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

**Mimi I. Hu**[1], Vivek Subbiah[1], Lori Wirth[2], Martin Schuler[3], Aaron S. Mansfield[4], Marcia S. Brose[5], Giuseppe Curigliano[6], Sophie Leboulleux[7], Viola W. Zhu[8], Bhumsuk Keam[9], Ignacio Matos[10], Chia-Chi Lin[11], Douglas Adkins[12], Christina S. Baik[13], Gilberto Lopes[14], Yann Godbert[15], Debashis Sarker[16], Hui Zhang[17], Christopher D. Turner[17], Matthew H. Taylor[18]

[1]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [2]Massachusetts General Hospital, Boston, Massachusetts, USA; [3]West German Cancer Center, University Hospital Essen, Essen, Germany; [4]Mayo Clinic, Rochester, Minnesota, USA; [5]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [6]European Institute of Oncology, IRCCS, and University of Milano, Milan, Italy; [7]Gustave Roussy, Villejuif, France; [8]University of California, Irvine School of Medicine, Orange, California, USA; [9]Seoul National University Hospital, Seoul, Republic of South Korea; [10]Vall d' Hebron Institute of Oncology, Barcelona. Spain; [11]National Taiwan University Hospital, Taipei, Taiwan; [12]Washington University School of Medicine, St. Louis, Missouri, USA; [13]University of Washington School of Medicine, Seattle, Washington, USA; [14]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, Florida, USA; [15]Bergonié Institute Cancer Center, Bordeaux, France; [16]Guy's Hospital, King's College London, London, UK; [17]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; [18]Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, Oregon, USA

# Disclosures

Mimi Hu has participated in advisory boards for Blueprint Medicines Corporation, Eli Lilly and Company, and Loxo Oncology, and has served as a consultant for Veracyte.

Pralsetinib is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with metastatic *RET* fusion-positive NSCLC. Pralsetinib has not been approved for the treatment of any other indication in the USA by the FDA or for any indication in any other jurisdiction by any other health authority.

# *RET* mutations are oncogenic drivers in MTC

- MTC accounts for **1–5%** of all thyroid cancers[1]
- *RET* mutations are present in **50–90%** of sporadic MTC and nearly **100%** of germline MTC cases as part of MEN2 syndrome[1,2]
- The MKIs cabozantinib and vandetanib are approved treatment options for advanced MTC, but have high rates of dose reductions and treatment discontinuations due to AEs[3,4]
- Pralsetinib is highly potent and selective inhibitor of wild-type *RET* and *RET* with oncogenic alterations, including V804M/L gatekeeper mutations[5]

1. Wells SA et al. *Thyroid.* 2015;25:567-610. 2. Subbiah V et al. *Cancer Discov.* 2020;38:1209–1221. 3. Elisei R et al. *J Clin Oncol.* 2013;31:3639-3646. 4. Wells SA, Jr. et al. *J Clin Oncol.* 2012;30:134-141. 5. Subbiah V, et al. *Cancer Discov.* 2018;8:836–849. MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; RET, rearranged during transfection.

# Registrational phase 1/2 study of pralsetinib in patients with solid tumors (ARROW)

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

**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**

- **Blinded, independent central review ORR and DOR per RECIST v1.1**
- **Safety**

ARROW (NCT03037385) is an ongoing, international multicenter phase 1/2 study across 84 sites in 11 countries

*Until protocol amended in July 2019 to allow enrollment of treatment-naïve, standard therapy-eligible patients. Data cutoff February 13, 2020.
ECOG PS, Eastern Cooperative Oncology Group performance score; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, overall response; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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# Baseline demographics and disease characteristics in *RET*-mutant MTC population

| Characteristic | All 400 mg pralsetinib (N=92)[a] | Prior cabozantinib and/or vandetanib treatment (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) |
| **History of CNS/brain metastases, n (%)** | 9 (10) | 5 (8) | 3 (14) |
| ***RET* mutation** | 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) |

[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 (1), L790F (1), A883F (2), K666E (1) and R844W (1). CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score.

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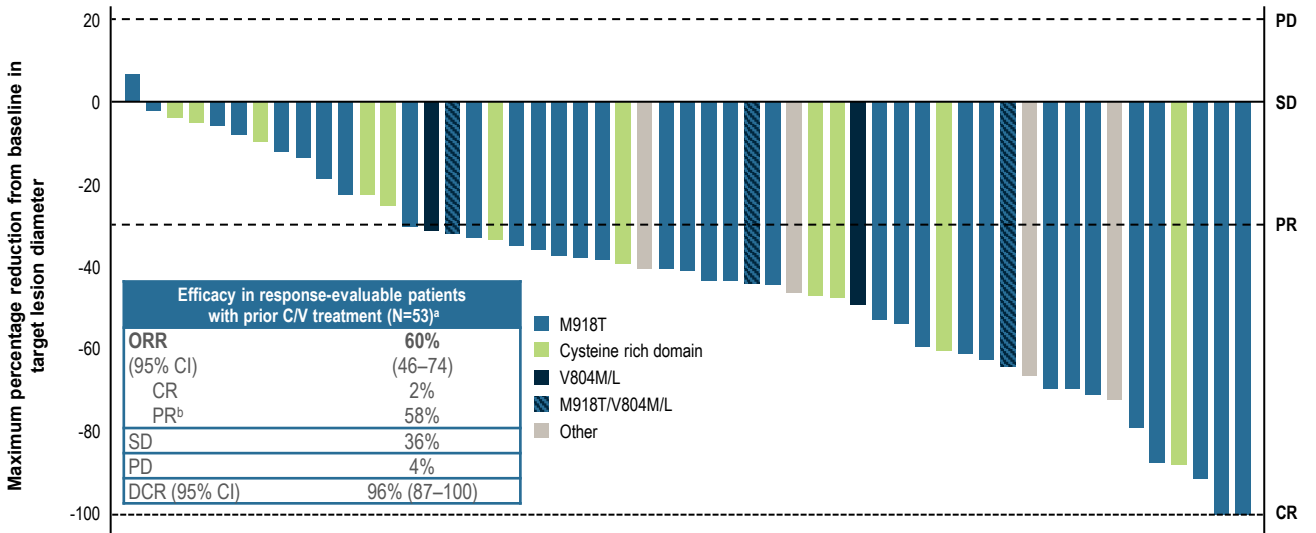
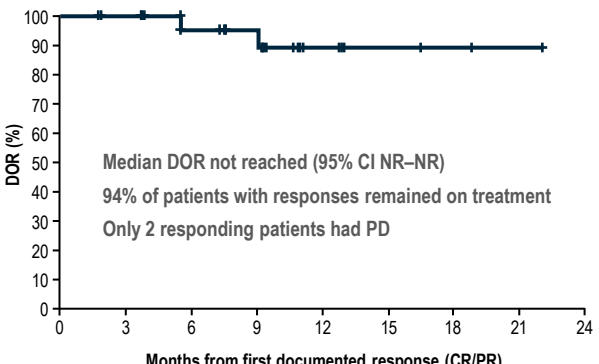
# Clinical response to pralsetinib in patients with prior cabozantinib and/or vandetanib treatment




[a]Blinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off 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]1 PR pending confirmation. C/V, cabozantinib and/or vandetanib; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

# DOR and PFS with pralsetinib in patients with prior cabozantinib and/or vandetanib treatment

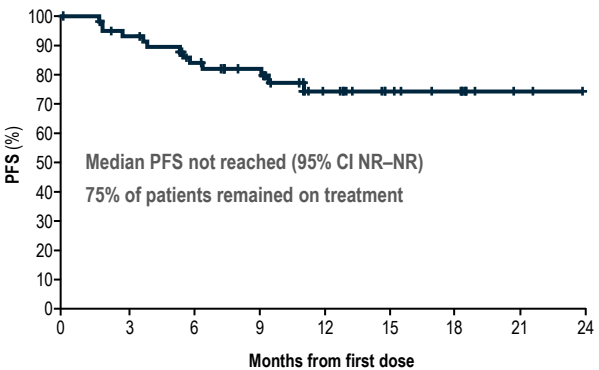
## DOR




Numbers at risk

| 31 | 28 | 20 | 17 | 7 | 3 | 2 | 1 | 0 |
|---|---|---|---|---|---|---|---|---|

## PFS




Numbers at risk

| 61 | 53 | 43 | 36 | 22 | 11 | 8 | 2 | 0 |
|---|---|---|---|---|---|---|---|---|

Blinded independent central review of tumor response; Patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. DOR presented for response-evaluable population and includes confirmed responses only; PFS presented for efficacy population.
DOR, duration of response; NR, not reached; PFS, progression-free survival.

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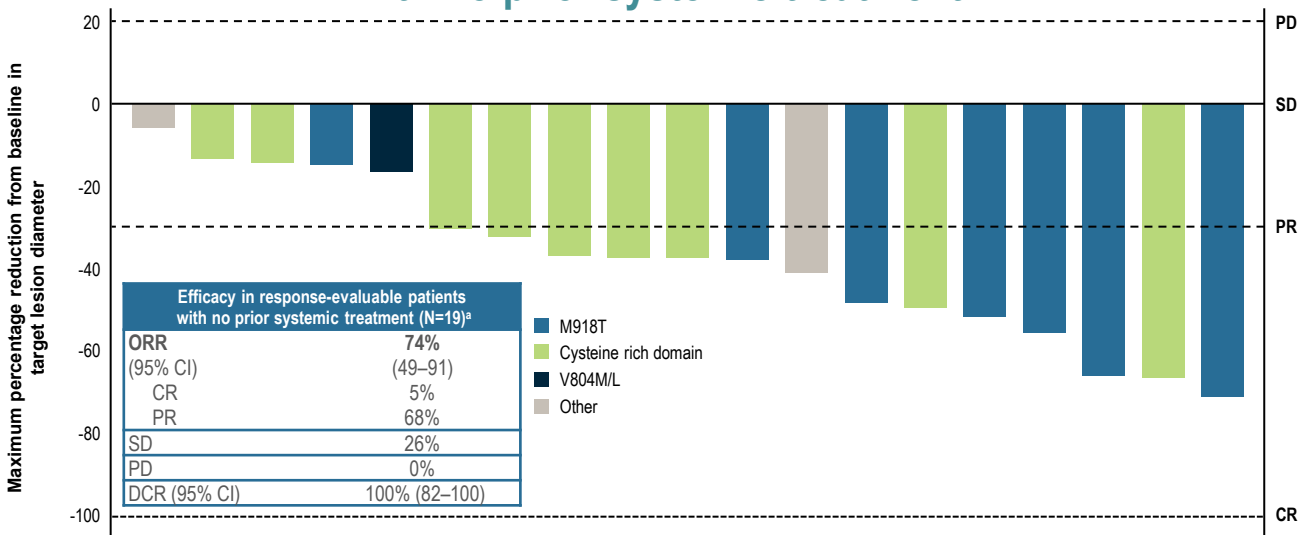
# Clinical response to pralsetinib in patients with no prior systemic treatment

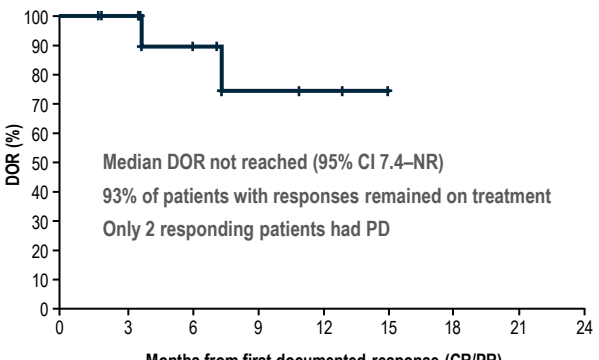



| Efficacy in response-evaluable patients with no prior systemic treatment (N=19)[a] | |
|---|---|
| **ORR** | **74%** |
| (95% CI) | (49–91) |
| CR | 5% |
| PR | 68% |
| SD | 26% |
| PD | 0% |
| DCR (95% CI) | 100% (82–100) |

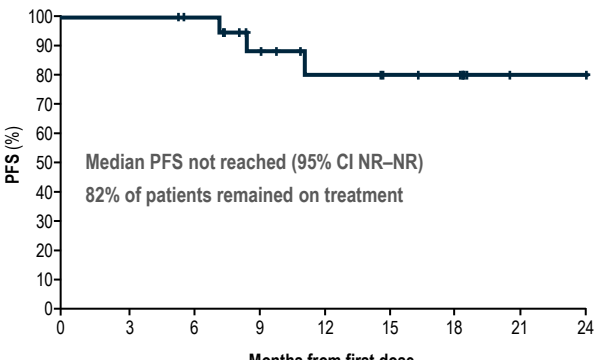
[a]Blinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. Two patients without measurable disease at baseline on central review and 1 patient who experienced major protocol violation were not response evaluable.

# DOR and PFS with pralsetinib in patients with no prior systemic treatment

## DOR




## PFS




Blinded independent central review of tumor response; Patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. DOR presented for response-evaluable population; PFS presented for efficacy population.

# Pralsetinib safety profile (all tumor types)

| TRAEs in ≥15% of patients | Pralsetinib 400 mg QD (N=438) | |
|---|---|---|
| | All grades | Grade ≥3 |
| Aspartate aminotransferase increased | 34% | 2% |
| Anemia | 24% | 8% |
| Alanine aminotransferase increased | 23% | 2% |
| Hypertension | 22% | 11% |
| Constipation | 23% | 1% |
| White blood cell count decreased | 18% | 3% |
| Neutropenia | 18% | 10% |
| Neutrophil count decreased | 16% | 6% |
| Hyperphosphatemia | 15% | 1% |

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

Data cut-off February 13, 2020. TRAE, treatment-related adverse event.

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# Summary

- 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 C/V treatment
  - 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 V804X gatekeeper mutation
- Pralsetinib was well tolerated at 400 mg QD; only 4% of patients discontinued due to TRAEs
- US NDA under review

NDA, new drug application.

# Acknowledgments


- Participating patients and families
- Pralsetinib investigators and research coordinators
- Colleagues at Blueprint Medicines Corporation