Results from the registrational phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced *RET* mutation–positive medullary thyroid cancer

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Background

- Medullary thyroid cancer (MTC) accounts for 1–5% of all thyroid cancers[1]
- *RET* mutations are present in 50–90% of sporadic MTC and nearly 100% of hereditary MTC cases as part of multiple endocrine neoplasia type 2 (MEN2) syndrome[1,2]
- The multikinase inhibitors cabozantinib and vandetanib are approved treatment options for advanced MTC, but have high rates of dose reductions and treatment discontinuations due to adverse events (AEs)[3,4]
- Pralsetinib is a highly potent and selective inhibitor of wild-type *RET* and *RET* with oncogenic alterations, including V804M/L gatekeeper mutations[5]
- In the phase 1/2 ARROW study (NCT03037385) of pralsetinib in patients with advanced *RET*-altered solid tumors, pralsetinib demonstrated rapid and durable responses in the *RET* fusion–positive non-small cell lung cancer cohort[6]
- Here, we report the registrational data for patients with advanced or metastatic *RET*-mutant MTC from the ARROW study

Methods

- ARROW is an ongoing, international, multicenter phase 1/2 study across 84 sites in 11 countries
  - Phase 1 dose escalation established the recommended phase 2 dose of pralsetinib as 400 mg administered orally once daily (QD)
  - Phase 2 expansion cohorts were defined by tumor type and/or *RET* alteration
- Efficacy results for response-evaluable patients with *RET*-mutant MTC and safety for all patients who initiated pralsetinib 400 mg QD are reported here

ARROW study design

- Advanced solid tumors
- *RET*-altered (local testing)
- No other driver mutations
- ECOG PS 0–1
- Prior receipt of or not candidates for standard therapy[a]

Pralsetinib dosing 400 mg PO QD N=438

- ***RET*-mutant MTC with prior cabozantinib and/or vandetanib n=67**
- ***RET*-mutant MTC with no prior systemic treatment n=42**
- ***RET*-mutant MTC with prior systemic treatment other than cabozantinib and vandetanib n=10**
- Other *RET*-altered tumors n=319

Key endpoints

- **ORR and DOR evaluated by blinded, independent central review per RECIST v1.1**
- **Safety**

Data cutoff: February 13, 2020

[a]Until protocol amended in July 2019 to allow enrollment of treatment-naïve, standard therapy-eligible patients.

ECOG PS, Eastern Cooperative Oncology Group performance score; DOR, duration of response; ORR, overall response; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

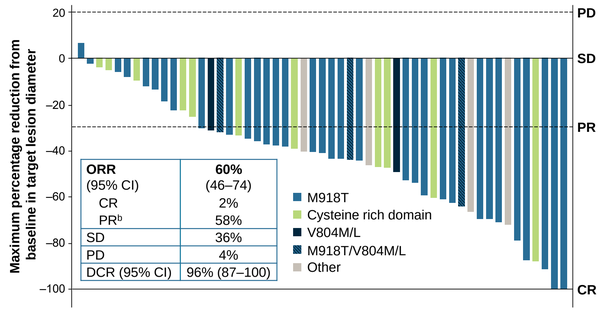
Results

Baseline characteristics

Characteristic	All 400 mg pralsetinib (N=92)[a]	Prior cabozantinib and/or vandetanib (n=61)	No prior systemic treatment (n=22)
Median age (range), years	59 (19–83)	58 (25–83)	60 (19–81)
Male, n (%)	63 (68)	41 (67)	16 (73)
ECOG PS, n (%)			
0	37 (40)	17 (28)	15 (68)
1–2[b]	55 (60)	44 (72)	7 (32)
Disease stage at screening, n (%)			
III	0	0	0
IV	37 (40)	27 (44)	5 (23)
IVA	10 (11)	5 (8)	4 (18)
IVB	17 (18)	10 (16)	5 (23)
IVC	28 (30)	19 (31)	8 (36)
History of CNS/brain metastases, n (%)	9 (10)	5 (8)	3 (14)
***RET* mutation, n (%)**	92 (100)	61 (100)	22 (100)
M918T	56 (61)	41 (67)[c]	8 (36)
Cysteine rich domain[d]	27 (29)	14 (23)	11 (50)
V804M/L	3 (3)	2 (3)	1 (5)
Other[e]	6 (7)	4 (7)	2 (9)

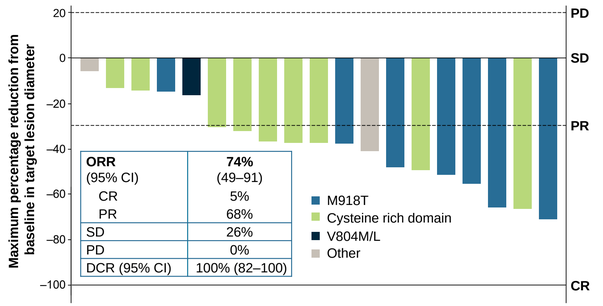
Percentages may not total 100 due to rounding. [a]Includes patients enrolled by July 11, 2019; data cutoff February 13, 2020. Patients enrolled by this date either received standard therapy or were not candidates for standard therapy; 9 patients received prior systemic therapy other than cabozantinib or vandetanib. [b]ECOG PS of 2 was allowed prior to a protocol amendment. [c]Three patients classified with M918T as the primary mutation also had a V804L or V804M mutation. [d]Cysteine rich domain includes: C609, C611, C618, C620, C630 and/or C634. [e]Other includes: D898_E901del (n=1), L790F (n=1), A883F (n=2), K666E (n=1) and R844W (n=1).
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score.

Clinical response to pralsetinib in response-evaluable patients with prior cabozantinib and/or vandetanib treatment (n=53)[a]



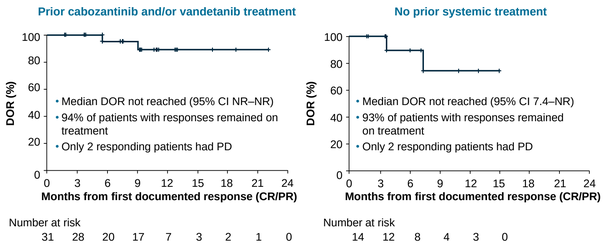
[a]Blinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cutoff February 13, 2020. Six patients without measurable disease at baseline on central review, and 2 patients without a post-baseline tumor response assessment were not response-evaluable. [b]One PR pending confirmation.
CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Clinical response to pralsetinib in response-evaluable patients with no prior systemic treatment (n=19)[a]



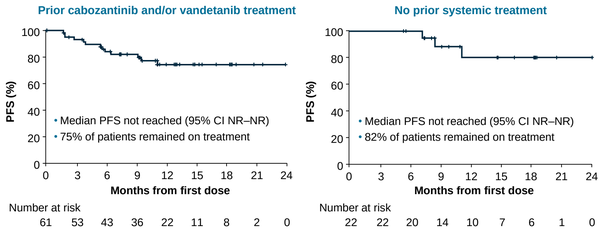
[a]Blinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cutoff February 13, 2020. Two patients without measurable disease at baseline on central review and 1 patient with another known driver mutation were not response-evaluable.

Duration of response



Blinded independent central review of tumor response; patients enrolled by July 11, 2019, as of a data cutoff February 13, 2020.
DOR presented for response-evaluable population and includes confirmed responses only.
DOR, duration of response; NR, not reached.

Progression-free survival



Blinded independent central review of tumor response; patients enrolled by July 11, 2019, as of a data cutoff February 13, 2020.
PFS presented for efficacy population. NR, not reached; PFS, progression-free survival.

Safety profile, all tumor types (N=438)

	Pralsetinib 400 mg QD (N=438)	
TRAEs in ≥15% of patients	**All grades**	**Grade ≥3**
Increased aspartate aminotransferase	34%	2%
Anemia	24%	8%
Increased alanine aminotransferase	23%	2%
Hypertension	22%	11%
Constipation	23%	1%
Decreased white blood cell count	18%	3%
Neutropenia	18%	10%
Decreased neutrophil count	16%	6%
Hyperphosphatemia	15%	1%

Data cutoff February 13, 2020.

- Pralsetinib was well tolerated
- Treatment-related adverse events (TRAEs) were primarily Grade 1–2 and reversible
- 4% of patients discontinued due to TRAEs
- Median dose intensity was 92% (range 18–100)

Conclusions

- Pralsetinib demonstrated potent and durable clinical activity in *RET*-mutant advanced MTC regardless of line of therapy
  - 60% ORR and 96% DCR in patients with prior treatment with cabozantinib and/or vandetanib
  - 74% ORR and 100% DCR in systemic treatment-naïve patients who were not candidates for standard therapies
- Responses were observed regardless of *RET* mutation genotype, including 5 of 6 (83%) patients with V804M/L gatekeeper mutation
- Pralsetinib was well tolerated at 400 mg QD; only 4% of patients discontinued due to TRAEs

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