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

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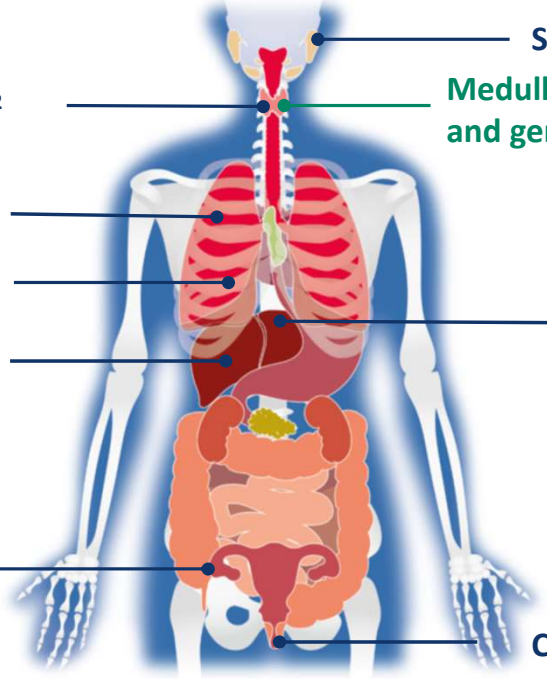
Pralsetinib is an investigational agent discovered by and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

RET fusions are oncogenic drivers in multiple tumor types



- **Standard therapies provide limited benefit for patients with *RET* fusion-positive tumors[12–16]**
- **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.

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151–167; 2. Kato S et al. *Clin Cancer Res.* 2017;23:1988–1997; 3. Paratala et al. *Nat Commun.* 2018;9:4821; 4. Skalova et al. *Am J Surg Pathol*. 2018;42:234–246; 5. Skalova et al. *Am J Surg Pathol*. 2018;42:1445–1455; 6. Krampitz GW et al. *Cancer* 2014;120:1920–1931; 7. Subbiah V et al. *J Clin Oncol.* 2020;38:1209–1221; 8. Gainor JF et al. *J Clin Oncol.* 2019;37:15(suppl):9008; 9. Le Rolle AF et al. *Oncotarget*. 2015;6:28929–28937; 10. Cremolini C et al. *Annals Oncol*. 2017;28:3009–3014; 11. Pietrantonio F et al. *Annals Oncol*. 2018;29:1394–1401; 12. Gandhi L et al. *N Engl J Med*. 2018;378:2078; 13. Hellman MD et al. *N Engl J Med.* 2018;378:2093–2104; 14. Mok TSK et al. *Lancet*. 2019;393:1819–1830; 15. Sandler A et al. *N Engl J Med*. 2006;355:2542–2550; 16. Scagliotti GV et al. *J Clin Oncol.* 2008;26:3543–3551; 17. Sabari JK et al. *J Clin Oncol.* 2018;36:9034; 18. Offin M et al. *JCO Precis Oncol.* 2019 May 16 [epub ahead of print]; 19. Tufman A et al, *J Clin Oncol* 2018;36(suppl 15):e21071; 20. Mazieres J et al. *Ann Oncol.* 2019;30:1321–1328.

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.

1. Subbiah V et al. *Cancer Discov*. 2018;8:836–849.

Pralsetinib Phase 1/2 ARROW study

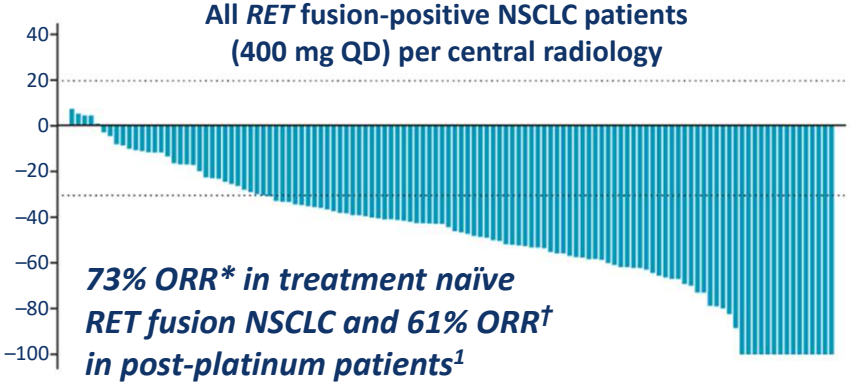
Phase 2 study design

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

Pralsetinib dosing: 400 mg PO QD

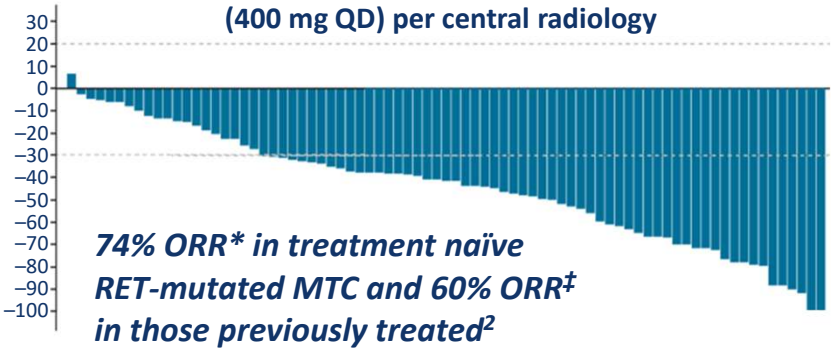
- *RET* fusion-positive NSCLC
- *RET* mutation-positive MTC
- ***RET* fusion-positive other tumors**

All *RET* fusion-positive NSCLC patients (400 mg QD) per central radiology



73% ORR* in treatment naïve RET fusion NSCLC and 61% ORR† in post-platinum patients[1]

All *RET* mutant MTC patients (400 mg QD) per central radiology



74% ORR* in treatment naïve RET-mutated MTC and 60% ORR‡ in those previously treated[2]

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.

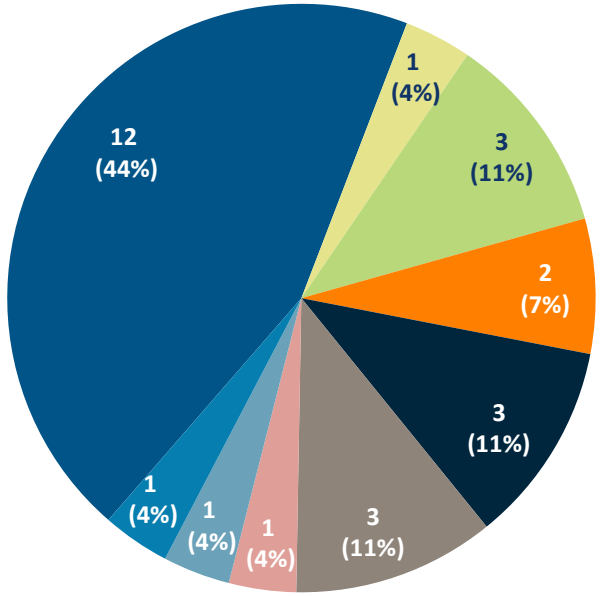
1. Phase 1/2 ARROW trial data in patients with RET fusion-positive NSCLC reported on January 8, 2020. Data cutoff: November 18, 2019. 2. Phase 1/2 ARROW trial data in patients with RET-mutated MTC reported on April 1, 2020. Data cutoff: February 13, 2020.

Baseline characteristics

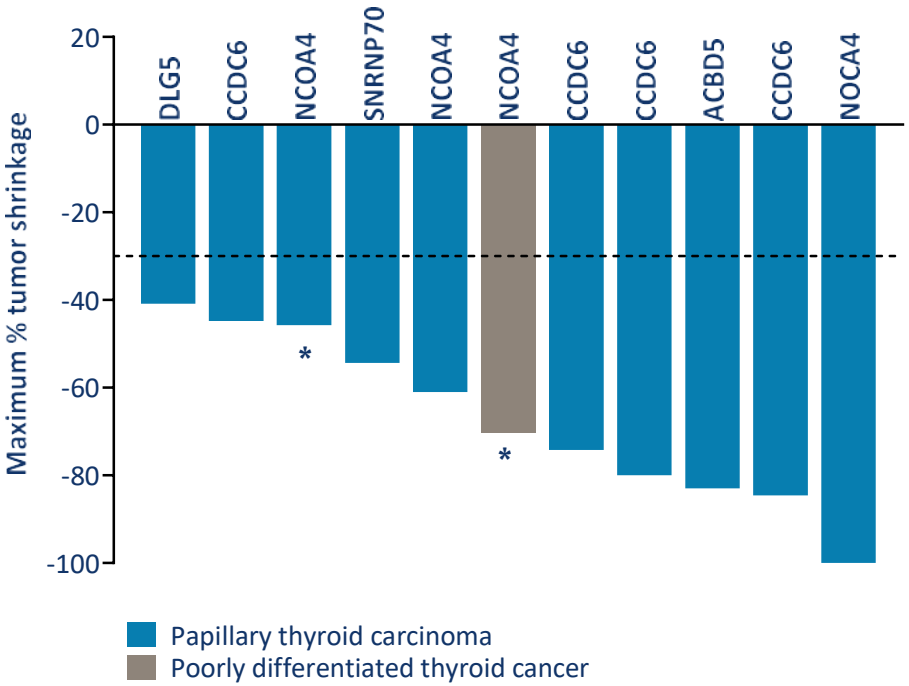
		RET fusion thyroid (n=13)*	Other *RET* fusion tumor types (N=14)†
Median age (range), years		63 (23–74)	54 (31–71)
Male, n (%)		7 (54)	6 (43)
ECOG performance status, n (%)	0	4 (31)	5 (36)
	1	8 (62)	9 (64)
	2‡	1 (8)	0
Disease stage, n (%)	III	0	1 (7)
	IV	13 (100)	13 (93)
Brain metastasis, n (%)		5 (38)	2 (14)
Prior therapies, n (%)	Any prior systemic therapy	12 (92)	14 (100)
	Radioactive iodine	12 (92)	0
	Lenvatinib/Sorafenib	7 (54)	0
	Cabozantinib/Vandetanib	2 (15)	1 (7)
	Chemotherapy	0	14 (100)
	Other anticancer therapy	0	7 (50)
Fusion partners, n (%)	CCDC6	6 (46)	4 (29)
	KIF5B	0	3 (21)
	NCOA4	4 (31)	2 (14)
	Other	3 (23)	1 (7)
	Unknown	0	4 (29)

*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)



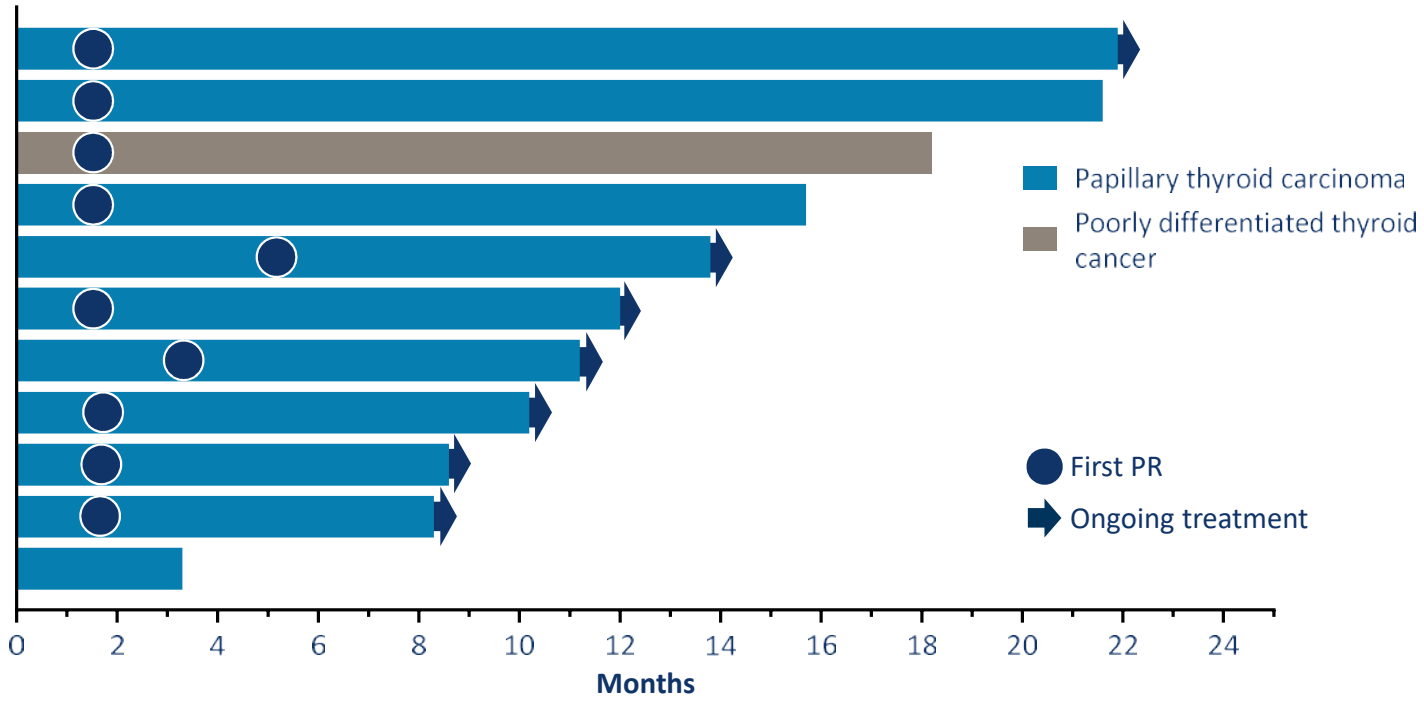
Activity of pralsetinib in *RET* fusion-positive thyroid tumors



Best response, (response evaluable), %	RET fusion-positive thyroid cancer (n=11)†
ORR (95% CI)	91 (59–100)
PR	91
SD	9
PD	0
DCR (95% CI)	100 (72–100)

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

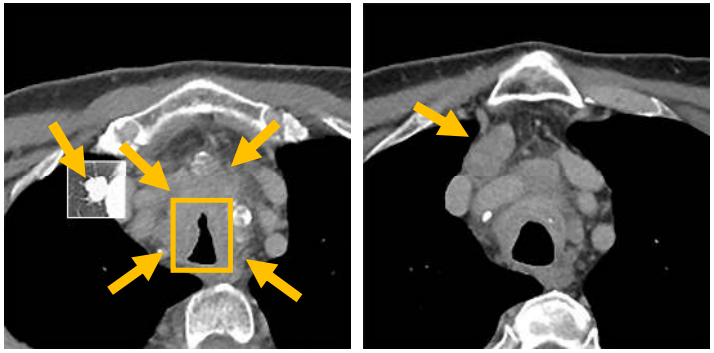


Blinded independent central review of tumor response; response-evaluable patients enrolled by Jul 11, 2019, as of a data cut-off Feb 13, 2020. PR, partial response.

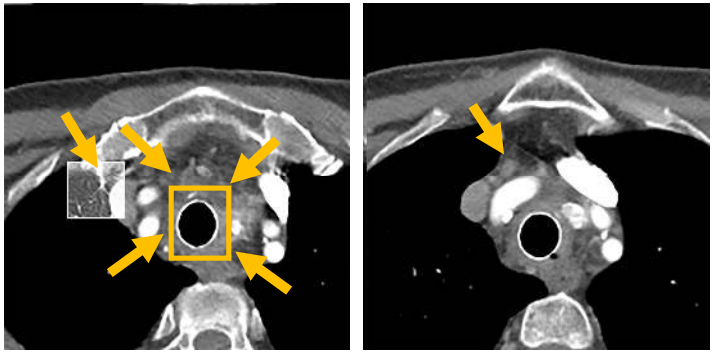
Case study: 66-year-old man with poorly differentiated thyroid cancer

- 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

Baseline

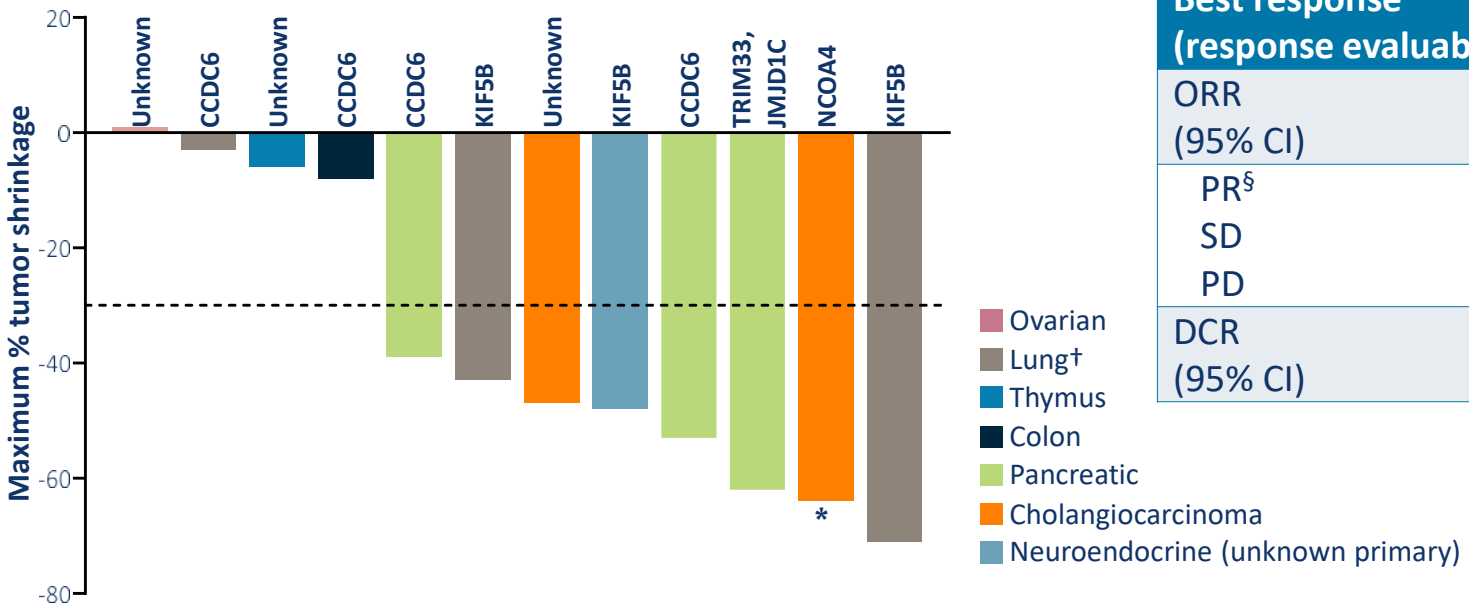


After 8 weeks of therapy



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

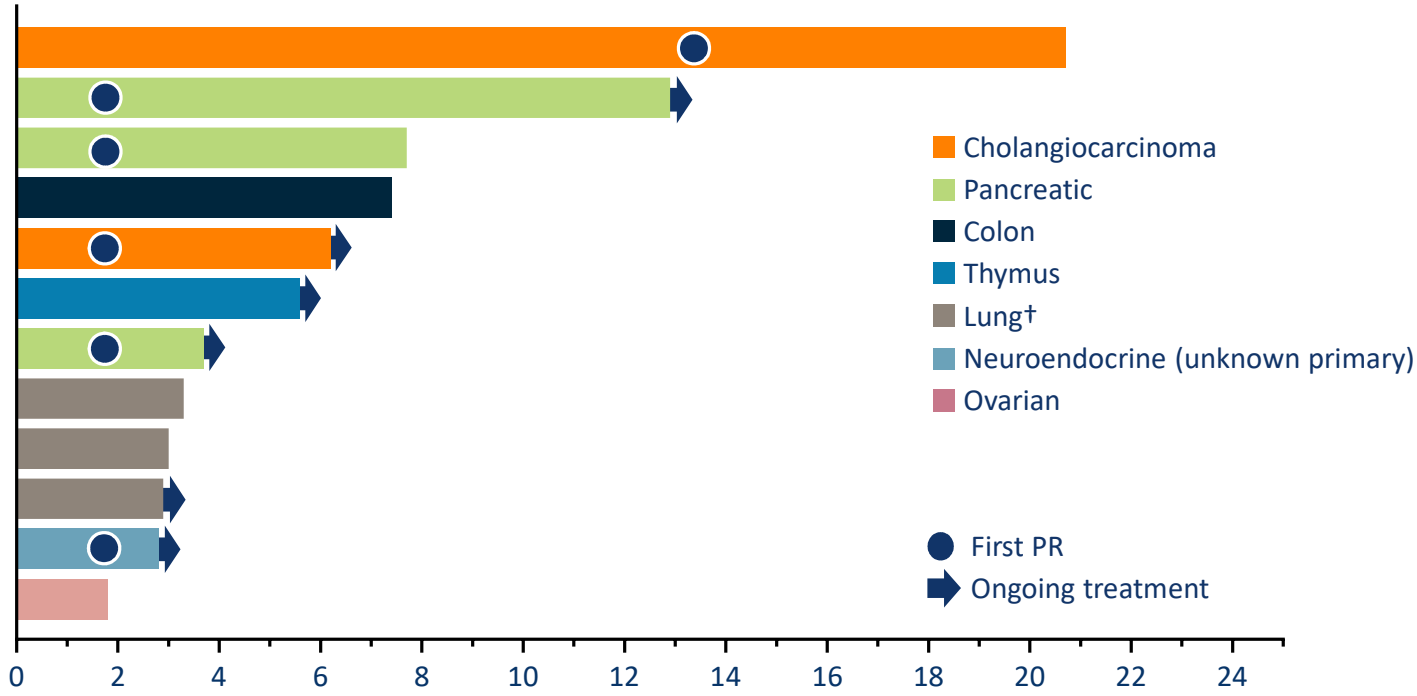


Best response (response evaluable), %	RET fusion-positive tumor (n=12)‡
ORR (95% CI)	50 (21–79)
PR§	50
SD	42
PD	8
DCR (95% CI)	92 (62–100)

- **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.

Pralsetinib treatment duration in patients with various *RET* fusion-positive tumors

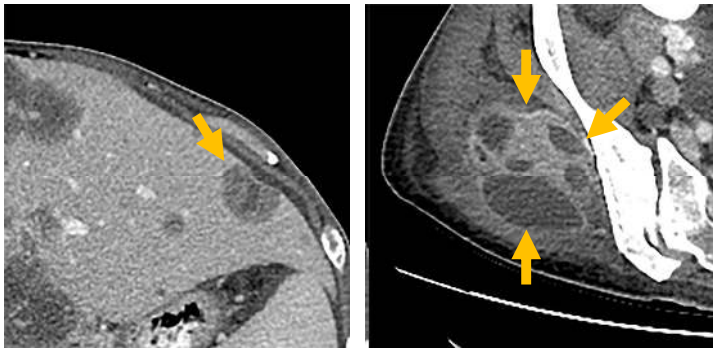


Investigator's assessment of tumor response; response-evaluable patients enrolled by Nov 19, 2019, as of a data cut-off Feb 13, 2020.
†Including mixed sarcoma/adenocarcinoma, mixed SCLC/NSCLC, and atypical carcinoid. NSCLC, non-small-cell lung cancer; PR, partial response; QD, once daily; SCLC, small-cell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

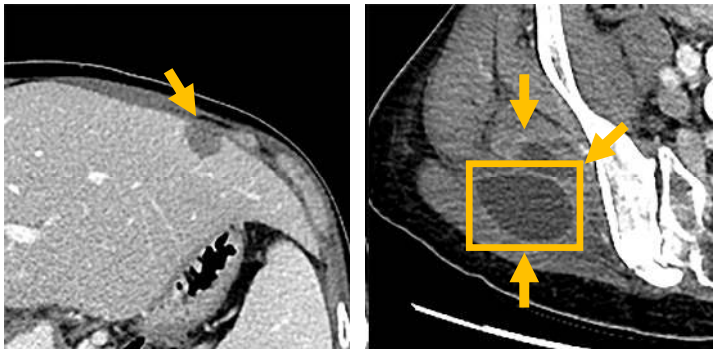
Case study: 51-year-old woman with cholangiocarcinoma

- 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

Baseline



After 8 weeks of therapy



Computed tomography images. CA, carbohydrate antigen; ctDNA, cell-free circulating tumor DNA; NCOA4, nuclear receptor coactivator 4; RET, rearranged during transfection; PD, progressive disease, PR, partial response.

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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