

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 III ARROW trial (NCT03037385; data cut-off: 22 May 2020)⁵
 - Overall response rates (ORR) by blinded independent central review (BICR): 80% (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.

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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)

	<i>RET</i> -mutant MTC: prior C/V (n=67)	<i>RET</i> -mutant MTC: treatment naïve (n=67)	<i>RET</i> -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 C/V / LIS	7 (10.4) / 3 (4.5)	No prior antineoplastic treatment	1 (4.8) / 0
Radioactive iodine	67 (100) / 5 (7.5)		3 (14.3) / 11 (52.4)
Other	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; LIS, 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		
	<i>RET</i> -mutant MTC: prior C/V (n=61)	<i>RET</i> -mutant MTC: treatment naïve (n=62)	<i>RET</i> -fp TC: systemic treatment (n=19)	<i>RET</i> -mutant MTC: prior C/V (n=67)	<i>RET</i> -mutant MTC: treatment naïve (n=67)	<i>RET</i> -fp TC: systemic treatment (n=21)
ORR*, n (%) [95% CI]	33 (54.1) [40.8–66.9]	48 (77.4) [65.0–87.1]	17 (89.5) [66.9–98.7]	34 (50.7) [38.2–63.2]	48 (71.6) [59.3–82.0]	18 (85.7) [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, [95% CI]	21.7 [18.0–NE]	NR [NE–NE]	17.5 [11.2–NE]	25.8 [18.0–NE]	NR [NE–NE]	17.5 [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, % [95% CI]	84.3 [71.6–96.9]	88.2 [77.0–99.3]	71.3 [46.9–95.7]	84.7 [72.4–97.1]	88.2 [77.0–99.3]	73.3 [50.4–96.2]
18-mo rate, % [95% CI]	67.2 [50.4–84.0]	74.0 [53.5–94.6]	42.6 [8.9–76.7]	68.2 [51.9–84.6]	74.0 [53.5–94.6]	48.9 [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; mos, months; 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.

Disclosures
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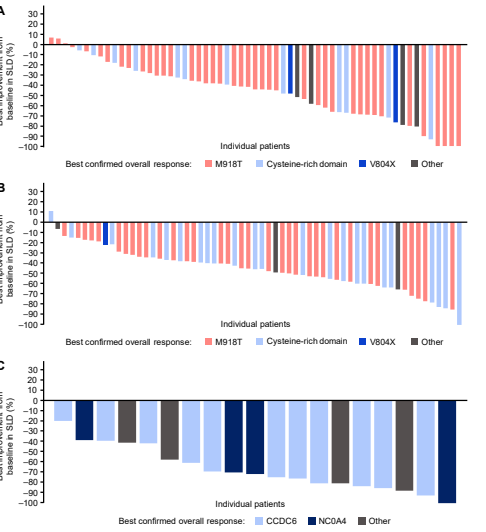
Efficacy: ORR

- 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.

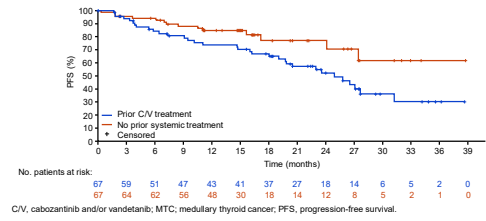
Figure 1. Best individual responses* (ITT) in A) patients with *RET*-mutant MTC who had received prior C/V; B) treatment-naïve patients with *RET*-mutant MTC; C) patients with previously treated *RET*-fp TC



*By central radiology assessment per RECIST v1.1. †Three patients in this cohort had both an M918T and a V604X 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.

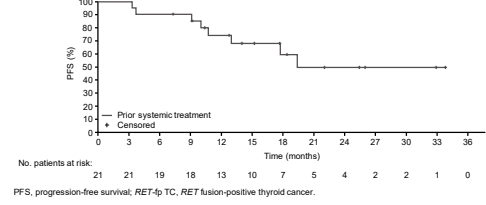
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Figure 2. PFS in patients with *RET*-mutant MTC who had received prior C/V, or treatment-naïve patients with *RET*-mutant MTC



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



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%)
 - Five 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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