary thyroid cancer did not require documented *RET* mutations for enrollment.
BICR, blinded independent central review; CBR, clinical benefit rate (CR or PR or SD of ≥16 weeks); CR, complete response; DCR, disease control rate (confirmed CR or PR or SD); DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection; SD stable disease.

Results

Patient disposition/analysis populations

Safety population, N=471[a]
Patients who received pralsetinib at the RP2D of 400 mg QD

RET fusion–positive NSCLC n=233

Other *RET*-altered solid tumors n=238

RET fusion–positive NSCLC Measurable disease population[b] n=216

115 discontinued treatment
- 70 disease progression
- 30 adverse event
  - 14 treatment-related
- 15 other[c]

101 continuing treatment

Data presented for patients enrolled between March 17, 2017, and May 22, 2020

Data cut-off date of November 6, 2020

Median follow-up: 17.1 months

[a]Includes all patients enrolled by May 22, 2020 (enrollment cut-off) in dose escalation (phase 1) and dose expansion (phase 2) who received 400 mg QD pralsetinib with any tumor type. [b]Subset of patients in the efficacy population with sufficient evidence of a *RET* fusion and baseline measurable disease confirmed on blinded independent central review. [c]Other reasons for discontinuation were withdrawn consent (n=10), investigator's decision (n=3), and administrative reason/other (n=2). RP2D, recommended phase 2 dose.

Baseline characteristics

	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
Median age (range), years	60 (26–87)	61 (30–87)	65 (30–87)	54 (35–80)	60 (26–85)	61 (47–84)
Male, n (%)	104 (48)	35 (51)	24 (56)	11 (44)	62 (49)	7 (32)
Race, n (%)						
White	113 (52)	48 (71)	27 (63)	21 (84)	51 (40)	14 (64)
Asian	83 (38)	14 (21)	12 (28)	2 (8)	64 (51)	5 (23)
Other/unknown	20 (9)	6 (9)	4 (9)	2 (8)	11 (9)	3 (14)
Smoking history, n (%)						
Current/former	80 (37)	31 (46)	20 (47)	11 (44)	45 (36)	4 (18)
Never	133 (62)	36 (53)	22 (51)	14 (56)	79 (63)	18 (82)
ECOG PS, n (%)						
0	73 (34)	29 (43)	18 (42)	11 (44)	34 (27)	10 (45)
1	137 (63)	38 (56)	24 (56)	14 (56)	87 (69)	12 (55)
2[b]	6 (3)	1 (1)	1 (2)	0	5 (4)	0
Brain metastases, n (%)[c]	82 (38)	22 (32)	15 (35)	7 (28)	52 (41)	8 (36)
Prior therapy type, n (%)						
Platinum-based	126 (58)	0	0	0	126 (100)	0
Multikinase inhibitor	40 (19)	0	0	0	34 (27)	6 (27)
PD-(L)1 inhibitor	66 (31)	0	0	0	52 (41)	14 (64)

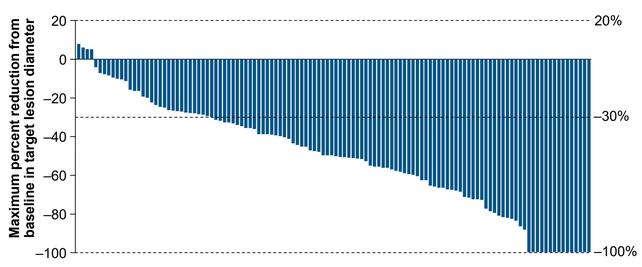
[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted. [b]ECOG PS of 2 was permitted prior to protocol amendment in July 2018. [c]History of or current.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death/programmed cell death ligand-1.

Efficacy summary (blinded independent central review)

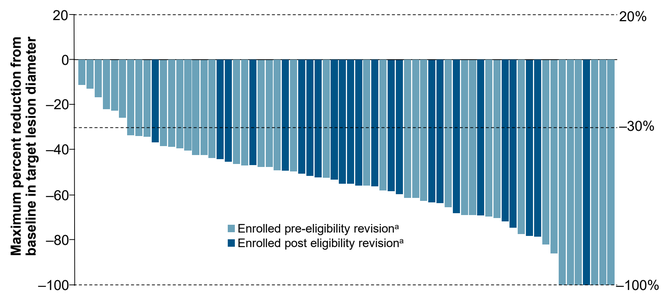
	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69** (62–75)	**79** (68–88)	**74** (59–87)	**88** (69–98)	**62** (53–70)	**73** (50–89)
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–98)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve 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.
CI, confidence interval; mDOR, median duration of response; mo, month; NE, not evaluable; NR, not reached; PD, progressive disease.

Tumor shrinkage in patients with prior platinum-based chemotherapy

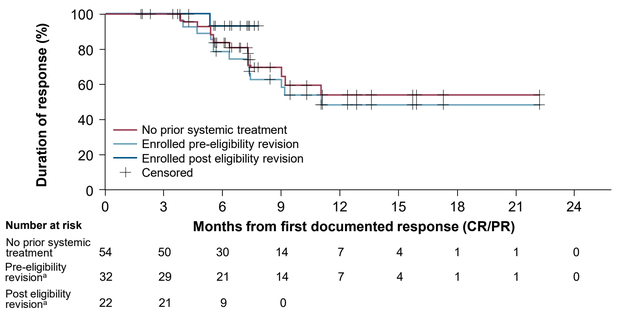


Tumor shrinkage in treatment-naïve patients



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

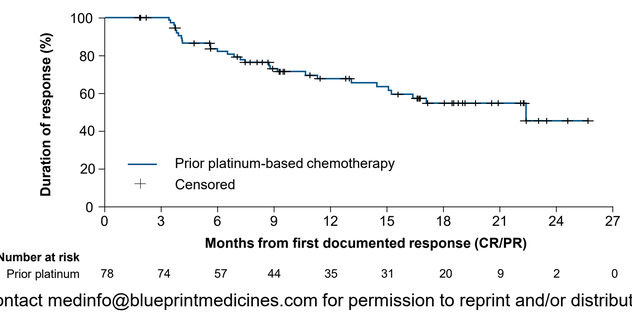
Duration of response in treatment-naïve patients



Number at risk									
No prior systemic treatment	54	50	30	14	7	4	1	1	0
Pre-eligibility revision[a]	32	29	21	14	7	4	1	1	0
Post eligibility revision[a]	22	21	9	0					

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

Duration of response in patients with prior platinum-based chemotherapy



Number at risk										
Prior platinum	78	74	57	44	35	31	20	9	2	0

Treatment-related adverse events

AE, %	*RET* fusion–positive NSCLC (n=233)		All patients (N=471)[a]	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia[b]	42	20	40	19
AST increased	39	3	39	3
Anemia[b]	38	13	35	13
White blood cell count decreased[b]	30	7	32	8
ALT increased	27	3	28	2
Hypertension[b]	25	12	26	12
Asthenia[b]	25	2	25	3
Constipation	24	1	26	1
Lymphopenia[b]	16	9	18	11
Diarrhea	16	1	16	1
Blood creatinine increased	15	0	15	0
Dysgeusia	15	0	14	0
Thrombocytopenia[b]	15	4	15	4
Dry mouth	15	0	13	0
Blood creatine phosphokinase increased	14	5	14	6
Edema[b]	13	0	14	0
Pneumonitis[b]	13	2	11	3
Hyperphosphatemia	11	0	17	0

Treatment-related AEs of any grade reported in ≥10% of patients in either the *RET* fusion–positive population (n=233) or the entire safety population (N=471) that received 400 mg QD pralsetinib on or before the May 22, 2020, enrollment cut-off.
[a]All patients (N=471) includes patients with other tumor types (including MTC irrespective of mutation status) who received pralsetinib 400 mg QD. [b]Grouped term.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTC, medullary thyroid cancer.

- A total of 26 of 471 patients (6%) in the overall safety population (all tumor types) discontinued due to treatment-related AEs
- Treatment-related neutropenia leading to treatment interruption or dose reduction was reported in 72 (15%) and 64 (14%) patients (all tumor types), respectively
- Only 2 (<1%) patients discontinued treatment due to treatment-related neutropenia (all tumor types)

Conclusions

- Pralsetinib is a well-tolerated once-daily oral treatment option for patients with *RET* fusion–positive metastatic NSCLC, with a safety profile consistent with previous reports and no new safety signals
- With a longer overall follow-up (17.1 months vs 8.8 months in previous analysis),[6] pralsetinib showed robust, durable responses across all *RET* fusion–positive NSCLC treatment groups
- Notably, ORR was 88% in the post eligibility revision subset, which included treatment-naïve patients who were otherwise eligible for standard platinum-based therapy, providing support for RET inhibitors as first-line standard of care
- These data solidify the importance of early biomarker testing for all patients with metastatic NSCLC prior to treatment initiation to inform optimal healthcare decisions
- Pralsetinib is currently approved for the treatment of metastatic *RET* fusion–positive NSCLC and advanced or metastatic *RET*-altered thyroid cancers in the USA,[5] and in locally advanced or metastatic NSCLC after platinum-based chemotherapy in China[7]

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