

# 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 4559

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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<sup>1</sup>
- Approximately 1–2% of patients with NSCLC and approximately 20% of patients with papillary thyroid cancer (PTC) harbor rearrangements resulting in RET fusions<sup>2</sup>
- 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.<sup>3</sup>

Pralsetinib: High kinase selectivity for RET <sup>a</sup>	Pralsetinib IC <sub>50</sub>	Cabozantinib IC <sub>50</sub>	Vandetanib IC <sub>50</sub>	Pralsetinib vs. pharmacologically relevant kinases:
Wild-type RET	0.4	11	4	<ul style="list-style-type: none"> <li>Pralsetinib is ~90-fold more selective for RET than VEGFR2</li> <li>Pralsetinib is 20-fold more selective for RET than JAK1</li> </ul>
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	

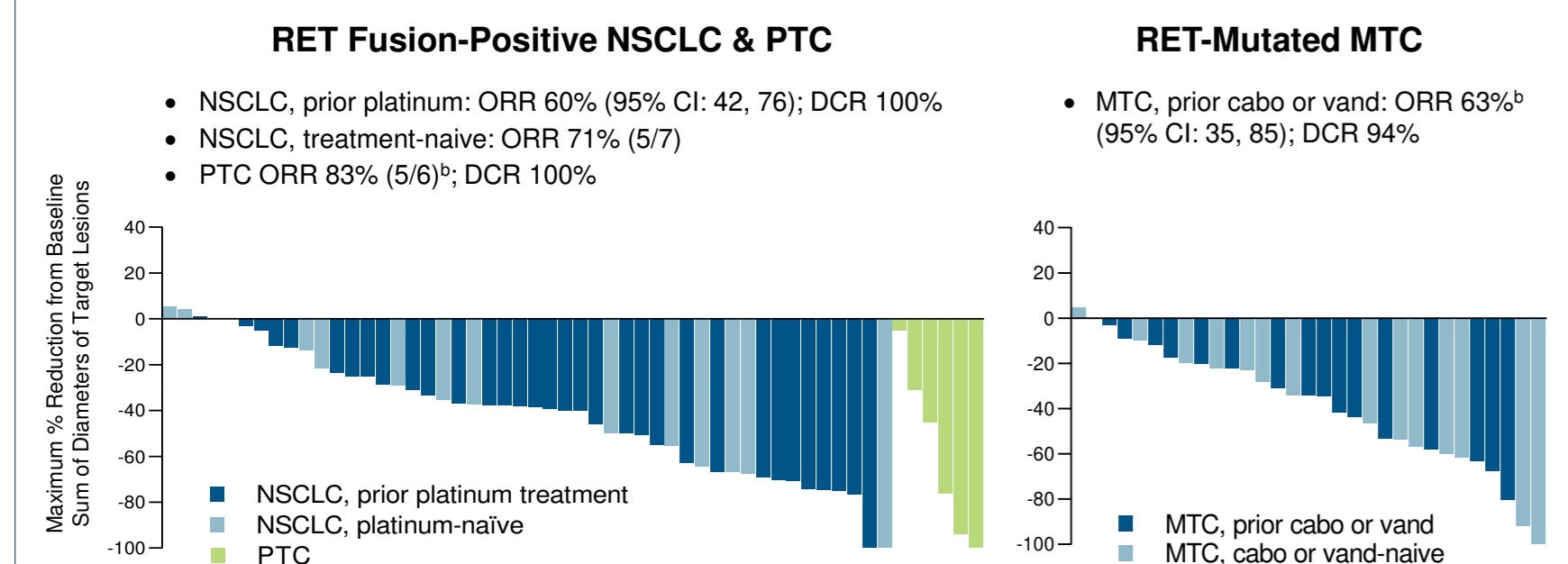
IC<sub>50</sub>, half maximal inhibitory concentration; MKI, multikinase inhibitor; VEGFR, vascular endothelial growth factor receptor. a. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines™ is not responsible for its content.

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

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| <p><b>Dose-escalation (complete)</b></p> <ul style="list-style-type: none"> <li>Phase 2 dose determined (400 mg QD)</li> </ul> <p><b>Expansion cohorts (ongoing)</b></p> <ul style="list-style-type: none"> <li>Unresectable, advanced RET fusion-positive NSCLC, thyroid cancer, and other RET-altered solid tumors</li> <li>RET alteration status by local tumor testing</li> <li>No additional driver mutation</li> </ul> | <p><b>Primary objectives</b></p> <ul style="list-style-type: none"> <li>Overall response rate (RECIST 1.1)</li> <li>Safety</li> </ul> <p><b>Exploratory analysis: RET variant ctDNA</b></p> <ul style="list-style-type: none"> <li>Early declines in ctDNA may predict for treatment outcome<sup>4,7</sup></li> <li>Plasma profiled with the Personal Genome Diagnostics PlasmaSELECT™ R64 sequencing panel</li> <li>Results were reported as ctDNA mutant allele fraction (RET mutations) or unique fusion reads (RET fusions)</li> </ul> |
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ctDNA, circulating tumor DNA; QD, once-daily dosing; RECIST, response evaluation criteria in solid tumors.

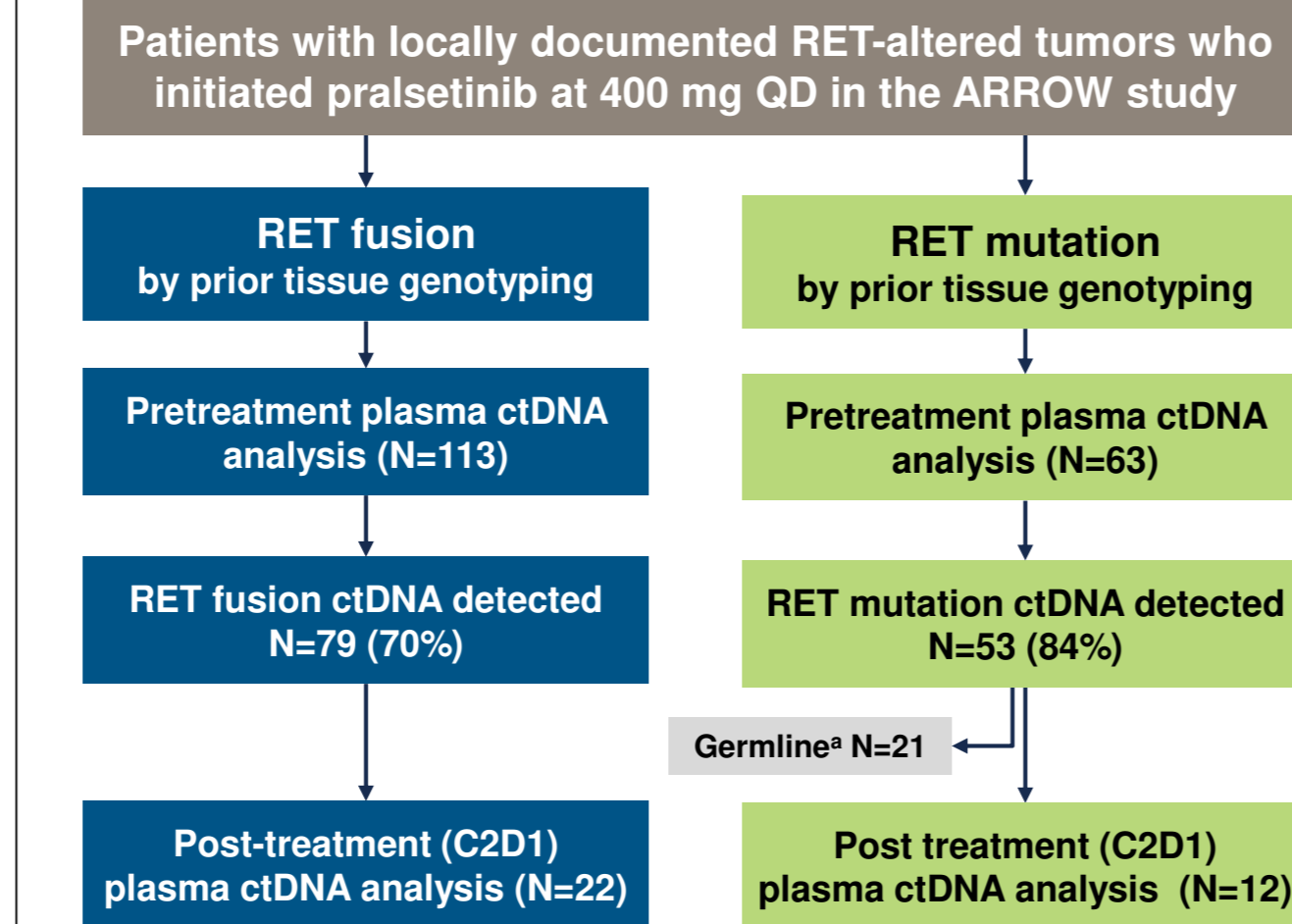
### Pralsetinib Has Demonstrated Significant Clinical Activity in RET-Altered Tumors and Has Been Well Tolerated<sup>a</sup>



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, vandetanib. a. ARROW study data as of 28 Apr 2019, presented at ASCO 2019.<sup>5,9</sup> b. One patient with PTC and one patient with MTC were pending response confirmation.

## RESULTS

### Analysis Dataset



C2D1, Cycle 2 Day 1 (approximately 8 weeks after initiation of pralsetinib). a. Mutations with allele fraction  $\geq 40\%$  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 <sup>a</sup> (N=8)	Total (N=132)
<b>RET fusion partner</b>				
KIF5B	59	-	-	59
CCDC6	12	-	4	16
Other	11	-	2	13
<b>RET mutation</b>				
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).

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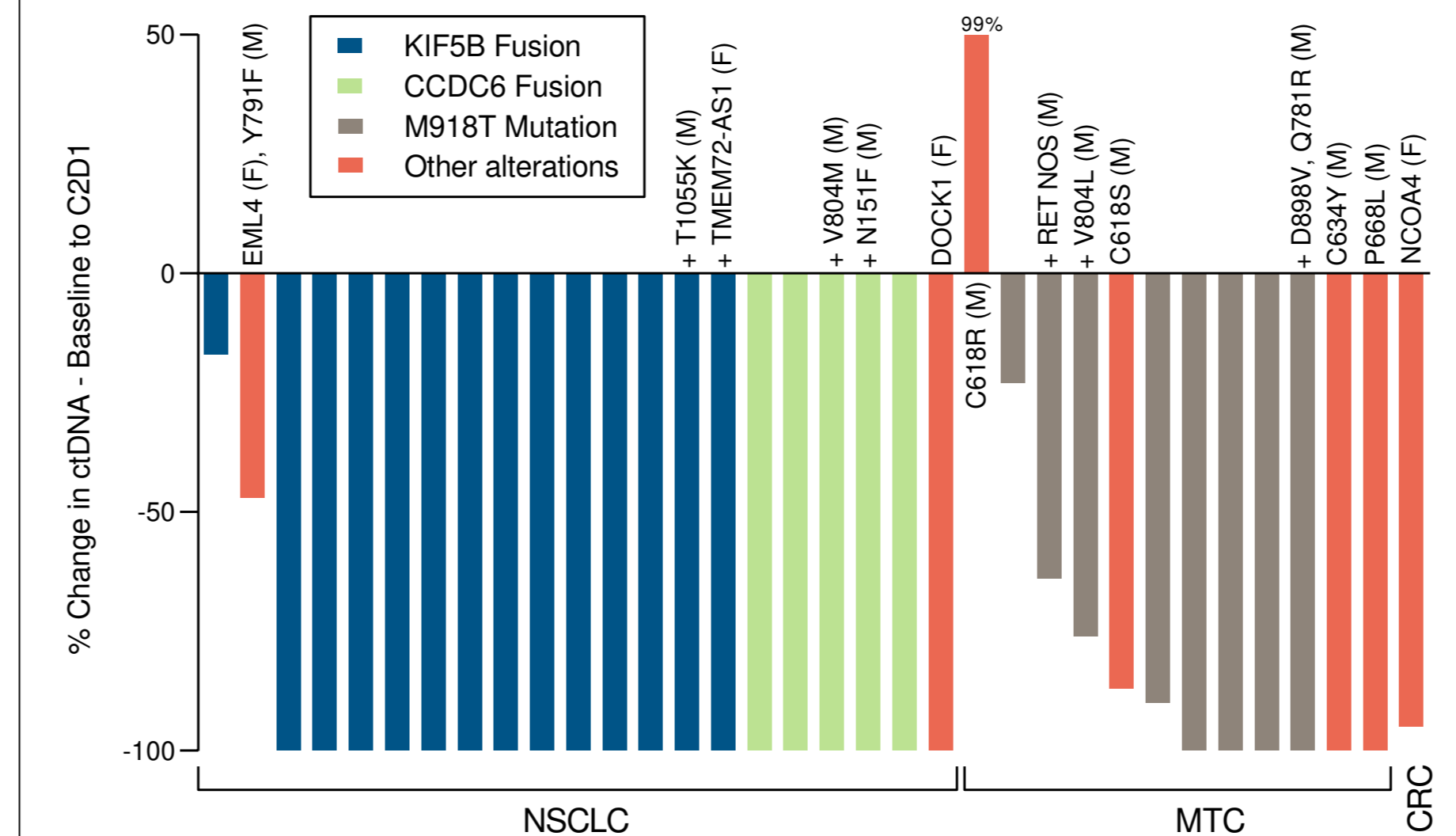
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### Clearance of RET Variants Across a Broad Range of RET Genotypes



- After 8 weeks of treatment with pralsetinib, RET ctDNA was undetectable for 90% of patients with NSCLC and 50% of patients with MTC harboring somatic RET mutations
- After 8 weeks of treatment with pralsetinib, RET ctDNA was reduced  $\geq 50\%$  for 90% of patients with NSCLC and 83% of patients with MTC harboring somatic RET mutations

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

### ctDNA Clearance and Clinical Benefit

	NSCLC (N=21)	MTC (N=12)
<b>Complete Clearance of RET Variant ctDNA at C2D1</b>		
Partial Response	11/11 (100%)	5 <sup>a</sup> /9 (56%)
Stable Disease	8/9 (89%)	1/2 (50%)
Progressive Disease	0/1 (0%)	0/1 (0%)

Data show the percentage of patients with complete clearance of RET variant ctDNA among those with best response of partial response, stable disease or progressive disease (per RECIST 1.1). a. Two responses are pending confirmation.

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

All data are preliminary and based on a data cut-off date of 6 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 sponsored by Blueprint Medicines.

**PRESENTING AUTHOR DISCLOSURE:** 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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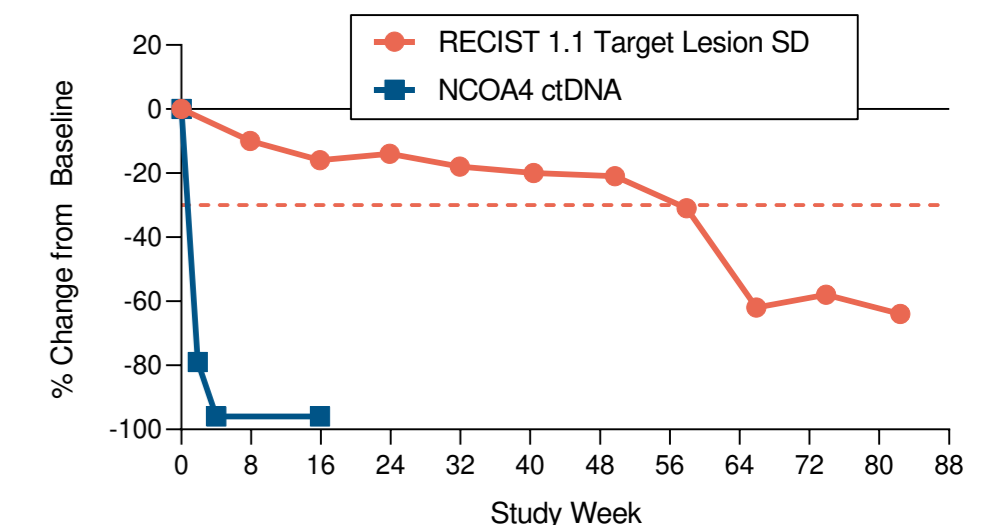
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### Clinical Benefit of Pralsetinib Across RET Genotypes Identified via ctDNA

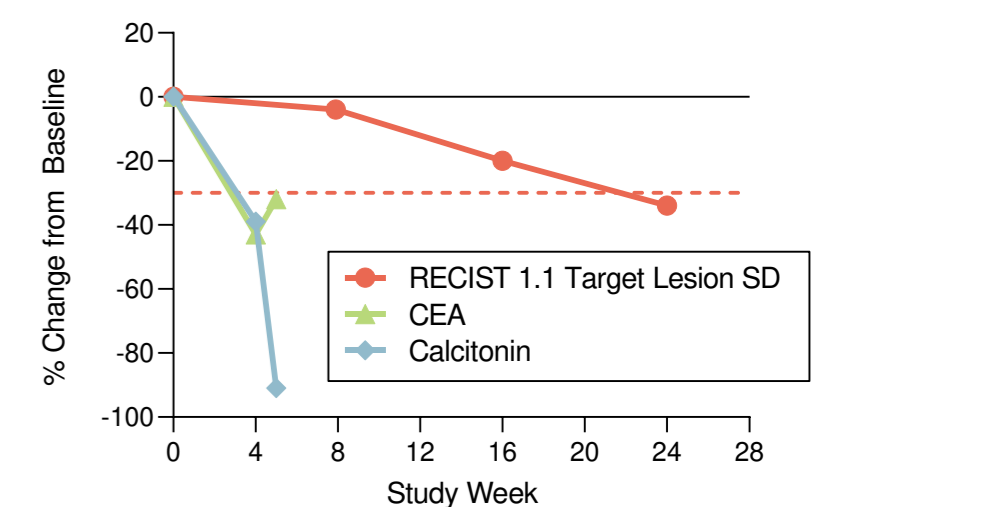
#### NCOA4-RET Fusion: Intrahepatic Bile Duct Cancer<sup>a</sup>

- 51-year-old woman with Stage IV disease including liver and bone
- Best response of progressive disease to three prior lines of therapy (nab-paclitaxel/gemcitabine/cisplatin; erlotinib/bevacizumab; osimertinib)
- With pralsetinib:
  - rapid and near-complete clearance of RET variant ctDNA
  - confirmed, ongoing RECIST 1.1 partial response
- Continues pralsetinib at 19.6 months



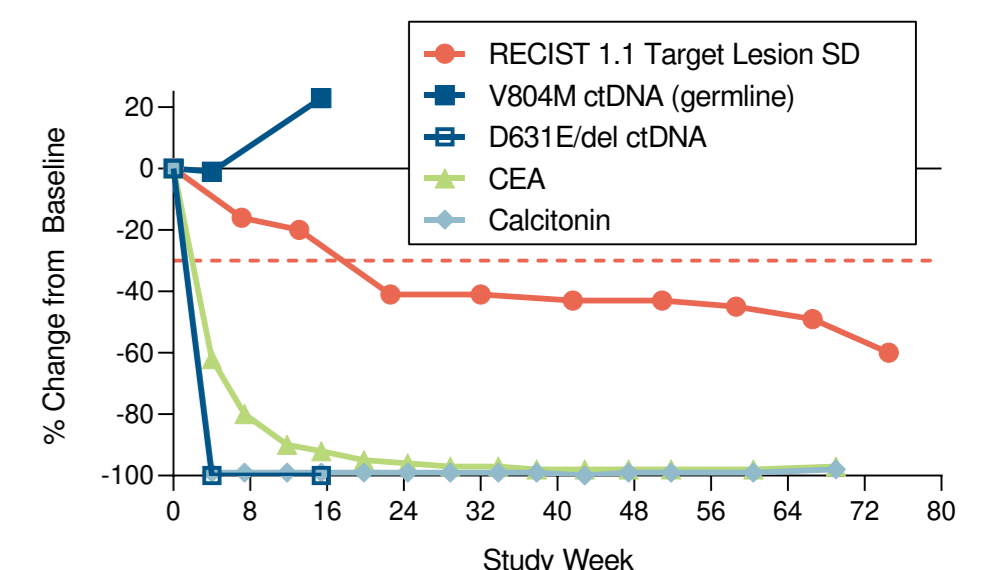
#### M918T and Somatic V804L Resistance Mutation: MTC

- 53-year-old woman with Stage IV disease including liver and lymph nodes
- Best response of stable disease, then progression at 10 months, with prior vandetanib
- With pralsetinib:
  - rapid reductions in CEA and calcitonin
  - tumor shrinkage evolving to partial response<sup>b</sup>
- Continues pralsetinib at 6.8 months



#### Germline V804L Mutation: MTC<sup>a</sup>

- 52-year-old man with Stage IV disease including liver, lung and lymph nodes
- Previously received sunitinib with best response of stable disease
- With pralsetinib:
  - rapid reductions in CEA and calcitonin
  - clearance of somatic RET D631del mutation
  - confirmed, ongoing RECIST 1.1 partial response
- Continues pralsetinib at 17.6 months



Pralsetinib treatment-related adverse events were generally grade 1–2 and manageable; all three patients continue treatment.

CEA, carcinoembryonic antigen; SD, sum of diameters. a. Patients initially received alternate pralsetinib starting doses in the dose-escalation study portion, and have since transitioned to 400 mg QD. b. Post treatment ctDNA analysis and confirmation of response are 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 durable responses as well as 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