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Updated ARROW data: pralsetinib in patients with advanced or metastatic *RET*-altered thyroid cancer

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BACKGROUND

- Oncogenic *RET* alterations are targetable biomarkers in thyroid cancer.[1]
- Multikinase inhibitors (MKI) are therapeutic options in medullary thyroid cancer ([MTC]; cabozantinib and vandetanib) and differentiated thyroid cancer (cabozantinib, lenvatinib and sorafenib); however, MKI-related adverse events leading to dose reductions and drug discontinuation are frequent.[2–4]
- **Pralsetinib is a potent, selective RET kinase inhibitor**[1] that has shown clinical activity in patients with *RET*-altered thyroid cancer in the phase 1/2 ARROW trial (NCT03037385; data cut-off: 12 Apr 2021; intention-to-treat [ITT] population):[5,6]
  - Overall response rate (ORR) by blinded independent central review (BICR) was 51% in patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib (C/V), 72% in treatment-naïve patients with *RET*-mutant MTC, and 86% in patients with previously treated *RET* fusion-positive thyroid cancer (*RET*-fp TC).
- We present updated data for these three cohorts (**data cut-off: 18 Oct 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 prior to the enrolment cut-off (**18 Feb 2021**) were included in the **ITT population**
  - The *RET*-altered **measurable disease population** included patients from the ITT population who had measurable disease at baseline (by BICR per RECIST v1.1).
- The *RET*-altered thyroid cancer **safety population** comprised all patients who had received ≥1 dose of pralsetinib 400 mg QD prior to the data cut-off.
- **Phase 2 primary endpoints: ORR by BICR** per RECIST v1.1, and safety.
- Key secondary endpoints: duration of response (DoR), progression-free survival (PFS) and overall survival (OS).
- ORR and DoR were evaluated in both the measurable disease and the ITT populations; PFS and OS were only assessed in the ITT population.

RESULTS

Patient population

- At data cut-off, the ITT population included 145 patients with *RET*-mutant MTC (prior C/V: n=67; other prior systemic therapy: n=11; treatment naïve: n=67) and 25 patients with *RET*-fp TC who had received prior systemic therapy, including radioactive iodine (**Table 1**).

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=25)
Median age, years (range)	59 (25–83)	55 (18–81)	60 (23–74)
Female, n (%)	23 (34.3)	24 (35.8)	16 (64.0)
Race, n (%)			
White / Asian	55 (82.1) / 3 (4.5)	27 (40.3) / 37 (55.2)	16 (64.0) / 8 (32.0)
Other or not reported	9 (13.4)	3 (4.5)	1 (4.0)
ECOG PS, n (%)			
0	18 (26.9)	38 (56.7)	11 (44.0)
1	46 (68.7)	29 (43.3)	14 (56.0)
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 (4.0) / 0
C/V / L/S	67 (100.0) / 5 (7.5)		3 (12.0) / 14 (56.0)
Radioactive iodine	4 (6.0)		23 (92.0)
No. of prior lines of systemic therapy, n (%)			
1 / 2	31 (46.3) / 24 (35.8)	*No prior antineoplastic treatment*	10 (40.0) / 5 (20.0)
≥3	12 (17.9)		10 (40.0)
Baseline CNS metastases, n (%)	7 (10.4)	6 (9.0)	10 (40.0)

*ECOG performance status of 2 was permitted before a protocol amendment. C/V, cabozantinib and/or vandetanib; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; 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			ITT population		
	RET-mutant MTC: prior C/V (n=61)	*RET*-mutant MTC: treatment naïve (n=62)	*RET*-fp TC: prior systemic treatment (n=22)	*RET*-mutant MTC: prior C/V (n=67)	*RET*-mutant MTC: treatment naïve (n=67)	*RET*-fp TC: prior systemic treatment (n=25)
ORR*, n (%) [95% CI]	34 (55.7) [42.4–68.5]	48 (77.4) [65.0–87.1]	20 (90.9) [70.8–98.9]	35 (52.2) [39.7–64.6]	48 (71.6) [59.3–82.0]	21 (84.0) [63.9–95.5]
CR	1 (1.6)	4 (6.5)	3 (13.6)	2 (3.0)	4 (6.0)	4 (16.0)
PR	33 (54.1)	44 (71.0)	17 (77.3)	33 (49.3)	44 (65.7)	17 (68.0)
SD	23 (37.7)	11 (17.7)	2 (9.1)	27 (40.3)	13 (19.4)	4 (16.0)
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*†, months, [95% CI]	25.8 [18.0–NE]	NR [NE–NE]	23.6 [15.1–NE]	25.8 [18.0–NE]	NR [NE–NE]	23.6 [15.1–NE]
Events, n (%)	18 (52.9)	8 (16.7)	8 (40.0)	18 (51.4)	8 (16.7)	8 (38.1)
18-month rate, % [95% CI]	67.5 [50.9–84.1]	79.8 [65.9–93.7]	50.2 [22.0–78.3]	68.5 [52.3–84.7]	79.8 [65.9–93.7]	53.9 [27.3–80.6]

*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; ITT, intention-to-treat; MTC, medullary thyroid cancer; NE, not estimable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; *RET*-fp TC, *RET* fusion-positive thyroid cancer; SD, stable disease.

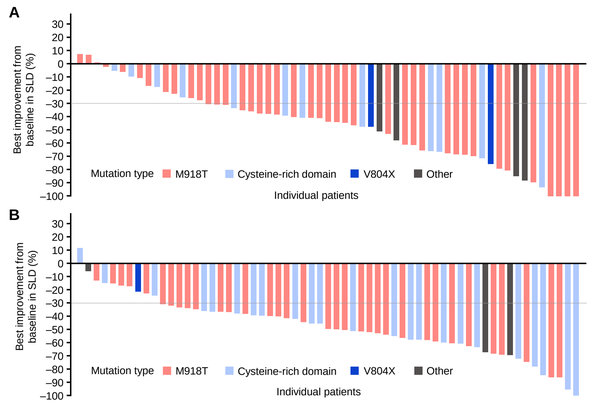
Overall efficacy

- In the ITT population ORR was (**Table 2**):
  - **52.2%** (95% CI: 39.7–64.6) in patients with *RET*-mutant MTC who had received prior C/V
  - **71.6%** (95% CI: 59.3–82.0) in treatment-naïve patients with *RET*-mutant MTC
  - **84.0%** (95% CI: 63.9–95.5) 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 (**Figure 1**).
- 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** in treatment-naïve patients with *RET*-mutant MTC
  - **23.6 months** in patients with previously treated *RET*-fp TC.

Survival endpoints

- In patients with *RET*-mutant MTC, median PFS was **25.8 months** (prior C/V) and **not reached** (treatment naïve; **Table 3**; **Figure 2A**).
- Patients with previously treated *RET*-fp TC had a median PFS of **25.4 months** (**Table 3**; **Figure 2B**).
- Median OS was **not reached** in any of the three populations (**Table 3**).

Figure 1. Best improvement from baseline in target lesion diameter in patients with *RET*-mutant MTC who A) had received prior C/V or B) were treatment naïve



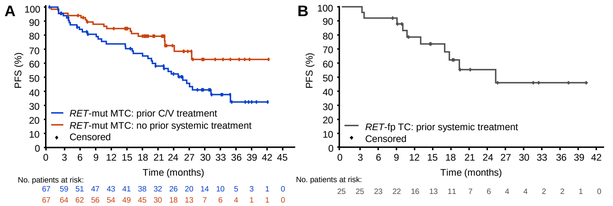
*By central radiology assessment per RECIST v1.1. ITT population. C/V, cabozantinib and/or vandetanib; ITT, intention-to-treat; MTC, medullary thyroid cancer; RECIST, Response Evaluation Criteria In Solid Tumors; SLD, sum of longest diameters.

Table 3. Survival endpoints (ITT population)

	RET-mutant MTC: prior C/V (n=67)	*RET*-mutant MTC: treatment naïve (n=67)	*RET*-fp TC: prior systemic treatment (n=25)
Median PFS*, months [95% CI]	25.8 [19.7–35.0]	NR [27.5–NE]	25.4 [17.0–NE]
18-month rate, % [95% CI]	66.9 [55.0–78.9]	79.4 [69.4–89.5]	62.3 [41.2–83.5]
Median OS, months [95% CI]	NR [36.9–NE]	NR [NE–NE]	NR [17.7–NE]
18-month rate, % [95% CI]	85.3 [76.3–94.2]	90.8 [83.7–97.8]	69.6 [48.9–90.4]

*Assessed by BICR per RECIST v1.1. PFS results per EMA censoring rules. BICR, blinded independent central review; C/V, cabozantinib and/or vandetanib; CI, confidence interval; EMA; European Medicines Agency; ITT, intention-to-treat; MTC, medullary thyroid cancer; NR, not reached; NE, not estimable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; *RET*-fp TC, *RET* fusion-positive thyroid cancer.

Figure 2. PFS in A) patients with *RET*-mutant MTC and B) patients with previously treated *RET*-fp TC



C/V, cabozantinib and/or vandetanib; PFS, progression-free survival; *RET*-fp TC, *RET* fusion-positive thyroid cancer; *RET*-mut MTC, *RET*-mutant medullary thyroid cancer.

Safety

- The *RET*-altered thyroid cancer safety population included 175 patients (**Table 4**):
  - 29 patients (16.6%) experienced serious treatment-related adverse events (TRAEs)
    - 17.9% of patients with *RET*-mutant MTC reported serious TRAEs; the most frequent was **pneumonitis** (2.8%)
    - Serious TRAEs (one event each: **anaemia**, **dizziness**, **hypotension** and **pneumonitis**) were reported in 3/30 (10.0%) of patients with *RET*-fp TC
  - One patient died due to a TRAE (*pneumocystis jirovecii* pneumonia)
  - TRAEs led to dose reduction or discontinuation in 52.6% and 5.7% of patients, respectively.

Table 4. Safety summary for TRAEs

Patients, n (%)	*RET*-altered thyroid cancer safety population (N=175)	
	RET-mutant MTC safety population (n=145)	*RET*-fp TC safety population (n=30)
TRAEs	142 (97.9)	28 (93.3)
Serious TRAEs	26 (17.9)	3 (10.0)
Grade ≥3 TRAEs	91 (62.8)	16 (53.3)
TRAE leading to dose reduction	77 (53.1)	15 (50.0)
TRAE leading to dose interruption	87 (60.0)	15 (50.0)
TRAE leading to discontinuation	8 (5.5)	2 (6.7)

Adverse events were coded using MedDRA 19.1. MTC, medullary thyroid cancer; *RET*-fp TC, *RET* fusion-positive thyroid cancer; TRAE, treatment-related adverse event.

CONCLUSIONS

In this updated analysis, pralsetinib continues to show efficacy and a manageable safety profile in patients with *RET*-altered thyroid cancer.

SUMMARY

ORR (ITT)

52.2%: *RET*-mutant MTC with prior C/V

71.6%: treatment-naïve *RET*-mutant MTC

84.0%: previously treated *RET*-fp TC

Consistent safety profile

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Disclosures

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