Updated efficacy and safety data from the phase I/II ARROW study of pralsetinib in patients (pts) with advanced *RET* fusion+ non-small cell lung cancer (NSCLC)

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BACKGROUND

- Pralsetinib is approved by the FDA and EMA for the treatment of advanced *RET* fusion-positive NSCLC[1,2] based on the global multicohort, open-label, phase I/II ARROW study (NCT03037385)[3]
- Prior results from ARROW show that pralsetinib has promising anti-tumour activity with a manageable safety profile in advanced *RET* fusion-positive NSCLC[3]
- Here, we present updated data from the *RET* fusion-positive NSCLC cohort after an additional 16 months of follow-up since the previous analysis

METHODS

- Phase I of ARROW established the recommended phase II dose of pralsetinib as 400 mg once daily
- In the *RET* fusion-positive NSCLC cohort, patients aged ≥18 years with ECOG PS 0–2 (limited to 0–1 after a protocol amendment) and locally documented *RET* fusions received pralsetinib until disease progression, intolerance or withdrawal
- Prior to 11 July 2019, only treatment-naïve patients who were not candidates for standard platinum-based chemotherapy as determined by the investigator were eligible for enrolment; the eligibility criteria were expanded to include all treatment-naïve patients (both patients eligible and ineligible for standard systemic therapy)
- Primary endpoints in phase II were overall response rate (ORR; blinded independent central review [BICR] per RECIST v1.1) and safety
- Key secondary endpoints in phase II were duration of response (DOR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS)

RESULTS

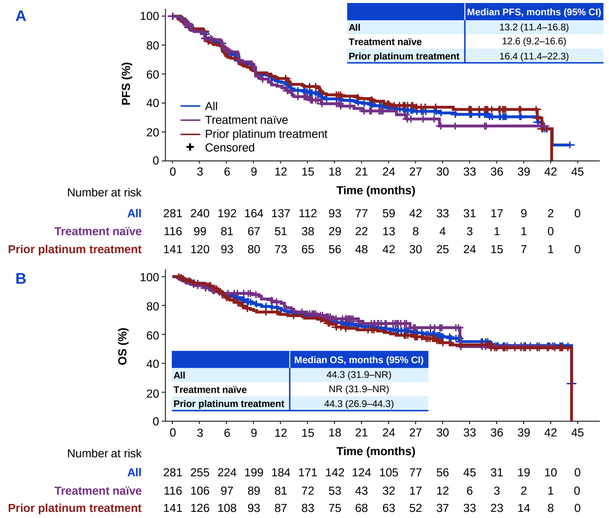
- At the updated data cut-off of 4 March 2022, 281 patients with *RET* fusion-positive NSCLC had received pralsetinib 400 mg (efficacy population), of whom 260 had measurable disease at baseline per BICR (measurable disease population)

Table 1. Baseline characteristics

n (%)	Measurable disease population: All (n=260)	Measurable disease population: Treatment naïve (n=107)	Measurable disease population: Prior platinum treatment (n=130)	Efficacy population: All (n=281)	Efficacy population: Treatment naïve (n=116)	Efficacy population: Prior platinum treatment (n=141)
Age, years						
<65 years	164 (63.1)	64 (59.8)	85 (65.4)	176 (62.6)	67 (57.8)	93 (66.0)
Male	121 (46.5)	50 (46.7)	64 (49.2)	129 (45.9)	55 (47.4)	67 (47.5)
Race						
White	119 (45.8)	52 (48.6)	52 (40.0)	130 (46.3)	57 (49.1)	57 (40.4)
Asian	118 (45.4)	48 (44.9)	65 (50.0)	128 (45.6)	52 (44.8)	71 (50.4)
Other	23 (8.8)	7 (6.5)	13 (10.0)	2 (0.7)	0	2 (1.4)
Smoking history						
Current/former	95 (36.5)	44 (41.1)	47 (36.2)	100 (35.6)	45 (38.8)	50 (35.5)
Never	161 (61.9)	61 (57.0)	81 (62.3)	176 (62.6)	68 (58.6)	89 (63.1)
Unknown	4 (1.5)	2 (1.9)	2 (1.5)	5 (1.8)	3 (2.6)	2 (1.4)
ECOG PS						
0	78 (30.0)	33 (30.8)	34 (26.2)	83 (29.5)	35 (30.2)	37 (26.2)
1	175 (67.3)	73 (68.2)	90 (69.2)	191 (68.0)	80 (69.0)	98 (69.5)
2	6 (2.3)	1 (<1)	5 (3.8)	6 (2.1)	1 (<1)	5 (3.5)
Brain metastases	91 (35.0)	30 (28.0)	53 (40.8)	97 (34.5)	34 (29.3)	55 (39.0)
Prior therapy type						
Platinum-based	130 (50.0)	0	130 (100)	141 (50.2)	0	141 (100)
Multikinase inhibitor	41 (15.8)	0	35 (26.9)	45 (16.0)	0	39 (27.7)
PD-(L)1 inhibitor	69 (26.5)	0	54 (41.5)	73 (26.0)	0	57 (40.4)
***RET* fusion**						
KIF5B	184 (70.8)	76 (71.0)	91 (70.0)	197 (70.1)	81 (69.8)	98 (69.5)
CCDC6	48 (18.5)	19 (17.8)	25 (19.2)	50 (17.8)	19 (16.4)	27 (19.1)
NCOA4	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)	1 (<1)
Other	27 (10.4)	12 (11.2)	13 (10.0)	32 (11.4)	15 (12.9)	15 (10.6)

PD-(L)1, programmed cell death protein-1 or programmed cell death ligand-1.

Figure 1. PFS[a] (A) and OS (B) in the efficacy population



[a]Per FDA censoring rule.
Median OS follow up: 26.8 months (95% CI 25.1–27.7) (All); 22.1 months (95% CI 19.4–24.5) (Treatment naïve); 29.4 months (95% CI 27.7–35.0) (Prior platinum treatment)

Table 3. CNS efficacy

	All (n=15)
CNS ORR, % (95% CI)	53.3 (26.6–78.7)
Complete response, n (%)	3 (20.0)
Partial response, n (%)	5 (33.3)
	n=8
Median DOR, months (95% CI)[a]	11.5 (9.2–NR)
Median follow-up (95% CI)	29.7 (24.1–35.3)

Of the 15 patients, 14 had prior platinum treatment and 1 was treatment naïve. [a]Per EMA censoring rule.

Table 2. Efficacy summary

	Measurable disease population: All (n=260)	Measurable disease population: Treatment naïve: Pre-eligibility revision (n=43)	Measurable disease population: Treatment naïve: Post eligibility revision (n=64)	Measurable disease population: Prior platinum treatment (n=130)	Efficacy population: All (n=281)	Efficacy population: Treatment naïve: Pre-eligibility revision (n=47)	Efficacy population: Treatment naïve: Post eligibility revision (n=69)	Efficacy population: Prior platinum treatment (n=141)
ORR, % (95% CI)	70.0 (64.0–75.5)	74.4 (58.8–86.5)	79.7 (67.8–88.7)	63.1 (54.2–71.4)	65.8 (60.0–71.4)	68.1 (52.9–80.9)	75.4 (63.5–84.9)	59.6 (51.0–67.7)
Complete response, n (%)	15 (5.8)	4 (9.3)	3 (4.7)	8 (6.2)	18 (6.4)	4 (8.5)	4 (5.8)	10 (7.1)
Partial response, n (%)	167 (64.2)	28 (65.1)	48 (75.0)	74 (56.9)	167 (59.4)	28 (59.6)	48 (69.6)	74 (52.5)
CBR, % (95% CI)	77.3 (71.7–82.3)	79.1 (64.0–90.0)	81.3 (69.5–89.9)	74.6 (66.2–81.8)	77.2 (71.9–82.0)	74.5 (59.7–86.1)	82.6 (71.6–90.7)	75.2 (67.2–82.1)
DCR, % (95% CI)	91.2 (87.0–94.3)	90.7 (77.9–97.4)	90.6 (80.7–96.5)	91.5 (85.4–95.7)	90.4 (86.3–93.6)	87.2 (74.3–95.2)	91.3 (82.0–96.7)	90.8 (84.7–95.0)
	n=182	n=32	n=51	n=82	n=185	n=32	n=52	n=84
Median DOR, months (95% CI)[a]	19.1 (14.5–27.9)	14.7 (7.4–27.9)	12.6 (9.4–NR)	38.8 (14.8–40.4)	19.1 (14.5–27.3)	14.7 (7.4–27.9)	13.4 (9.4–NR)	23.4 (14.8–39.4)
Median follow-up (95% CI)	23.9 (21.4–27.6)	27.6 (21.2–30.2)	17.4 (14.3–20.3)	29.3 (24.1–33.1)	24.1 (21.6–27.6)	27.6 (21.2–30.2)	17.4 (14.3–20.3)	31.4 (25.3–33.1)
Median PFS, months (95% CI)[b]	13.1 (11.0–16.7)	11.0 (9.0–24.9)	12.6 (9.2–21.1)	14.5 (10.5–22.1)	13.2 (11.4–16.8)	10.9 (7.7–20.1)	13.2 (9.2–21.1)	16.4 (11.4–22.3)
Median follow-up (95% CI)	26.1 (23.8–28.1)	29.0 (18.2–34.7)	19.7 (15.9–22.1)	29.3 (26.6–34.9)	25.8 (23.8–27.7)	29.0 (16.6–34.7)	19.7 (15.9–22.1)	28.1 (26.1–34.9)

The measurable disease population was the primary population for analysis of ORR, CBR, DCR and DOR and the efficacy population was the primary population for analysis of PFS and OS. [a]DOR for the measurable disease population per FDA censoring rule and DOR for the efficacy population per EMA censoring rule; [b]PFS for the measurable disease and efficacy populations per FDA censoring rule.
CI, confidence interval; NR, not reached.

Safety

- In the safety population (n=281), median treatment duration was 15.0 months with a median relative dose intensity of 86.1%
- Overall, 10% of patients discontinued pralsetinib due to treatment-related adverse events (TRAEs)

Table 4. Safety summary

n=281, n (%)	Any causality: Any grade	Any causality: Grade ≥3	Treatment related: Any grade	Treatment related: Grade ≥3
Patients with any AE	280 (99.6)	231 (82.2)	265 (94.3)	176 (62.6)
Anaemia	151 (53.7)	65 (23.1)	119 (42.3)	55 (19.6)
AST increased	137 (48.8)	18 (6.4)	125 (44.5)	11 (3.9)
Constipation	125 (44.5)	2 (<1)	76 (27.0)	2 (<1)
Hypertension	103 (36.7)	50 (17.8)	75 (26.7)	39 (13.9)
ALT increased	101 (35.9)	13 (4.6)	92 (32.7)	9 (3.2)
Neutrophil count decreased	88 (31.3)	40 (14.2)	87 (31.0)	37 (13.2)
Diarrhoea	84 (29.9)	7 (2.5)	50 (17.8)	3 (1.1)
Cough	81 (28.8)	1 (<1)	15 (5.3)	1 (<1)
Pyrexia	81 (28.8)	2 (<1)	22 (7.8)	0
White blood cell count decreased	77 (27.4)	16 (5.7)	74 (26.3)	15 (5.3)
Fatigue	75 (26.7)	6 (2.1)	46 (16.4)	5 (1.8)
Blood creatinine increased	70 (24.9)	2 (<1)	48 (17.1)	1 (<1)
Neutropenia	64 (22.8)	30 (10.7)	60 (21.4)	26 (9.3)
Dyspnoea	62 (22.1)	8 (2.8)	5 (1.8)	1 (<1)
Pneumonia	56 (19.9)	36 (12.8)	18 (6.4)	12 (4.3)

The table includes AEs which occurred in ≥20% of patients.
AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 5. TRAEs by history of immune checkpoint inhibitor treatment

n=281, n (%)	Any grade: Prior PD-(L)1 treatment (n=73)	Any grade: Treatment naïve (n=116)	Grade ≥3: Prior PD-(L)1 treatment (n=73)	Grade ≥3: Treatment naïve (n=116)
Neutropenia	33 (45.2)	55 (47.4)	14 (19.2)	22 (19.0)
Anaemia	30 (41.1)	54 (46.6)	15 (20.5)	25 (21.6)
AST increased	28 (38.4)	51 (44.0)	4 (5.5)	3 (2.6)
Leukopenia	25 (34.2)	50 (43.1)	7 (9.6)	10 (8.6)
ALT increased	22 (30.1)	41 (35.3)	4 (5.5)	2 (1.7)
Hypertension	22 (30.1)	28 (24.1)	8 (11.0)	16 (13.8)
Fatigue	21 (28.8)	35 (30.2)	2 (2.7)	1 (<1)
Blood creatinine increased	18 (24.7)	18 (15.5)	0	1 (<1)
Constipation	15 (20.5)	36 (31.0)	1 (1.4)	0

The table includes grouped AE terms which occurred in ≥20% of patients.

CONCLUSIONS

With additional follow-up, pralsetinib demonstrated robust and durable clinical activity in patients with advanced *RET* fusion-positive NSCLC, including systemic treatment-naïve patients.

No new or unexpected safety findings emerged from this updated data cut with a low discontinuation rate due to TRAEs.

Disclosures
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