# Treatment with Pralsetinib (BLU-667), a Potent and Selective RET Inhibitor, Provides Rapid Clearance of ctDNA in Patients with RET-altered Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer



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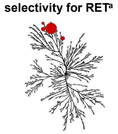
## BACKGROUND AND METHODS

- RET alterations are targetable oncogenic drivers in multiple tumor types
- Approximately 90% of advanced medullary thyroid cancer (MTC) is characterized by single nucleotide variants and short insertions/deletions in the RET gene.[1]
- In NSCLC, approximately 1-2% of patients harbor rearrangements resulting in RET fusions.[2]
- No selective RET inhibitors are approved

### Pralsetinib: Designed to Treat RET-Altered Cancers

Pralsetinib potently and selectively inhibits RET alterations, including those that confer resistance to MKI, while sparing VEGFR.[3]

**Pralsetinib: High kinome selectivity for RET[a]**



| | Pralsetinib $IC_{50}$ | Cabozantinib $IC_{50}$ | Vandetanib $IC_{50}$ |
|---|---|---|---|
| **Wild-type RET** | 0.4 | 11 | 4 |
| **RET V804L** Gatekeeper resistance | 0.3 | 45 | 3597 |
| **RET V804M** Gatekeeper resistance | 0.4 | 162 | 726 |
| **RET M918T Mutation** | 0.4 | 8 | 7 |
| **CCDC6-RET Fusion** | 0.4 | 34 | 20 |
| **VEGFR2** Anti-target | 35 | 2 | 4 |

Pralsetinib vs. pharmacologically relevant kinases:
- Pralsetinib is ~90-fold more selective for RET than VEGFR2
- Pralsetinib is 20-fold more selective for RET than JAK1

$IC_{50}$, half maximal inhibitory concentration; MKI, multikinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

### ARROW: Pralsetinib Dose-Escalation/Expansion Study

**Dose-Escalation (Complete)**
- Phase 2 dose determined (400 mg QD)

**Expansion Cohorts (Ongoing)**
- Unresectable, advanced RET fusion-positive NSCLC, thyroid cancer, and other RET-altered solid tumors
- RET alteration status by local tumor testing
- No additional driver mutation

**Primary objectives**
- Overall response rate (RECIST 1.1)
- Safety

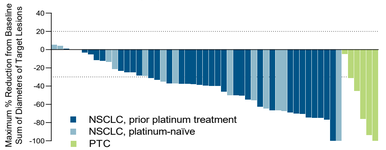
**Exploratory analysis: RET variant ctDNA**
- Early declines in ctDNA may predict for treatment outcome.[4-7]
- Plasma profiled with the Personal Genome Diagnostics PlasmaSELECT™ R64 sequencing panel.
- Results were reported as ctDNA mutant allele fraction (RET mutations) or unique fusion reads (RET fusions)

ctDNA, circulating tumor DNA; QD, once daily dosing; RECIST, response evaluation criteria in solid tumors

### Pralsetinib has demonstrated significant clinical activity in RET-altered NSCLC and MTC and has been well tolerated[a]

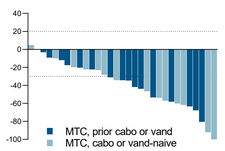
**RET Fusion-Positive NSCLC & PTC**

- NSCLC, prior platinum: ORR 60% (95% CI: 42, 76); DCR 100%
- NSCLC, treatment-naïve: ORR 71% (5/7)
- PTC ORR 83% (5/6)[b]; DCR 100%




**RET-Mutated MTC**

- MTC, prior cabo or vand: ORR 63%[b] (95% CI: 35, 85); DCR 94%

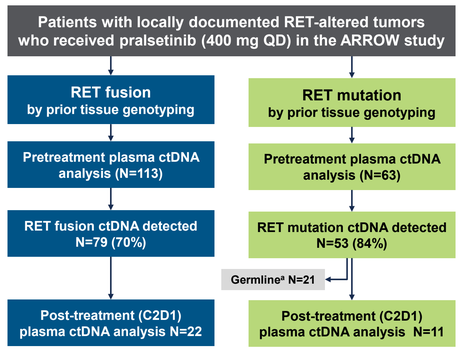



Overall rate of treatment discontinuation due to treatment-related toxicity was 4%.

Cabo, cabozantinib; DCR, disease control rate (best RECIST 1.1 response of stable disease or better); ORR, objective response rate; PTC, papillary thyroid cancer; vand, vandetinib.
a. ARROW study data as of 28 Apr 2019, presented at ASCO 2019[8,9]
b. One patient with PTC and one patient with MTC were pending response confirmation.

## RESULTS

### Analysis Dataset




C2D1, Cycle 2 Day 1 (approximately eight weeks after initiation of pralsetinib)
a. Mutations with allele fraction ≥ 40% were considered germline and excluded from post-treatment analyses of ctDNA clearance.

### Baseline ctDNA Analysis: Multiple RET Variants Detected Across Tumor Types

| | NSCLC (N=73) | MTC (N=51) | Other[a] (N=8) | Total (N=132) |
|---|---|---|---|---|
| **RET fusion partner** | | | | |
| KIF5B | 59 | - | - | 59 |
| CCDC6 | 12 | - | 4 | 16 |
| Other | 11 | - | 2 | 13 |
| **RET mutation** | | | | |
| M918T | - | 27 (24/3) | - | 27 (24/3) |
| C634F/R/S/W/Y | - | 10 (4/6) | - | 10 (4/6) |
| V804L/M | 1 (1/0) | 4 (1/3) | - | 5 (2/3) |
| C620R/Y | - | 3 (2/1) | - | 3 (2/1) |
| C618R/S | - | 2 (2/0) | - | 2 (2/0) |
| D631E/del | - | 1 (0/1) | 1 (0/1) | 2 (0/2) |
| Other | 7 (5/2) | 13 (7/6) | 2 (2/0) | 22 (14/8) |

Data for mutations shown as total n (somatic n/germ line n). Patients with multiple RET fusions and/or mutations are tabulated in all relevant categories. a."Other" tumor types: colon cancer (n=3), papillary thyroid cancer (n=3), pancreatic cancer (n=1), and small cell lung cancer (n=1).

Baseline ctDNA levels correlated with tumor burden in NSCLC (p=0.010) and MTC (p=0.038)
- Analysis of variance (ANOVA) based on ctDNA level, using groups with undetectable ctDNA and 2 (MTC) or 3 (NSCLC) quantiles of those with detectable ctDNA.

**References**
1. Romei, et al. Oncotarget, 2018;9:9875-9884
2. Santoro, et al. J Clin Invest. 1992;89(5):1517-1522
3. Subbiah, et al. Cancer Discov. 2018;8(7):836-849
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ARROW is registered with clinicaltrials.gov (NCT03037385)

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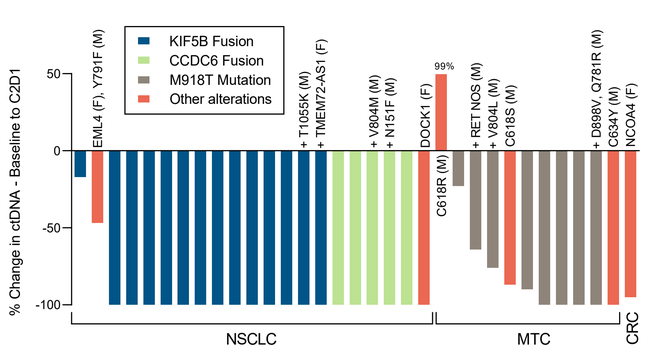
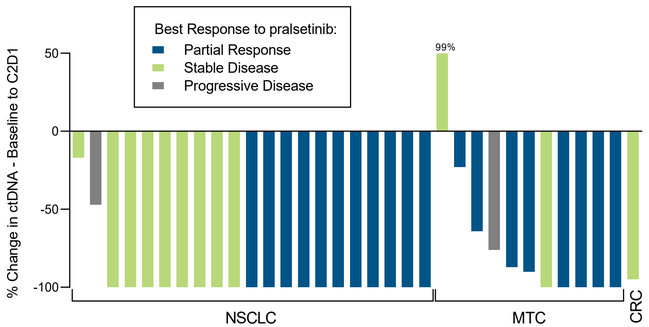
### Clearance of RET Variants Across a Broad Range of RET Genotypes




- After 8 weeks of treatment with pralsetinib, RET ctDNA was undetectable for 90% of pts with NSCLC and 45% of pts with MTC harboring somatic RET mutations
- After 8 weeks of treatment with pralsetinib, RET ctDNA was reduced ≥50% for 90% of pts with NSCLC and 82% of pts with MTC harboring somatic RET mutations

CRC, colorectal cancer. F, fusion; M, mutation.

### Rapid Declines in RET Variant ctDNA Across Tumor Types




Best tumor response assessed per RECIST 1.1.

**All data are preliminary and based on a data cut-off date of 06 Sept 2019 unless otherwise noted.**

Pralsetinib is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines). The ARROW study is study is sponsored by Blueprint Medicines.

**PRESENTING AUTHOR DISCLOSURE**: Blueprint Medicines is a sponsor of this study. GC has received honoraria from Seattle Genetics, Roche, Novartis, Eli Lilly, Bristol-Myers Squibb, and Pfizer; has served in advisory and consultancy roles for Seattle Genetics, Roche, Novartis, Eli Lilly, Bristol-Myers Squibb, and Pfizer; has given expert testimony for Seattle Genetics, Roche, Novartis, Eli Lilly, Bristol-Myers Squibb, and Pfizer; and has received travel accommodation and funding from Roche and Pfizer.

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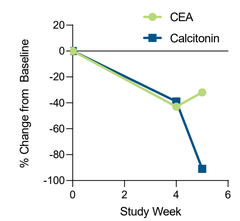
### Responses in Patients with Somatic and Germ-Line V804 Mutations

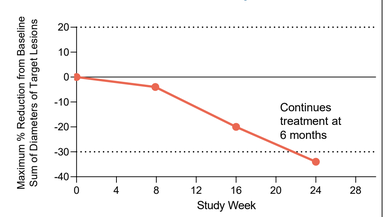
#### M918T and somatic V804L resistance mutation

- 53 year-old woman with Stage IV MTC
- Disease in liver and lymph nodes
- Previously experienced progression of disease on vandetinib
- Pralsetinib starting dose 400 mg QD

**Significant Reductions in CEA and Calcitonin**



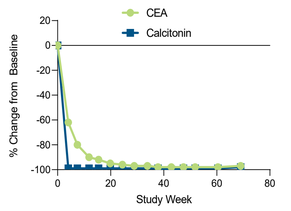

**Tumor Shrinkage Evolving to Partial Response[a]**



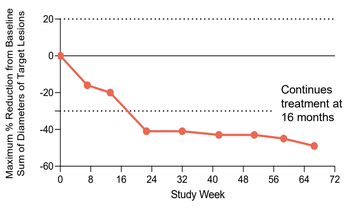

#### Germ-line V804L mutation

- 52 year-old man with Stage IV MTC
- Disease in liver, lung and lymph nodes
- Previously received sunitinib with best response of stable disease
- Pralsetinib starting dose: 200 mg BID

**Significant Reductions in CEA and Calcitonin**




**Confirmed Partial Response**




a. Confirmation of response is pending.

## CONCLUSIONS

- Plasma ctDNA analysis can successfully identify a broad array of targetable RET alterations and mutations, including somatic resistance mutations
- Treatment with pralsetinib leads to a robust and rapid decline in RET variant ctDNA regardless of tumor diagnosis or RET alteration genotype
- ctDNA clearance occurred in the majority of patients, including patients with prolonged disease stabilization
- Results support pralsetinib as a potent and selective RET inhibitor and are consistent with the broad clinical activity observed with pralsetinib, including high objective tumor response and disease control rates.