Abstract 6080 / Poster 72

Pralsetinib in patients with advanced or metastatic *RET*-altered thyroid cancer: updated data from the ARROW trial

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BACKGROUND

- Oncogenic *RET* alterations are common in thyroid cancers and are therapeutically targetable.[1]
- Current treatment options for patients with advanced thyroid cancer include the multikinase inhibitors cabozantinib and vandetanib for medullary thyroid cancer (MTC), and cabozantinib, lenvatinib and sorafenib for differentiated thyroid cancer; these are often associated with dose reduction or discontinuation of treatment due to adverse events.[2–4]
- Pralsetinib is a highly potent, selective *RET* inhibitor.[1]
- Pralsetinib at 400 mg once-daily (QD) has demonstrated clinical activity in patients with *RET*-altered thyroid cancer and measurable disease at baseline in the phase I/II ARROW trial (NCT03037385; data cut-off: 22 May 2020)[5]
  - Overall response rates (ORR) by blinded independent central review (BICR): 60% (n=33/55) in patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib (C/V), 71% (n=15/21) in patients with treatment-naïve *RET*-mutant MTC, and 89% (n=8/9) in patients with previously treated *RET* fusion-positive thyroid cancer (*RET*-fp TC).
- We present updated data of these cohorts in the **intention-to-treat (ITT) population** (**data cut-off: 12 April 2021**).

METHODS

- Adult patients with *RET*-altered locally advanced/metastatic thyroid cancer, who had enrolled in ARROW and initiated oral pralsetinib at 400 mg QD, were included (enrollment cut-off: 23 August 2020).
- **Phase II primary endpoints: ORR by BICR** per RECIST v1.1, and safety; key secondary endpoints include: duration of response (DoR), progression-free survival (PFS), and overall survival (OS)
  - ORR and DoR: evaluated in both the measurable disease and the ITT populations; PFS and OS: assessed only in the ITT population
  - Safety was evaluated in all patients with *RET*-altered thyroid cancer who initiated pralsetinib at 400 mg QD prior to the data cut-off.

RESULTS

Patient characteristics

- At data cut-off (12 April 2021), the ITT population comprised 145 patients with *RET*-mutant MTC (with/without prior systemic therapy, including C/V), and 22 patients with *RET*-fp TC, of which 21 had received prior systemic therapy, including radioactive iodine (**Table 1**)
  - Treatment-naïve patients had received no prior systemic therapy.

Table 1. Patient demographics and baseline characteristics (ITT population)

	RET-mutant MTC: prior C/V (n=67)	*RET*-mutant MTC: treatment naïve (n=67)	*RET*-fp TC: prior systemic treatment (n=21)
Median age, years (range)	59 (25–83)	55 (18–81)	61 (23–74)
Male, n (%)	44 (65.7)	43 (64.2)	9 (42.9)
Race group, n (%)			
White / Asian	55 (82.1) / 3 (4.5)	27 (40.3) / 37 (55.2)	15 (71.4) / 6 (28.6)
Other	9 (13.4)	3 (4.5)	0
ECOG performance status, n (%)			
0	18 (26.9)	38 (56.7)	9 (42.9)
1	46 (68.7)	29 (43.3)	12 (57.1)
2*	3 (4.5)	0	0
Prior systemic therapy in any setting, n (%)			
Chemotherapy / immunotherapy	7 (10.4) / 3 (4.5)	*No prior antineoplastic treatment*	1 (4.8) / 0
C/V / L/S	67 (100) / 5 (7.5)		3 (14.3) / 11 (52.4)
Radioactive iodine	4 (6.0)		20 (95.2)
Number of prior lines of therapy, n (%)			
1 / 2	31 (46.3) / 24 (35.8)	*No prior antineoplastic treatment*	8 (38.1) / 4 (19.0)
≥3	12 (17.9)		9 (42.9)
CNS/brain metastases	7 (10.4)	6 (9.0)	9 (42.9)

*ECOG performance status of 2 was permitted before a protocol amendment. C/V, cabozantinib and/or vandetanib; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; L/S, lenvatinib and/or sorafenib; MTC, medullary thyroid cancer; *RET*-fp TC, *RET* fusion-positive thyroid cancer.

Table 2. Overall efficacy

	Measurable disease population			Intention-to-treat population		
	RET-mutant MTC: prior C/V (n=61)	*RET*-mutant MTC: treatment naïve (n=62)	*RET*-fp TC: prior systemic treatment (n=19)	*RET*-mutant MTC: prior C/V (n=67)	*RET*-mutant MTC: treatment naïve (n=67)	*RET*-fp TC: prior systemic treatment (n=21)
ORR*, n (%)	33 (**54.1**)	48 (**77.4**)	17 (**89.5**)	34 (**50.7**)	48 (**71.6**)	18 (**85.7**)
[95% CI]	[40.8–66.9]	[65.0–87.1]	[66.9–98.7]	[38.2–63.2]	[59.3–82.0]	[63.7–97.0]
CR	1 (1.6)	4 (6.5)	2 (10.5)	2 (3.0)	4 (6.0)	3 (14.3)
PR	32 (52.5)	44 (71.0)	15 (78.9)	32 (47.8)	44 (65.7)	15 (71.4)
SD	24 (39.3)	11 (17.7)	2 (10.5)	28 (41.8)	13 (19.4)	3 (14.3)
PD	2 (3.3)	2 (3.2)	0	2 (3.0)	2 (3.0)	0
Not evaluable	2 (3.3)	1 (1.6)	0	3 (4.5)	4 (6.0)	0
Median DoR*†, mos,	21.7	NR	17.5	25.8	NR	17.5
[95% CI]	[18.0–NE]	[NE–NE]	[11.2–NE]	[18.0–NE]	[NE–NE]	[16.0–NE]
No. of events, n (%)	16 (48.5)	6 (12.5)	6 (35.3)	16 (47.1)	6 (12.5)	6 (33.3)
12-mo rate, %	84.3	88.2	71.3	84.7	88.2	73.3
[95% CI]	[71.6–96.9]	[77.0–99.3]	[46.9–95.7]	[72.4–97.1]	[77.0–99.3]	[50.4–96.2]
18-mo rate, %	67.2	74.0	42.8	68.2	74.0	48.9
[95% CI]	[50.4–84.0]	[53.5–94.6]	[8.9–76.7]	[51.9–84.6]	[53.5–94.6]	[17.3–80.4]

*Assessed by central radiology review per RECIST v1.1. †DoR analysis includes patients with confirmed CR/PR; DoR results per EMA censoring rules. C/V, cabozantinib and/or vandetanib; CI, confidence interval; CR, complete response; DoR, duration of response; EMA, European Medicines Agency; mo(s), month(s); MTC, medullary thyroid cancer; NE, not estimable; NR, not reached; ORR, overall response rate; PR, partial response; PD, progressive disease; *RET*-fp TC, *RET* fusion-positive thyroid cancer; SD, stable disease.

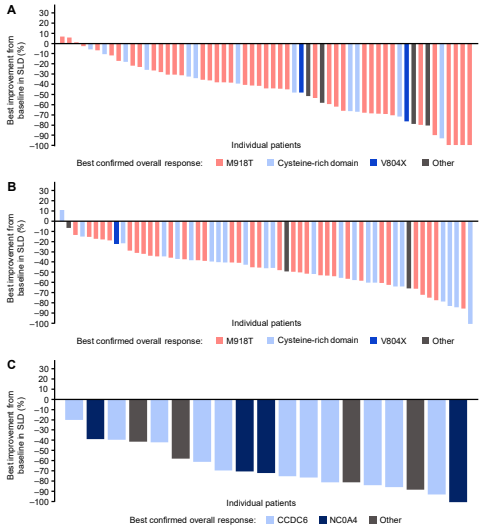
Efficacy: ORR

- In the ITT population, the ORR was (**Table 2**):
  - **51%** in patients with *RET*-mutant MTC who had received prior C/V
  - **72%** in treatment-naïve patients with *RET*-mutant MTC
  - **86%** in patients with previously treated *RET*-fp TC.
- Similar results were observed in the measurable disease population (**Table 2**).
- Responses were observed regardless of the *RET* mutation genotype or *RET* fusion partner (**Figure 1**).

Efficacy: time-to-event endpoints

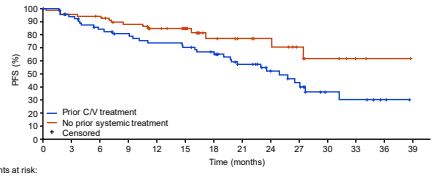
- In the ITT population, median DoR was (**Table 2**):
  - **25.8 months** in patients with *RET*-mutant MTC who had received prior C/V
  - **Not reached (NR)** in treatment-naïve patients with *RET*-mutant MTC
  - **17.5 months** in patients with previously treated *RET*-fp TC.
- DoR remains immature, with fewer than 50% of events having occurred by the data cut-off.
- Median PFS: **24.9 months** (95% CI 19.7–31.2) in patients with *RET*-mutant MTC who had received prior C/V; **NR** (95% CI 27.5–not estimable [NE]) in treatment-naïve patients with *RET*-mutant MTC; **19.4 months** (95% CI 13.0–NE) in patients with previously treated *RET*-fp TC (**Figures 2** and **3**).
- Median OS was **NR** for all three cohorts.

Figure 1. Best individual responses* (ITT) in A) patients with *RET*-mutant MTC who had received prior C/V†; B) treatment-naïve patients with *RET*-mutant MTC; C) patients with previously treated *RET*-fp TC



*By central radiology assessment per RECIST v1.1. †Three patients in this cohort had both an M918T and a V804X mutation. These patients are shown as M918T in the figure. C/V, cabozantinib and/or vandetanib; ITT, intention-to-treat; MTC, medullary thyroid cancer; *RET*-fp TC, *RET* fusion-positive thyroid cancer; SLD, sum of longest diameters.

Figure 2. PFS in patients with *RET*-mutant MTC who had received prior C/V, or treatment-naïve patients with RET-mutant MTC

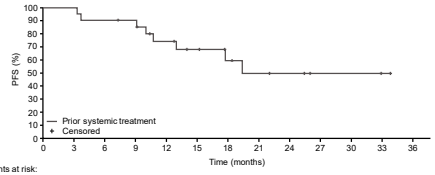


No. patients at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Prior C/V treatment	67	59	51	47	43	41	37	27	18	14	6	5	2	0
No prior systemic treatment	67	64	62	56	48	30	18	14	12	8	5	2	1	0

C/V, cabozantinib and/or vandetanib; MTC; medullary thyroid cancer; PFS, progression-free survival.

Figure 3. PFS in patients with previously treated *RET*-fp TC



No. patients at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	
Prior systemic treatment	21	21	19	18	13	10	7	5	4	2	2	1	0	

PFS, progression-free survival; *RET*-fp TC, *RET* fusion-positive thyroid cancer.

Safety

- *RET*-altered thyroid cancer safety population: 172 patients treated at 400 mg QD
  - The most frequent treatment-related adverse events (TRAEs) were **increased aspartate aminotransferase** (39%), **anemia** (35%), **hypertension** (33%) and **decreased white blood cell count** (30%)
  - Serious TRAEs were reported in 16% of patients; the most frequent serious TRAE was **pneumonitis** (3%)
  - 5% of patients discontinued pralsetinib due to a TRAE
  - One patient died due to a TRAE (*pneumocystis jirovecii* pneumonia) following 44 days (<3 cycles) on pralsetinib.

CONCLUSIONS

In this updated analysis including more patients, pralsetinib continues to show high efficacy and a manageable safety profile in patients with *RET*-altered thyroid cancer, regardless of mutation genotype or fusion partner.

SUMMARY

ORR (ITT)

51%: *RET*-mutant MTC with prior C/V

72%: treatment-naïve *RET*-mutant MTC

86%: previously treated *RET*-fp TC

Acceptable safety profile

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