Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors

Vivek Subbiah¹, Mimi I Hu¹, Justin F. Gainor², Aaron Scott Mansfield³, Guzman Alonso⁴, Matthew H Taylor⁵, Viola Weijia Zhu⁶, Pilar Garrido López⁷, Alessio Amatu⁸, Robert C Doebele⁹, Philippe Alexandre Cassier¹⁰, Bhumsuk Keam¹¹, Martin H. Schuler¹², Hui Zhang¹³, Corinne Clifford¹³, Michael Palmer¹³, Jennifer Green¹³, Christopher D. Turner¹³, and Giuseppe Curigliano¹⁴

¹University of Texas MD Anderson Cancer Center, Houston, TX; ²Massachusetts General Hospital, Boston, MA; ³Mayo Clinic, Rochester, MN; ⁴Vall d’ Hebron Institute of Oncology, Barcelona, Spain; ⁵Earle A. Chiles Research Institute, Portland, OR; ⁶University of California, Irvine School of Medicine, Orange, CA; ⁷IRYCIS. Hospital Universitario Ramón y Cajal, Madrid, Spain; ⁸Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ⁹University of Colorado Cancer Center, Aurora, CO; ¹⁰Centre Léon Bérard, Lyon, France; ¹¹Seoul National University Hospital, Seoul, Republic of South Korea; ¹²West German Cancer Center, University Hospital Essen, Essen, Germany; ¹³Blueprint Medicines Inc, Cambridge, MA; ¹⁴European Institute of Oncology, IRCCS and University of Milano, Milan, Italy.
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Pralsetinib is an investigational agent discovered by and currently in development by Blueprint Medicines Corporation (Blueprint Medicines).
**RET** fusions are oncogenic drivers in multiple tumor types

- **Papillary thyroid cancer** (~10–20%)\(^1,2\)
- **Breast** (0.1%)\(^3\)
- **NSCLC** (1% to 2%)\(^1\)
- **Pancreatic adenocarcinoma** (0.6%)\(^2\)
- **Ovarian epithelial carcinoma** (1.9%)\(^2\)
- **Colorectal** (0.2% to 7.6%)\(^9–11\)
- **Cholangiocarcinoma**\(^2,8\)
- **Salivary gland (intraductal)** including MASC\(^4,5\)
- **Medullary thyroid cancer (**\(RET\) mutations, sporadic in ~50% and germline as part of MEN2 syndrome in ~100%)\(^6,7\)

**Outcomes with immunotherapies in patients with **\(RET\) fusion-positive NSCLC are poor\(^17–20\)**

The prevalence of **\(RET\) fusion** is shown. MASC, mammary analog secretory carcinoma of the salivary gland; NSCLC, non-small cell lung cancer; **\(RET\)**, rearranged during transfection.

Pralsetinib has the potential to address unmet medical need across a broad range of tumor types

- Recent tumor-agnostic drug approvals have resulted in a paradigm shift in cancer treatment away from organ/histology specific indications to biomarker-guided tumor-agnostic approaches
- Pralsetinib is a potent and selective RET inhibitor that targets RET alterations, including fusions and mutations, regardless of the tissue of origin
- Pralsetinib is specific and has high selectivity for activating RET alterations and very low affinity for other kinases:¹
  - 81-fold more selective for RET than VEGFR2 in a biochemical assay

JAK1, Janus kinase 1; RET, rearranged during transfection; VEGFR2, vascular endothelial growth factor receptor 2.
Pralsetinib Phase 1/2 ARROW study

Phase 2 study design

- Advanced solid tumors
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

Pralsetinib dosing: 400 mg PO QD

Primary endpoints

- Centrally reviewed ORR per RECIST v1.1
- Safety

ARROW is registered with clinicaltrials.gov (NCT03037385). Data cutoff, November 18, 2019. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance score; MTC, medullary thyroid cancer; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; ORR, overall response rate; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection. Data shown for response evaluable population. *All responses confirmed. †Two responses pending confirmation. ‡One response pending confirmation.

1. Phase 1/2 ARROW trial data in patients with RET fusion-positive NSCLC reported on January 8, 2020. Data cutoff: November 18, 2019. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance score; MTC, medullary thyroid cancer; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; ORR, overall response rate; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection. Data shown for response evaluable population. *All responses confirmed. †Two responses pending confirmation. ‡One response pending confirmation.

Baseline characteristics

<table>
<thead>
<tr>
<th>RET fusion thyroid (n=13)*</th>
<th>Other RET fusion tumor types (N=14)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>63 (23–74)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (31)</td>
</tr>
<tr>
<td>1</td>
<td>8 (62)</td>
</tr>
<tr>
<td>2‡</td>
<td>1 (8)</td>
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<tr>
<td>Disease stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Brain metastasis, n (%)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Any prior systemic therapy</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>12 (92)</td>
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<tr>
<td>Lenvatinib/Sorafenib</td>
<td>7 (54)</td>
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<tr>
<td>Cabozantinib/Vandetanib</td>
<td>2 (15)</td>
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<tr>
<td>Chemotherapy</td>
<td>0</td>
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<tr>
<td>Other anticancer therapy</td>
<td>0</td>
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<tr>
<td>Fusion partners, n (%)</td>
<td></td>
</tr>
<tr>
<td>CCDC6</td>
<td>6 (46)</td>
</tr>
<tr>
<td>KIF5B</td>
<td>0</td>
</tr>
<tr>
<td>NCOA4</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
</tr>
</tbody>
</table>

*Enrolled by July 11, 2019. †Enrolled by November 19, 2019. ‡ECOG performance status of 2 was permitted prior to a protocol amendment.

ECOG, Eastern Cooperative Oncology Group; KIF5B, kinesin family member 5b; NCOA4, nuclear receptor coactivator 4; RET, rearranged during transfection.

RET fusion tumor types (N=27)

- Papillary thyroid carcinoma
- Poorly differentiated thyroid cancer
- Pancreatic
- Cholangiocarcinoma
- Thymus

- Colon
- Mixed histology lung
- Ovarian
- Neuroendocrine (unknown primary)
Activity of pralsetinib in RET fusion-positive thyroid tumors

<table>
<thead>
<tr>
<th>Best response, (response evaluable), %</th>
<th>RET fusion-positive thyroid cancer (n=11)†</th>
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<tbody>
<tr>
<td>ORR</td>
<td>91 (59–100)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>91</td>
</tr>
<tr>
<td>SD</td>
<td>9</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>DCR</td>
<td>100 (72–100)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
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</tbody>
</table>

Blinded independent central review of tumor response; response-evaluable patients enrolled by Jul 11, 2019, as of a data cut-off Feb 13, 2020. *Patients initially received alternate pralsetinib starting doses in the dose-escalation study portion, but subsequently transitioned to 400 mg QD. †Response-evaluable population excludes two patients with papillary thyroid carcinoma without measurable disease at baseline per blinded central review. These two patients were assessed with CR and SD, and continue treatment at 12.9 and 23.3 months, respectively. CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease.
Pralsetinib treatment duration in patients with RET fusion-positive thyroid cancer

First PR
Ongoing treatment

Case study: 66-year-old man with poorly differentiated thyroid cancer

- NCOA4-RET fusion; no previous treatments
- Deep and durable PR with pralsetinib (18 months duration; 94% shrinkage of target lesions)
- At first disease evaluation (8 weeks on treatment):
  - Spiculated mass in the right upper pulmonary lobe previously measuring 6.3 cm resolved with residual scar
  - Infiltrative mass previously surrounding and compressing the upper thoracic trachea lost definition and decreased in size
  - Superior mediastinal lymph node decreased from 1.6 to 0.6 cm in short-axis dimension
- Throughout treatment:
  - Thyroglobulin antibodies reduced from 1411 IU/mL to <1 IU/mL
  - Complete clearance of NCOA4-RET fusion ctDNA

Computed tomography images. ctDNA, cell-free circulating tumor DNA; NCOA4, nuclear receptor coactivator 4; RET, rearranged during transfection PR, partial response.
**Activity of pralsetinib in various RET fusion-positive tumors**

- Responses were observed in all patients with pancreatic adenocarcinoma (3/3) and cholangiocarcinoma (2/2)

Investigator’s assessment of tumor response; response-evaluable patients enrolled by 19 Nov 2019, as of a data cut-off 13 Feb 2020. *Patient initially received alternate pralsetinib starting doses in the dose-escalation study portion, but subsequently transitioned to 400 mg QD. † Including mixed sarcoma/adenocarcinoma, mixed SCLC/NSCLC, and atypical carcinoid. ‡ Response-evaluable population excludes two patients with colon cancer that had alternate driver mutations. These two patients were assessed with SD, and continue treatment at 9.7 and 3.7 months, respectively. § One PR pending confirmation. CI, confidence interval; DCR, disease control rate; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RET, rearranged during transfection; SCLC, small-cell lung cancer; SD, stable disease.

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Investigator's assessment of tumor response; response-evaluable patients enrolled by 19 Nov 2019, as of a data cut-off 13 Feb 2020. *Patient initially received alternate pralsetinib starting doses in the dose-escalation study portion, but subsequently transitioned to 400 mg QD. † Including mixed sarcoma/adenocarcinoma, mixed SCLC/NSCLC, and atypical carcinoid. ‡ Response-evaluable population excludes two patients with colon cancer that had alternate driver mutations. These two patients were assessed with SD, and continue treatment at 9.7 and 3.7 months, respectively. § One PR pending confirmation. CI, confidence interval; DCR, disease control rate; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RET, rearranged during transfection; SCLC, small-cell lung cancer; SD, stable disease.
Pralsetinib treatment duration in patients with various \textit{RET} fusion-positive tumors

Investigator’s assessment of tumor response; response-evaluable patients enrolled by Nov 19, 2019, as of a data cut-off Feb 13, 2020. †Including mixed sarcoma/adenocarcinoma, mixed SCLC/NSCLC, and atypical carcinoid. NSCLC, non-small-cell lung cancer; PR, partial response; QD, once daily; SCLC, small-cell lung cancer.
Case study: 51-year-old woman with cholangiocarcinoma

- NCOA4-RET fusion
- Three previous treatments with PD for all (nab-paclitaxel/gemcitabine/cisplatin; erlotinib/bevacizumab; osimertinib)
- Deep and durable PR with pralsetinib (20 months duration; 64% shrinkage of target lesions)
- At first disease evaluation (8 weeks on treatment):
  - Left hepatic lobe lesion previously measuring 2 x 3 cm decreased to 1.2 x 1.9 cm
  - Prior heterogeneously enhancing soft tissue mass in the right gluteal muscles with decreased size and enhancement, and increased cystic/necrotic components
- Throughout treatment:
  - CA 19-9 reduced from 1,000,000 to 82 U/mL
  - CA 125 reduced from 1591 to 16.4 U/mL
  - Rapid and near-complete clearance of NCOA4-RET fusion ctDNA
Safety

• Safety among the 27 patients with other RET fusion-positive tumors is consistent with the safety of the overall population (n=354, ASCO 2020 poster 9515)
  – Majority of adverse events were low-grade (CTCAE grade 1–2)
  • The most frequent treatment-related AEs (≥15%) were anemia (33%), increased AST (33%), decreased WBC count (33%), hypertension (30%), increased ALT (26%), hyperphosphatemia (19%), and neutropenia (19%)
  – Treatment duration was up to 23.5 months with median relative dose intensity of 96% (range 58–150)
  – No patients discontinued due to treatment-related AEs

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; WBC, white blood cell.
Conclusions

- Pralsetinib has broad and durable antitumor activity with multiple advanced solid tumor types
  - 91% ORR and 100% DCR in RET fusion thyroid cancer
  - 50% ORR* and 92% DCR across various other RET fusion-positive solid tumors
    - Including responses in RET fusion-positive cholangiocarcinoma, pancreatic tumors, and neuroendocrine tumors
- Pralsetinib was well-tolerated, and its safety profile was consistent across the overall population treated
- The ARROW study is still ongoing and currently continues to enroll patients with various RET fusion-positive solid tumors

DCR, disease control rate; RET, rearranged during transfection. *One PR pending confirmation
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Presenter’s contact information

Email: vsubbiah@mdanderson.org
Twitter: @VivekSubbiah