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 cancers[15]
- 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

Phase 1: Dose escalation (Completed)

Pralsetinib dosing: 30–600 mg PO QD or BID

Phase 2: Dose expansion (Ongoing)

Pralsetinib dosing: 400 mg PO QD

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

1º endpoints:
- ORR (BICR per RECIST v1.1)
- Safety

Key 2º 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

	RET 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)
***RET* fusion partner, n (%)**	
CCDC6	5 (24)
KIF5B	5 (24)
NCOA4	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)

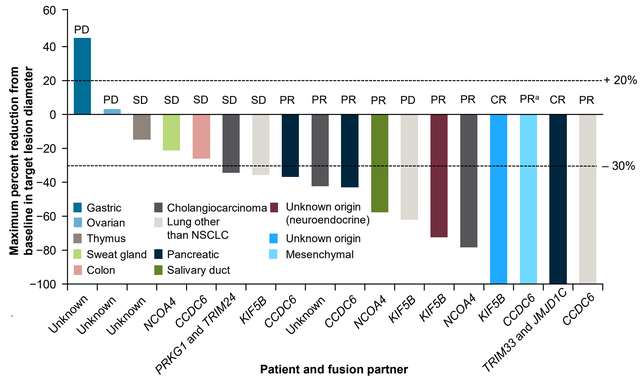
Percentages may not add up to 100 due to rounding. [a]Data for patients enrolled by May 22, 2020; data cut-off Nov 6, 2020. 1 patient initiated alternate pralsetinib dose in the dose-escalation part before transitioning to 400 mg QD, all others initiated 400 mg QD. [b]Includes adenocarcinoma with mixed neuroendocrine differentiation (n=1), atypical carcinoid (n=1), non-small cell/small cell (n=1), and sarcoma/adenocarcinoma (n=1). [c]Includes gastric (n=1), malignant mesenchymal tumor (n=1), salivary duct (n=1), sweat gland (n=1), ovarian (n=1), and thymus adenocarcinoma (n=1). [d]Gastric, mesenchymal and ovarian tumors. [e]Includes *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

	RET 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)

[a]2 patients with colon cancer were excluded from efficacy analyses due to alternate driver mutations (*KRAS, PIK3CB*); [b]Includes 1 patient with mesenchymal tumor had unconfirmed ongoing CR at data cut-off. [c]Confirmed CR, PR, or SD with duration ≥16 weeks.

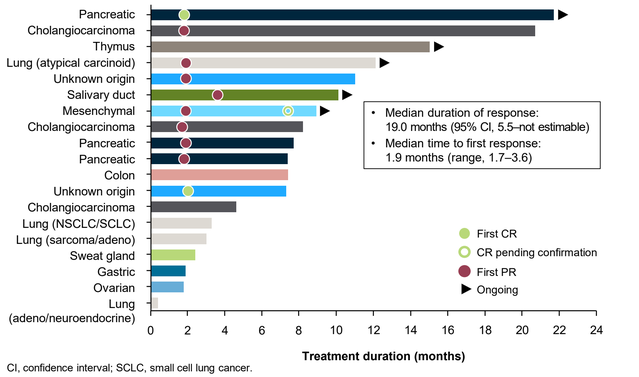
Best overall tumor response



[a]Patient 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 (%)	*RET* 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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