

Clinical activity and safety of the RET inhibitor pralsetinib in patients with *RET* fusion–positive solid tumors: update from the ARROW trial

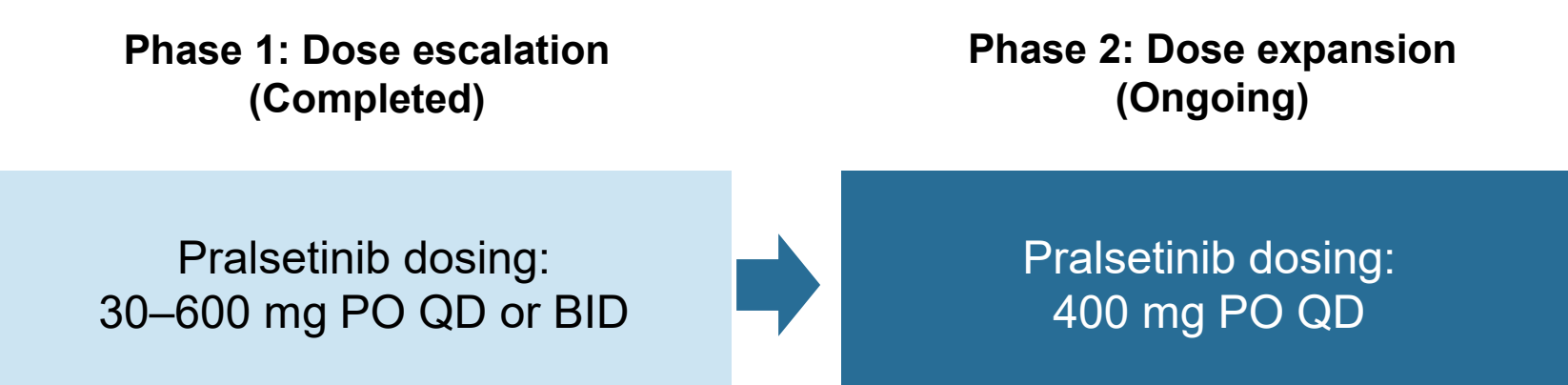
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Background and methods

- Rearranged during transfection (*RET*) fusions are oncogenic drivers in several tumor types^{1–10}
- 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^{11,12}
- Pralsetinib is a highly potent, oral, selective *RET* inhibitor that targets *RET* alterations, including fusions and mutations, regardless of the tissue of origin^{13,14}
- Data from the ongoing global phase 1/2 ARROW study (NCT03037385) supported the US FDA approval of pralsetinib once daily (QD) for *RET* fusion–positive non-small cell lung cancer (NSCLC) and advanced/metastatic *RET*-altered thyroid cancers¹⁵
- Here we provide an update on the clinical activity of pralsetinib in patients with advanced *RET* fusion–positive solid tumors other than NSCLC and thyroid cancer (“other” *RET* fusion–positive solid tumors)

ARROW study design



Eligibility criteria

- Age ≥18 years
- Advanced or metastatic solid tumor
- RET* alteration per local assessment
- Measurable disease (RECIST v1.1)
- ECOG PS 0–1

Other *RET* fusion–positive tumors (other than NSCLC and thyroid)

Data presented for patients enrolled between March 17, 2017, and May 22, 2020

Data cut-off November 6, 2020

- 1° endpoints:**
- ORR (BICR per RECIST v1.1)
 - Safety
- Key 2° endpoints:**
- DOR
 - PFS
 - CBR
 - OS
 - DCR

BICR, Blinded Independent Centralized Review; BID, twice daily; CBR, clinical benefit rate: CR or PR or SD of ≥16 weeks; CR, complete response; DCR, disease control rate: confirmed CR or PR or SD; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; ORR, overall response rate: confirmed CR or PR; OS, overall survival; PFS, progression-free survival; PO, by mouth; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection; SD, stable disease.

Baseline characteristics

<i>RET</i> fusion–positive solid tumors (N=21) ^a	
Median age (range), years	55 (31–71)
Male / female, n (%)	8 (38) / 13 (62)
ECOG PS, n (%)	
0	7 (33)
1	14 (67)
Tumor type, n (%)	
Lung (other than NSCLC) ^b	4 (19)
Pancreatic	3 (14)
Cholangiocarcinoma	3 (14)
Colon	3 (14)
Primary unknown	2 (10)
Other tumor types ^c	6 (29)
History of CNS metastases, n (%)	4 (19)
TNM stage at screening, n (%)	
III	3 (14) ^d
IV	18 (86)
<i>RET</i> fusion partner, n (%)	
<i>CCDC6</i>	5 (24)
<i>KIF5B</i>	5 (24)
<i>NCOA4</i>	4 (19)
Other ^e	2 (10)
Unknown	5 (24)
Median prior lines of therapy, n (range)	2 (1–9)
Prior lines of therapy, n (%)	
0	2 (10)
1–2	13 (62)
≥3	6 (29)
Prior therapies, n (%)	19 (91)
Multikinase inhibitor	7 (33)
Chemotherapy	18 (86)
PD-(L)1 inhibitor	2 (10)
Other systemic therapies	8 (38)
Prior radiation therapy, n (%)	8 (38)
Prior cancer-related surgery, n (%)	14 (67)

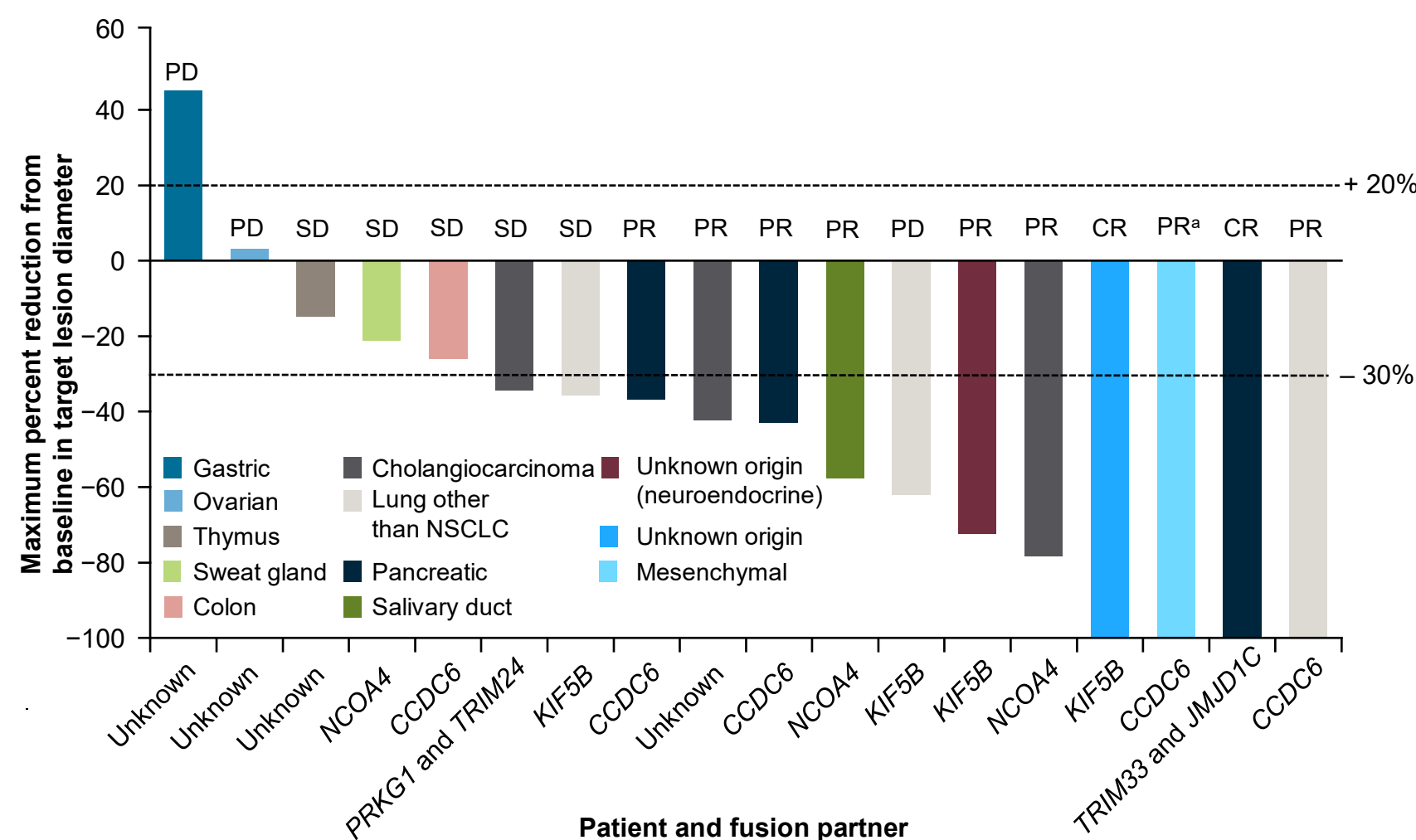
Percentages may not add up to 100 due to rounding. ^aData for patients enrolled by May 22, 2020; data cut-off Nov 6, 2020. 1 patient initiated alternate pralsetinib dose in the dose-escalation part before transitioning to 400 mg QD, all others initiated 400 mg QD. ^bIncludes adenocarcinoma with mixed neuroendocrine differentiation (n=1), atypical carcinoid (n=1), non-small cell/small cell (n=1), and sarcoma/adenocarcinoma (n=1). ^cIncludes gastric (n=1), malignant mesenchymal tumor (n=1), salivary duct (n=1), sweat gland (n=1), ovarian (n=1), and thymus adenocarcinoma (n=1). ^dGastric, mesenchymal and ovarian tumors. ^eIncludes *PRKG* and *TRIM24* (n=1) and *TRIM33* and *JMJD1C* (n=1). *CCDC6*, coiled-coil domain containing 6; CNS, central nervous system; *KIF5B*, kinesin family member 5b; *NCOA4*, nuclear receptor coactivator 4; PD-(L)1, programmed cell death/programmed cell death ligand-1; TNM, tumor node metastasis.

Efficacy summary

<i>RET</i> fusion–positive solid tumors (N=19) ^a	
ORR, % (95% CI)	53 (29–76)
CR, n (%)	2 (11)
PR, n (%)	8 (42) ^b
SD, n (%)	5 (26)
PD, n (%)	4 (21)
CBR, % (95% CI) ^c	68 (43–87)
DCR, % (95% CI)	79 (54–94)

^a2 patients with colon cancer were excluded from efficacy analyses due to alternate driver mutations (*KRAS*, *PIK3CB*); ^bIncludes 1 patient with mesenchymal tumor had unconfirmed ongoing CR at data cut-off. ^cConfirmed CR, PR, or SD with duration ≥16 weeks.

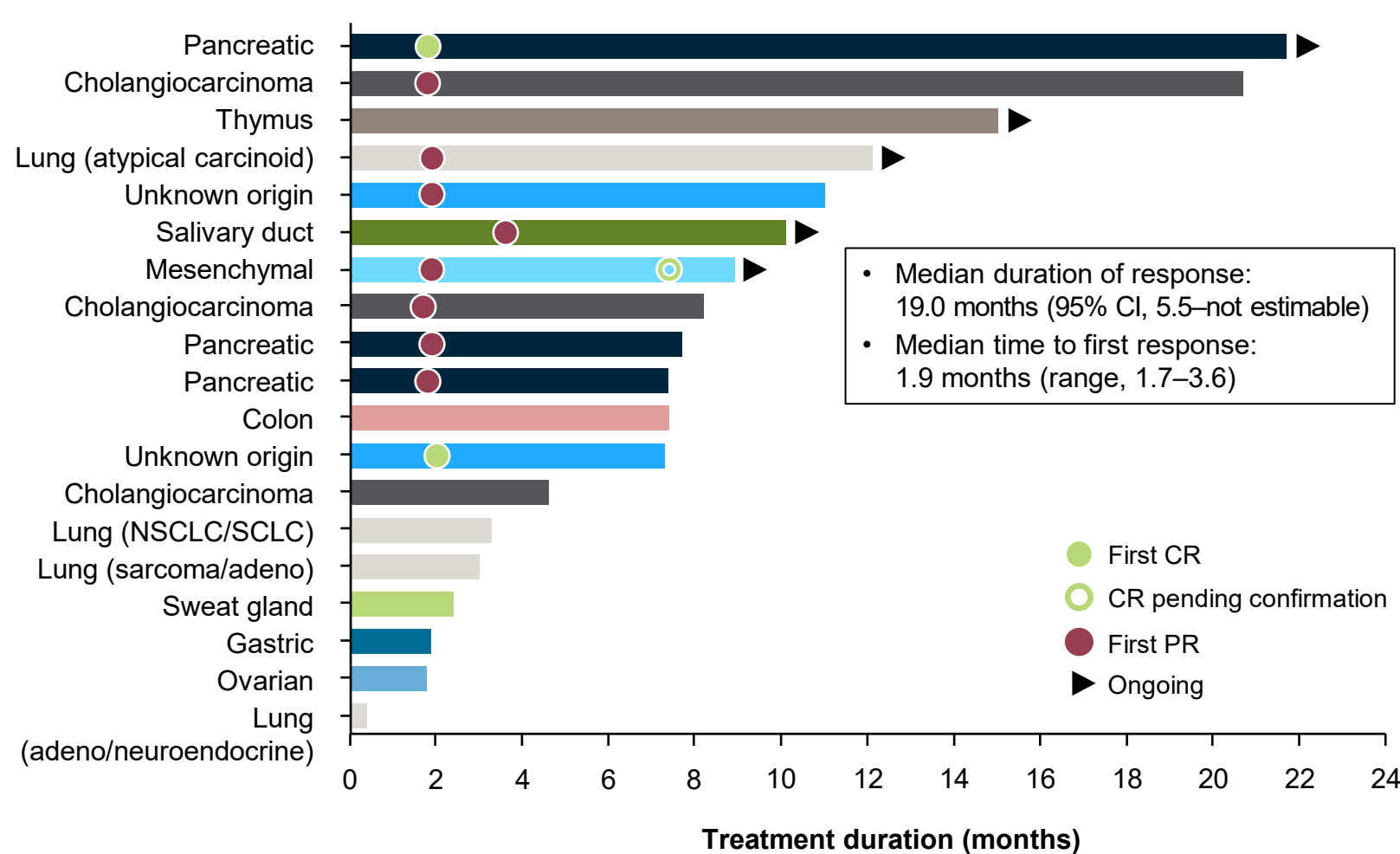
Best overall tumor response



^aPatient with PR had CR at one scan which was pending confirmation at data cut-off. *PRKG1*, cGMP-dependent protein kinase 1; *JMJD1C*, jumonji domain containing 1C; *TRIM24*, tripartite motif containing 24; *TRIM33*, tripartite motif containing 33.

- Responses occurred across multiple tumor types, including all 3 patients with pancreatic cancer (including a CR ongoing at 20.8 months on treatment), 2 of 2 with unknown primary tumors, 2 of 3 with cholangiocarcinoma, and 1 each with mesenchymal, salivary duct, and lung carcinoid tumors
- Tumor shrinkage was observed in 89% of 18 evaluable patients with post-baseline tumor assessment (1 of 19 evaluated for efficacy did not have a complete post-baseline scan due to a new lesion)

Duration of treatment



CI, confidence interval; SCLC, small cell lung cancer.

Treatment-related adverse events

AE, n (%)	<i>RET</i> fusion–positive solid tumors (N=21)	
	Any grade	Grade ≥3
Increased ALT	9 (43)	1 (5)
Increased AST	8 (38)	1 (5)
Neutropenia	7 (33)	6 (29)
Anemia	7 (33)	4 (19)
Thrombocytopenia	5 (24)	2 (10)
Hypertension	4 (19)	2 (10)
Decreased white blood cell count	4 (19)	1 (5)
Fatigue	4 (19)	0
Constipation	4 (19)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Most treatment-related AEs were primarily Grade 1–2
- 1 patient discontinued treatment due to treatment-related AEs
- Overall, 8 patients (38%) had dose reductions due to treatment-related AEs

Conclusions

- Pralsetinib showed robust, durable antitumor activity in patients across a variety of *RET* fusion–positive, heavily pre-treated, advanced solid tumors
- Pralsetinib was well tolerated with a safety profile generally consistent with that previously reported in the overall safety population (all tumor types), with no new safety signals
- Over half of patients (53%) experienced objective tumor responses and tumor shrinkage was observed in 89% of evaluable patients, irrespective of *RET* fusion partner
- These data highlight the need for broad *RET* testing to identify candidates who may benefit from treatment with pralsetinib
- Enrollment of patients with other *RET* fusion–positive solid tumors in ARROW is ongoing

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