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Pan-cancer efficacy of pralsetinib in patients with *RET* fusion-positive solid tumors from the phase 1/2 ARROW trial

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Oncogenic *RET* fusions occur in diverse cancers. Pralsetinib is a potent, selective inhibitor of *RET* receptor tyrosine kinase. ARROW (NCT03037385, ongoing) was designed to evaluate pralsetinib efficacy and safety in patients with advanced *RET*-altered solid tumors. Twenty-nine patients with 12 different *RET* fusion-positive solid tumor types, excluding non-small-cell lung cancer and thyroid cancer, who had previously received or were not candidates for standard therapies, were enrolled. The most common *RET* fusion partners in 23 efficacy-evaluable patients were *CCDC6* (26%), *KIF5B* (26%) and *NCOA4* (13%). Overall response rate, the primary endpoint, was 57% (95% confidence interval, 35–77) among these patients. Responses were observed regardless of tumor type or *RET* fusion partner. Median duration of response, progression-free survival and overall survival were 12 months, 7 months and 14 months, respectively. The most common grade ≥ 3 treatment-related adverse events were neutropenia (31%) and anemia (14%). These data validate *RET* as a tissue-agnostic target with sensitivity to *RET* inhibition, indicating pralsetinib's potential as a well-tolerated treatment option with rapid, robust and durable anti-tumor activity in patients with diverse *RET* fusion-positive solid tumors.

The *RET* proto-oncogene (*RET*) encodes a transmembrane receptor tyrosine kinase (proto-oncogene tyrosine protein kinase receptor *RET*) that has a physiological role in the embryonic development of the nervous system and the kidneys^{1,2}. *RET* fusions and mutations induce oncogenic transformation, leading to the aberrant activation of *RET* receptor tyrosine kinase³. *RET* fusions can be found in 1–2% of non-small-cell lung cancers (NSCLCs), approximately 20% of papillary thyroid cancers and <1% of many other solid tumors, including ovarian, pancreatic, salivary and colorectal cancers^{4–8}.

Pralsetinib (formerly known as BLU-667, Blueprint Medicines Corporation) is a selective *RET* inhibitor that potently targets *RET* kinases, including *RET* fusion proteins. The recommended phase 2 dose of 400 mg once daily (QD) orally administered pralsetinib was determined in phase 1 of the ARROW study⁹. Pralsetinib has low affinity for off-target kinases. In a biochemical assay, pralsetinib was 88-fold more selective for *RET* than for vascular endothelial growth factor receptor 2 (*VEGFR2*), a tyrosine kinase receptor that is targeted by multi-kinase inhibitors such as cabozantinib and vandetanib². Based on the results from the registrational phase 1/2 ARROW study (NCT03037385)^{10,11}, pralsetinib was approved in

several countries globally, including the United States, for treatment of metastatic *RET* fusion-positive NSCLC, advanced or metastatic *RET*-mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer¹², as well as in the European Union for treatment of advanced *RET* fusion-positive NSCLC¹³.

Pre-clinical and early clinical evidence suggests that *RET* fusions lead to oncogene addiction across tumor types and have the potential to be targeted by selective *RET* inhibition. Recent tumor-agnostic drug approvals have demonstrated that patients can benefit from select molecularly targeted therapies irrespective of tumor histology^{14–18}. These landmark approvals have heralded the era of precision oncology for tissue-agnostic targets. Since the approvals of pralsetinib and selpercatinib in NSCLC and thyroid cancer^{12,19}, biomarker testing for *RET* alterations is recommended in treatment guidelines for patients with these tumor types^{20–22}. However, this is not standard of care across all disease indications where *RET* alterations are recognized as oncogenic drivers^{23,24}.

ARROW is a phase 1/2 study of the highly selective *RET* inhibitor pralsetinib in patients with medullary thyroid cancer, *RET*-altered NSCLC and other *RET*-altered solid tumors. Efficacy and safety of pralsetinib in patients with *RET*-altered NSCLC and thyroid cancer

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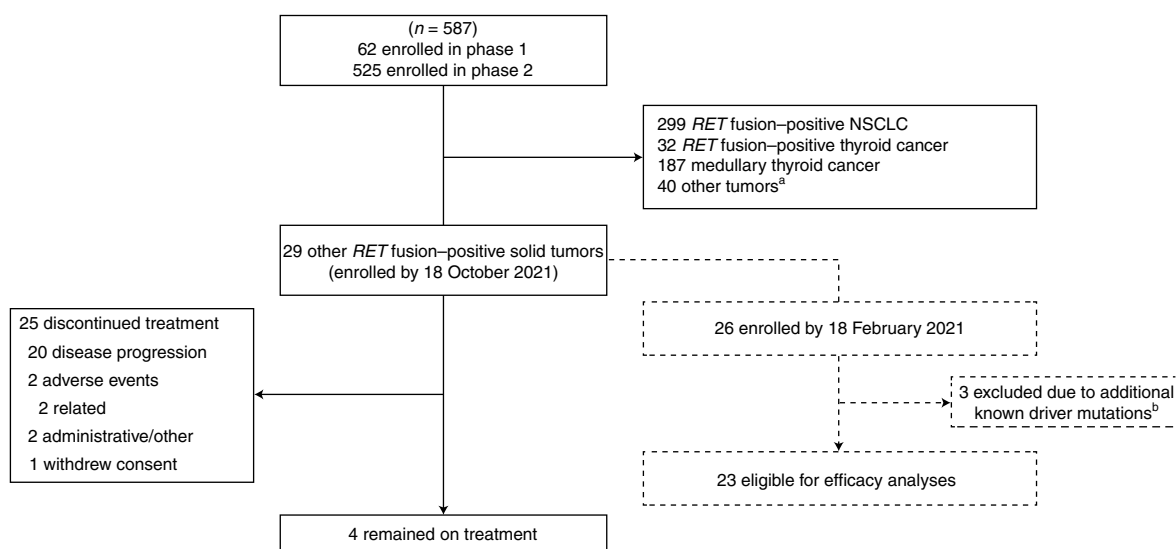


Fig. 1 | Patient disposition. A flowchart that illustrates enrollment of patients with *RET* fusion-positive solid tumors in the safety ($n=29$) and efficacy-evaluable ($n=23$) populations in the context of the overall study population of 587 patients, as well as the status of these patients at the data cutoff. ^aOther *RET*-mutant tumors ($n=15$), no or unknown *RET* status ($n=2$) and prior treatment with a *RET* inhibitor ($n=23$). ^bThree patients (two with colon cancer and one with cholangiocarcinoma) had additional driver mutations (*KRAS*, *PIK3CB* and *BRAF*).

from the ARROW study were previously reported^{10,11}. After recent approvals of pralsetinib in patients with *RET*-altered NSCLC and thyroid cancers and respective publications of these data, here we present interim data on the efficacy and safety of pralsetinib in prospectively identified patients with diverse *RET* fusion-positive tumors.

Results

Patients. Between 17 March 2017 and the data cutoff date of 18 October 2021, 587 patients were enrolled across all groups (Fig. 1 and Extended Data Fig. 1). Of these, 29 patients had *RET* fusion-positive solid tumors, excluding *RET* fusion-positive NSCLC or thyroid cancer, and were included in the safety population presented here. In total, 28 patients (96%) received a starting dose of pralsetinib 400 mg QD, and one patient (4%) received a starting dose of pralsetinib 200 mg/100 mg twice daily but transitioned to 400 mg QD after 3.4 months; the latter patient was the only patient included from the dose-escalation phase of the ARROW trial. At the data cutoff date, four patients (14%) remained on treatment, and 25 patients (86%) had discontinued treatment for the following reasons: disease progression (20 patients (69%)); administrative/other (two patients (7%)); adverse events (AEs) (two patients (7%)), of which both were treatment-related—grade 3 thrombocytopenia and grade 3 neutropenia; and withdrew consent (one patient (3%)).

Twenty-six of the 29 patients in the safety population enrolled by the 18 October 2021 data cutoff, with *RET* fusion-positive solid tumors excluding *RET* fusion-positive NSCLC or thyroid cancer, were enrolled by the efficacy enrollment cutoff date of 18 February 2021. Fourteen of 26 patients were confirmed to have co-occurring alterations at study entry (Extended Data Fig. 2). *RET* fusions were identified as the only oncogenic driver in 23 patients (three patients had other oncogenic drivers in addition to *RET* and were excluded from the efficacy-evaluable population due to this pre-specified criterion). Among these 23 patients evaluable for efficacy, the median age was 53 years (range, 31–71); 14 patients (61%) were female; 20 (87%) patients had metastatic disease; and 20 (87%) patients had received prior therapies at baseline (Table 1 and Extended Data Fig. 3). The most common cancer diagnoses in the efficacy-evaluable population were pancreatic cancer (four patients (17%)), cholangiocarcinoma (three patients (13%)), neuroendocrine cancer (three patients (13%)),

sarcoma (three patients (13%): malignant mesenchymal tumor (one patient (4%)), mixed sarcoma and adenocarcinoma (one patient (4%)), malignant isolated fibroma (one patient (4%))), head and neck cancer (two patients (9%): sweat gland cancer (one patient (4%)), salivary duct cancer (one patient (4%))), colorectal cancer (two patients (9%)) and small-cell lung cancer (SCLC) (two patients (9%)). Three patients had stage 3 disease, including one patient with stage 3 ovarian cancer who had received nine prior lines of therapy and one patient each with stage 3B gastric cancer or sarcoma who had both received one prior line of therapy. Two patients had not received prior systemic therapy, both of whom had stage 4 head and neck cancer.

RET fusions were identified by next-generation sequencing (NGS) in 16 patients (70%), by fluorescence in situ hybridization (FISH) in five patients (22%) and by GeneTrails Solid Tumor Fusion Panel and local NGS each in one patient (4%). Central circulating tumor DNA (ctDNA) analysis was also performed in patients for whom FISH was used, with the aim of identifying the *RET* fusion partners. The most common *RET* fusion partners were *CCDC6* (six patients (26%)), *KIF5B* (six patients (26%)) and *NCOA4* (three patients (13%)) (Table 1). None of the tumors in the patients with pancreatic cancer was identified to harbor *KRAS* mutations.

Efficacy. Overall response rate (ORR) was the primary endpoint of phase 2 of this study. In the 23 patients eligible for efficacy analyses, the ORR was 57% (95% confidence interval (CI), 35–77); three (13%) had a confirmed complete response (CR); and ten (43%) had a confirmed partial response (PR) (Table 2). Target tumor shrinkage per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was seen in 91% of patients with post-baseline tumor assessments (Fig. 2a); one patient with progression based on a new site of disease did not have post-baseline assessment of RECIST target lesions.

Confirmed tumor responses were observed in all four patients with pancreatic cancer (including one CR), two of three patients with cholangiocarcinoma, two of three patients with sarcoma (including one CR), two of three patients with neuroendocrine cancer and single patients with head and neck cancer and unknown primary tumor (CR). The other patient with cholangiocarcinoma had a single timepoint response before discontinuing treatment due to an AE.

Table 1 | Patient demographics and baseline characteristics

Demographic/characteristic	RET fusion-positive solid tumors	
	Efficacy-evaluable population ^a (n = 23)	Safety population ^b (n = 29)
Median age (range), years	53 (31–71)	55 (25–75)
Sex, n (%)		
Female	14 (61)	18 (62)
Male	9 (39)	11 (38)
Race, n (%)		
White	15 (65)	20 (69)
Asian	7 (30)	8 (28)
Black	1 (4)	1 (3)
ECOG performance status, n (%)		
0	7 (30)	11 (38)
1	16 (70)	18 (62)
Tumor type, n (%)		
Pancreatic	4 (17)	5 (17)
Cholangiocarcinoma	3 (13)	4 (14)
Neuroendocrine	3 (13)	3 (10)
Sarcoma	3 (13)	3 (10)
Head and neck	2 (9)	2 (7)
Colorectal	2 (9)	5 (17)
SCLC	2 (9)	2 (7)
Unknown primary	1 (4)	1 (3)
Gastric	1 (4)	1 (3)
Ovarian	1 (4)	1 (3)
Thymic	1 (4)	1 (3)
CNS	0	1 (3)
History of CNS metastases, n (%)	6 (26)	7 (24)
TNM stage, n (%)		
III	3 (13)	4 (14)
IV	20 (87)	24 (83)
Unknown	0	1 (3)
RET fusion partner, n (%)		
CCDC6	6 (26)	9 (31)
KIF5B	6 (26)	6 (21)
NCOA4	3 (13)	4 (14)
Other ^c	5 (22)	6 (21)
Unknown	3 (13)	4 (14)
Median prior lines of therapy, n (range)	2 (1–9)	2 (1–9)

Baseline demographic and clinical characteristics of patients in the safety population (n = 29) and efficacy-evaluable population (n = 23) with RET fusion-positive solid tumors. Three patients in the safety population were not enrolled by the efficacy enrollment date of 18 February 2021, and an additional three patients had oncogenic drivers in addition to RET and were excluded from the efficacy-evaluable population. ^aEnrollment as of 18 February 2021 and data cutoff date 18 October 2021. ^bEnrollment and data cutoff date as of 18 October 2021. ^cIncludes ANKRD26, MYH10, NUP93, SATB1, PRKG1 and TRIM24, and TRIM33 and JMJD1C. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastases.

The clinical benefit rate (CBR) was 70% (16/23 patients), and the disease control rate (DCR) was 83% (19/23 patients) (Table 2). Median duration of response (DOR) was 11.7 months (95% CI, 5.5–19.0)

Table 2 | Summary of tumor response

Response, n (%)	RET fusion-positive solid tumors (n = 23) ^a
ORR ^b (95% CI)	13 (57) (35–77)
CR	3 (13)
PR	10 (43)
SD	6 (26)
PD	4 (17)
CBR ^c (95% CI)	16 (70) (47–87)
DCR ^d (95% CI)	19 (83) (61–95)
Median DOR, months (95% CI) ^e	11.7 (5.5–19.0)

Response rates and the number of patients with each individual response per RECIST version 1.1 in the efficacy-evaluable population (n = 23). Two-sided 95% CIs were based on exact binomial distributions using the Clopper-Pearson method. ^aEnrollment as of 18 February 2021 and data cutoff date 18 October 2021. Excludes three patients (two with colon cancer and one with cholangiocarcinoma) with additional driver mutations (KRAS, PIK3CB and BRAF). ^bConfirmed CR or PR. ^cConfirmed CR, PR or SD \geq 16 weeks. ^dConfirmed CR, PR or SD. ^eKaplan-Meier estimated.

with a median follow-up of 26.7 months (95% CI, 9.3–26.7) (Extended Data Fig. 4a). DOR rates were 69% (95% CI, 44–94) at 6 months and 39% (95% CI, 8–69) at 12 months. Of the 13 patients with CR or PR, DOR was \geq 6 months for nine (69%) (Fig. 2b); two (15%) had response durations of \geq 18 months, one (8%) of whom had a response duration of \geq 24 months. Median time to response was 1.9 months (range, 1.7–3.6); at data cutoff, 31% (4/13) of patients had ongoing responses.

Although individual results may vary, among the patients with tumor response, three cases were particularly notable. A man in his early 30s had pancreatic cancer (2.5-cm pancreatic head mass) with multiple hepatic metastases (largest 2.3 cm and 2.4 cm) and multiple peripancreatic lymph nodes at treatment initiation, and his tumor harbored RET-TRIM33 and RET-JMJD1C fusions; other genomic alterations detected on liver biopsy were FGFR4 p.R493Q, which was a variant of unknown significance, and PTCH1 p.1287_1303del and PTEN copy number loss, which were not considered actionable drivers. Baseline cancer antigen (CA) 19-9 was 12.6 U ml⁻¹, and baseline carcinoembryonic antigen was 2.5 ng ml⁻¹. This patient, who had previously experienced progressive disease (PD) and treatment-limiting toxicity on one prior line of chemotherapy (PD and toxicity on capecitabine), had a CR with pralsetinib (100% decrease in the sum of lesion diameters (SLD)). This patient continued treatment with an ongoing CR at a treatment duration of 33.1 months as of the 18 October 2021 data cutoff.

A woman in her early 50s had an intrahepatic cholangiocarcinoma with a RET-NCOA4 fusion and metastases to liver and bone on diagnosis. Diagnostic imaging revealed a large mass with at least a 13 × 8 cm diameter and 20 satellites of different diameters (most ~15 mm) (Fig. 3a,b). The patient had a PR with pralsetinib after experiencing a best response of PD on all three prior lines of therapy (received for \leq 3 months: gemcitabine/cisplatin/abraxane, erlotinib/bevacizumab and osimertinib). Other genomic alterations identified in this patient were EGFR A1118T, which was not an actionable driver, and CDKN2A/B loss, which was a variant of unknown significance; microsatellite status was stable, and tumor mutation burden was low (three mutations per megabase). Liver immunohistochemistry was positive for CK7 and CDX-2 and negative for CK20. Throughout treatment with pralsetinib, CA 19-9 reduced from 1 × 10⁶ U ml⁻¹ to 82 U ml⁻¹, and CA-125 reduced from 1,591 U ml⁻¹ to 16.4 U ml⁻¹, with rapid and near-complete clearance of RET-NCOA4 fusion ctDNA. This patient received treatment with continued tumor shrinkage (to a maximum of 77% reduction in measurable disease) for 20.7 months before ultimately succumbing

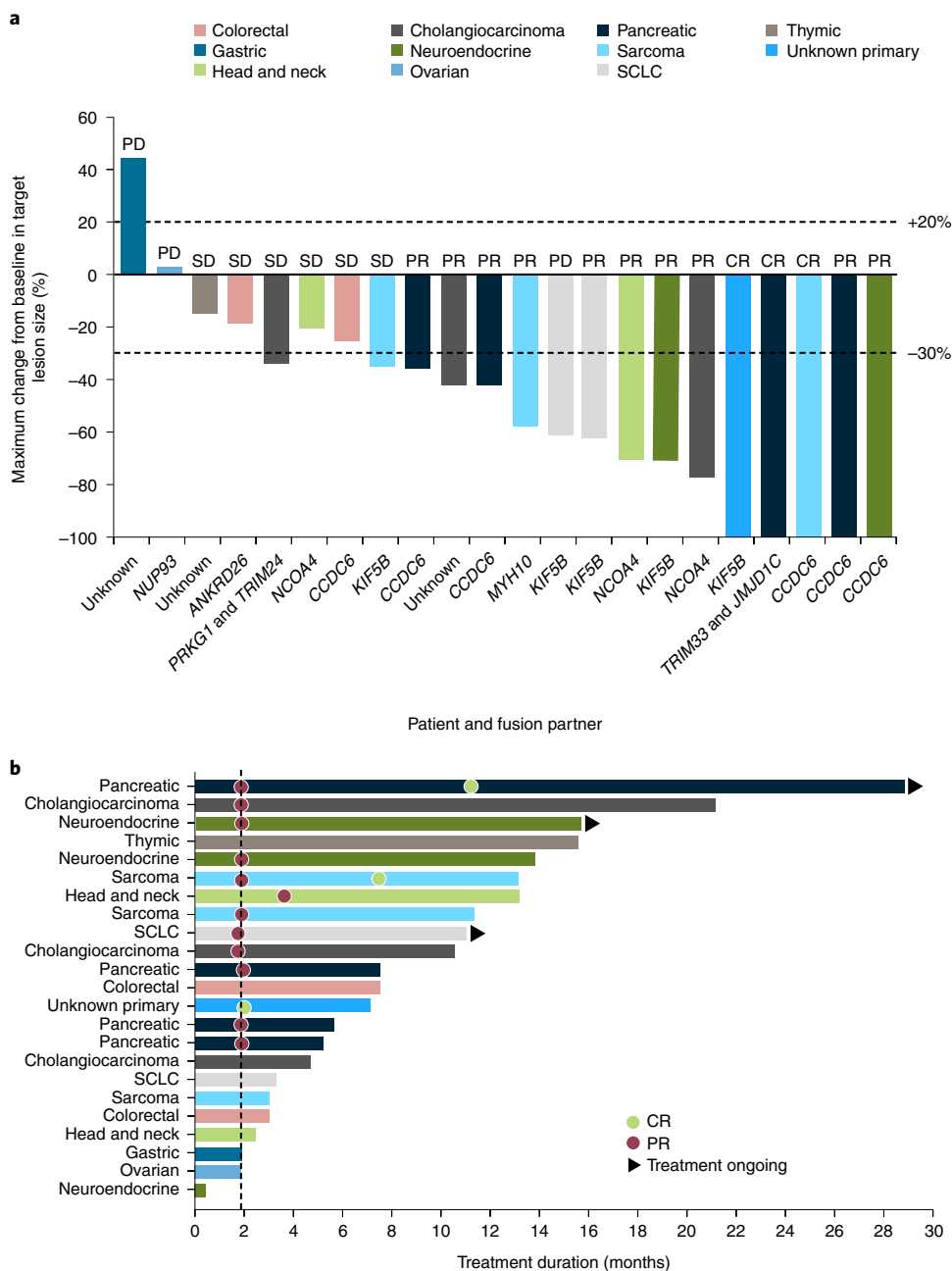


Fig. 2 | Individual tumor response and treatment duration waterfall and swimlane plots for the efficacy-evaluable population. In 23 patients eligible for efficacy analyses: **a**, tumor response by BICR and maximum change from baseline in target lesion size, showing each patient’s tumor type and *RET* fusion partner; **b**, treatment duration, indicating the corresponding tumor type and the timeline for response, where the dotted line represents median time to response (1.9 months). One patient with progression based on a new site of disease did not have post-baseline assessment of RECIST target lesions and so is not shown in **a**.

to PD, leading to treatment discontinuation and death before the data cutoff.

A woman in her early 60s with a sarcoma (malignant mesenchymal tumor) with a *RET-CCDC6* fusion and no metastases had a PR after 1.9 months of pralsetinib treatment that had evolved to a CR at the time of the data cutoff (100% decrease in SLD), with treatment duration of 19.4 months (Fig. 3c). She had two muscular masses on her right upper arm, and the initial pathologic diagnosis after resection was pigmented villonodular synovitis (PVNS). Given this diagnosis, the patient received imatinib as first-line therapy but progressed, with locoregional recurrence with at least four macroscopic tumor nodules in the right arm that were considered inoperable. In

parallel to RNA sequencing analysis that confirmed a *RET-CCDC6* fusion, transcriptomic analysis suggested that the diagnosis was not PVNS but, rather, an undifferentiated histiocytic tumor. Other mutations in the whole-exome RNA sequence included an in-frame fusion of type FN1-PRG4 as well as the reciprocal transcript (also in-frame) and mutations in exon 43 of *ATM* (p.R2105G) and exon 5 of *PDGFRB* (p.R251H). These three mutations were variants of unknown significance. At the time of treatment initiation, a total of seven nodules (8–50 mm) were found on pre-treatment magnetic resonance imaging (MRI) in the soft tissue of the right arm as well as two right axillary lymph nodes (10 mm and 12 mm). As of October 2021, the CR was ongoing after 19.6 months of follow-up.

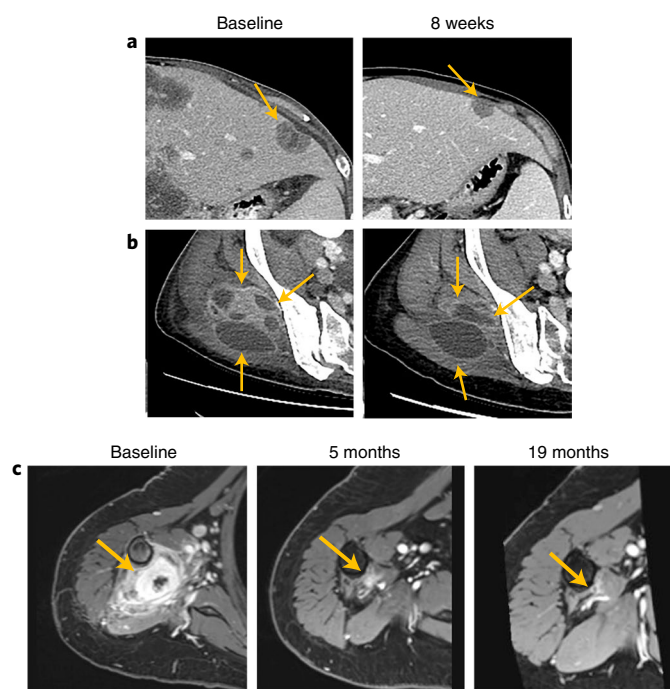


Fig. 3 | Time-dependent disease evaluations in two patients after pralsetinib treatment. Baseline and 8-week disease evaluation in a 51-year-old woman with *RET-NCOA4* fusion-positive cholangiocarcinoma: **a**, at first disease evaluation after 8 weeks receiving pralsetinib, a left hepatic lobe lesion measuring 2 × 3 cm at baseline had reduced to 1.2 × 1.9 cm; **b**, a prior heterogeneously enhancing soft tissue mass in the right gluteal muscles had decreased in size and enhancement and showed increased cystic and necrotic components compared to baseline scans. **c**, Baseline, 5-month and 19-month disease evaluation in a 60-year-old woman with a *RET-CCDC6* fusion-positive sarcoma presenting as two muscular masses in the right upper arm.

Among all 23 patients, median progression-free survival (PFS) was 7.4 months (95% CI, 5.1–13.6) at a median follow-up of 28.5 months (95% CI, 10.9–28.5) (Extended Data Fig. 4b), with a PFS rate of 60% (95% CI, 39–80) at 6 months and 41% (95% CI, 20–62) at 12 months. Median overall survival (OS) was 13.6 months (95% CI, 7.5–not reached) with median follow-up of 23.5 months (95% CI, 19.8–23.9) (Extended Data Fig. 4c), with an OS rate of 78% (95% CI, 61–95) at 6 months and 54% (95% CI, 33–75) at 12 months.

Safety. For the 29 patients in the safety population, median relative dose intensity was 86% (range, 51–124), with a median daily dose of 397 mg (range, 212–400), and median time on treatment was 7.0 months (range, 0.4–33.1). Dose intensity was calculated based on starting dose; as the patient who initiated at 200 mg/100 mg twice daily dosing subsequently received 400 mg QD, this patient had a dose intensity >100%. All patients experienced treatment-emergent AEs, of whom 21 (72%) experienced grade ≥ 3 events (Extended Data Fig. 5). Treatment-related adverse events (TRAEs) occurred in 25 patients (86%), of whom 20 (69%) experienced a grade ≥ 3 TRAE (Table 3). The most common any-grade TRAEs were increased aspartate transaminase (AST; 11 patients (38%)), increased alanine transaminase (ALT; ten patients (34%)) and neutropenia (ten patients (34%)). Grade 4 events were experienced by two patients (7%); one patient experienced thrombocytopenia, and one patient experienced thrombocytopenia, pancytopenia and acute kidney injury. One death occurred in which the cause was unknown; this patient had multiple possible causes of death, including disease progression, pulmonary infection, respiratory failure, cardiac insufficiency and hypertensive

Table 3 | Treatment-related adverse events (TRAEs)

Preferred term, n (%)	<i>RET</i> fusion-positive solid tumors (n = 29) ^a	
	All grades	Grade ≥ 3
Patients with TRAEs	25 (86)	20 (69)
Increased AST	11 (38)	3 (10)
Increased ALT	10 (34)	2 (7)
Neutropenia	10 (34)	9 (31)
Anemia	9 (31)	4 (14)
Constipation	7 (24)	0
Decreased white blood cell count	6 (21)	2 (7)
Thrombocytopenia	5 (17)	2 (7)
Hypertension	5 (17)	2 (7)
Asthenia	5 (17)	0

TRAEs that occurred in $\geq 15\%$ of patients in the safety population (n = 29), which were graded according to the Common Terminology Criteria for Adverse Events version 4.03, with terms pooled. ^aEnrollment and data cutoff date as of 18 October 2021.

heart disease. The death was recorded as treatment related because the cause could not be unequivocally excluded.

In total, 17 patients (59%) had transient dose interruptions due to TRAEs, and 13 patients (45%) had permanent dose reductions due to TRAEs. The most common TRAEs leading to dose interruption were neutropenia (eight patients (28%)), anemia and increased AST (each three patients (10%)) and thrombocytopenia and increased ALT (each two patients (7%)). The most common TRAEs leading to dose reduction were neutropenia (eight patients (28%)), anemia, increased AST and increased ALT (each two patients (7%)).

Discussion

In this phase 1/2 study of pralsetinib in patients with advanced or metastatic *RET* fusion-positive solid tumors, almost all of whom were previously treated with systemic therapy, pralsetinib showed robust and durable anti-tumor activity regardless of tumor type or *RET* fusion partner. *RET* fusions have been identified as oncogenic drivers in multiple tumor types^{4–8,25} and, generally, standard therapies that are effective in tumors without oncogenic drivers are less effective than targeted therapies^{26–28}. Precision oncology paradigms that comprise identification of oncogenic alterations through clinical NGS and subsequent application of genomically targeted therapies are applicable to multiple malignancies. Herein, *RET* fusions defined a unique subset of alterations across multiple tumor types (>15 including NSCLC and multiple subtypes of thyroid cancer) targeted by pralsetinib, validating *RET* as a tissue-agnostic target.

In this patient group, whose disease was resistant to prior treatments where available, treatment with pralsetinib resulted in an ORR of 57% across seven tumor types, and clinical benefit was reported in 70% of patients by blinded independent central review (BICR). This compares to an ORR of 61% and 70% in patients with *RET* fusion-positive NSCLC who received prior platinum therapy and no prior systemic treatment, respectively, and an ORR of 89% for patients with *RET* fusion-positive thyroid cancer in previously published data on the ARROW study^{10,11}. Despite the small number of patients, responses were seen in all four patients with pancreatic cancer (including an ongoing CR with treatment duration of 33.1 months) as well as in two of the three patients with cholangiocarcinoma (including a patient who received treatment for over 20 months after a best response of PD on all three prior lines of therapy). These are encouraging findings because these tumor types are difficult to treat, and the unmet need for better treatments to improve clinical benefit is high. Indeed, response rates for standard-of-care therapies are 26% in

biliary cancers (cisplatin plus gemcitabine²⁹) and 23–32% (first-line oxaliplatin-based combination chemotherapy and first-line gemcitabine plus nab-paclitaxel) in pancreatic cancer^{30,31}. In ARROW, responses were seen in treatment-naïve patients who were not candidates for standard therapies and in patients who had received several prior lines of therapy, highlighting the need for targeted therapies across a range of tumor types for patients who currently have no standard of care and for those who have exhausted all other options. The strategy of treating patients with *RET* fusion-positive solid tumors with targeted therapies is also supported by results with selpercatinib: in an analysis that included adult patients with locally advanced or metastatic *RET* fusion-positive non-lung/non-thyroid solid tumors who received selpercatinib twice daily, the ORR was 47%³². The efficacy-evaluable population comprised patients who were enrolled long enough to allow a 6-month follow-up from their first dose.

The safety profile reported in this analysis is consistent with previously reported results in patients with *RET* fusion-positive NSCLC and thyroid cancer from the ARROW study^{10,11}, with no new safety signals identified, and no effect of pralsetinib on QT interval was observed¹¹. The most common TRAEs were increased ALT/AST and neutropenia. Common TRAEs seen with selpercatinib include increased ALT/AST, dry mouth, diarrhea and fatigue^{1,32}. For patients with other solid tumors who received selpercatinib in the LIBRETTO-001 study, a grade ≥ 3 TRAE of QT interval prolongation was reported in 4% of patients³².

ARROW is a single-arm study with no comparator group. The safety population for the cohort analyzed here included a small heterogeneous number of patients ($n=29$); despite this, all but two patients included in the efficacy-evaluable population ($n=23$), a subset of the safety population, experienced a tumor shrinkage. In combination with the robust activity seen in patients with NSCLC and thyroid cancer in the ARROW study^{10,11}, these data further support the potential of pralsetinib to address the unmet medical need across a broad range of *RET*-altered tumor types with differing histology.

Overall, these data highlight the need for broad *RET* testing, preferably by NGS, to identify candidates who may benefit from treatment with pralsetinib. Enrollment of patients with other *RET* fusion-positive solid tumors in ARROW is ongoing.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-022-01931-y>.

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Methods

Study design and patient population. ARROW (NCT03037385) is an open-label, international, phase 1/2 study evaluating the efficacy and safety of pralsetinib across various *RET*-altered solid tumors conducted at 84 sites across 13 countries. The phase 1 dose-escalation portion identified the maximum tolerated dose and recommended phase 2 dose of pralsetinib as 400 mg QD¹⁰. Adults with unresectable, locally advanced or metastatic solid tumors were enrolled into nine phase 2 groups as defined by disease type and prior therapy status. This current analysis reports results for the subgroup of patients with *RET* fusion-positive solid tumor types, excluding NSCLC and thyroid cancer, who were enrolled in the phase 1 study portion and in the phase 2 expansion group 5. In accordance with study eligibility requirements, these patients had previously received or were not candidates for appropriate standard-of-care therapy. Additional eligibility criteria were as previously reported¹⁰.

This study was conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki, and was based on the International Council for Harmonisation E6 requirements. The full protocol was approved by the institutional review board or independent ethics committee of each participating site, and all patients provided signed informed consent. The name of each participating institute, organization or site whose ethical committee approved the protocol is provided in the Supplementary Information.

Outcomes. Phase 2 primary endpoints were ORR (defined as the proportion of patients who had confirmed CR or PR per RECIST version 1.1) and safety. Key secondary endpoints included CBR (defined as the proportion of patients who had confirmed CR, PR or SD lasting ≥ 16 weeks); DCR (defined as the proportion of patients who had confirmed CR, PR or SD); DOR (defined as time from first documented tumor response (CR/PR) until first documented disease progression or death); PFS (defined as time from first dose of pralsetinib to first documented disease progression or death due to any cause); and OS (defined as time from first dose of pralsetinib to death due to any cause).

Assessments. Tumor response per RECIST version 1.1 was assessed by BICR. Computed tomography or MRI of all known disease sites was performed at screening and approximately every 8 weeks during treatment. For the purpose of study eligibility, *RET* fusions were identified by local testing using NGS, FISH or GeneTrails Solid Tumor Fusion Panel, which used DNA and RNA, with RNA used to identify *RET* fusions. In accordance with the statistical analysis plan, patients were confirmed as *RET* fusion positive if any one of these methods returned a positive fusion result. The presence of concurrent non-*RET* fusion oncogenic drivers was determined prospectively based on local testing and/or by retrospective central analysis if necessary. As per the study protocol, concurrent drivers were defined as known primary driver alterations consistent with the scientific literature for different tumor types, and the final decision was made by the sponsor. AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.03, and terms were pooled.

Statistical analysis. All patients with *RET* fusion-positive solid tumors, excluding NSCLC and thyroid cancer, who were enrolled by the analysis cutoff date (18 October 2021) were included in the safety analyses. Of these patients, those who began treatment by the enrollment cutoff date (18 February 2021), who had baseline measurable disease per BICR, who had at least one evaluable post-baseline disease response assessment and who were without other known oncogenic mutations were included in efficacy analyses. The enrollment cutoff for efficacy analyses was employed to provide adequate follow-up time for responses to pralsetinib. Two-sided 95% CIs were based on exact binomial distributions using the Clopper–Pearson method. DOR, PFS and OS were analyzed using the Kaplan–Meier method. Estimates of follow-up duration for DOR, PFS and OS were based on the inverse Kaplan–Meier method, with 95% CIs based on the Greenwood formula.

For group 5, which excluded patients with *RET* fusion-positive NSCLC but included patients with *RET* fusion-positive thyroid cancer, a total sample size of 100 patients with solid tumors harboring a *RET* fusion was intended to allow $>90\%$ power at the two-sided significance level of 0.05 for testing the assumption of null hypothesis of ORR = 0.1 versus the alternative ORR = 0.3. As results for 20 patients with *RET* fusion-positive thyroid cancer were reported previously¹¹, patients with these cancers were excluded from this interim analysis. All statistical analyses were performed with SAS version 9.4 software.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The anonymized derived data from the registration ARROW study (NCT03037385) that underlie the results reported in this article may be made available after Roche and/or Blueprint Medicines have received regulatory approval for pralsetinib in the United States and the European Union in the tumor-agnostic setting described herein or upon terminating its clinical development in this setting. Qualified researchers can then request access to individual patient-level

clinical data through a data request platform. At the time of writing, this platform is Vivli (<https://vivli.org/ourmember/roche/>). As *RET* fusions are rare alterations, the anonymization of patient-level data in patient subgroups or trial cohorts of fewer than 50 patients may be difficult to achieve. As a result, Roche will assess the feasibility of anonymization and, therefore, data release as part of the review of inquiries. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing.

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Author contributions

All authors were involved in data interpretation and in the writing, revision and critical review of the article. All authors have approved the submitted version and are accountable for their contributions and the integrity of the work.

Competing interests

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Additional information

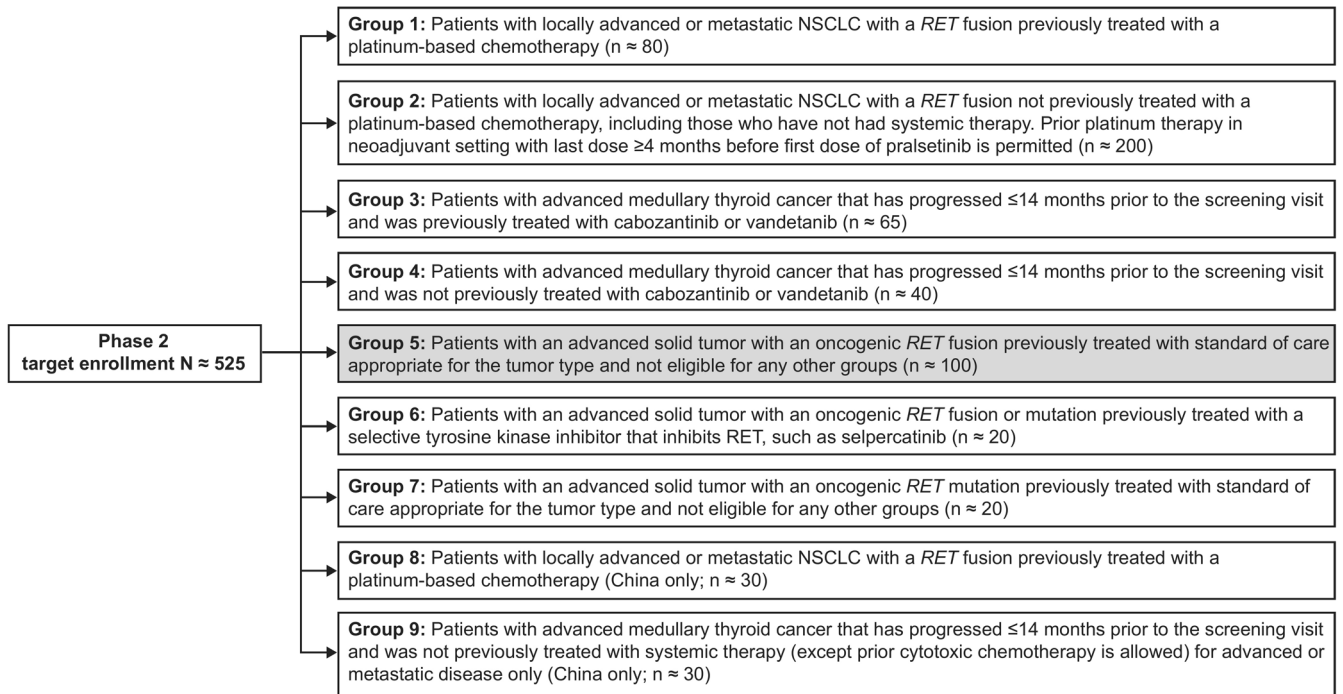
Extended data is available for this paper at <https://doi.org/10.1038/s41591-022-01931-y>.

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Extended Data Fig. 1 | Prior therapies at baseline. All Ns are target enrollment. Safety and efficacy analyses presented herein were based on the shaded group (5).

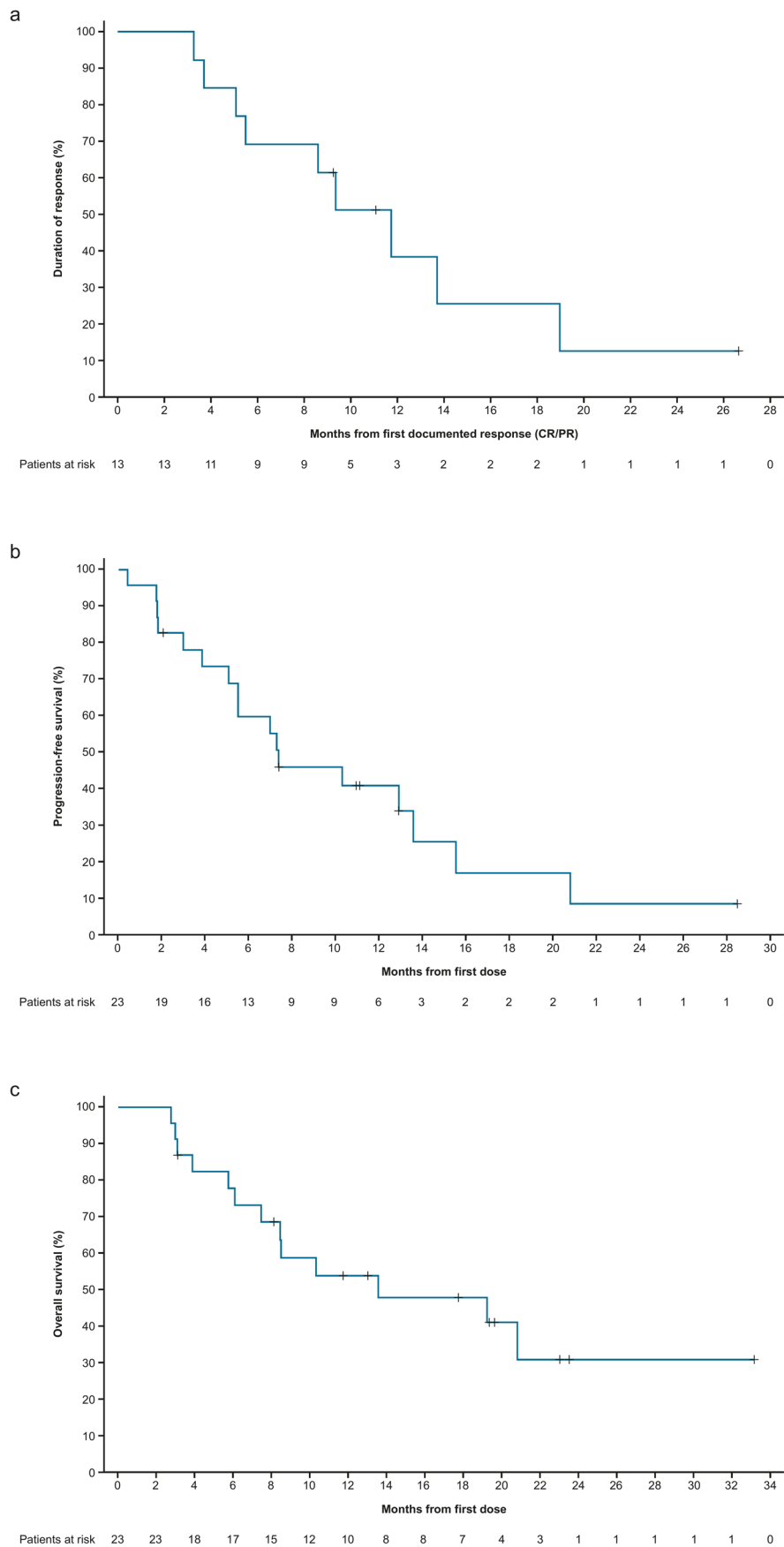
	<i>RET</i> fusion–positive patients with co-occurring alterations at study entry (n = 14) ^a	
	Tumor type	Alterations
Patient 1	Neuroendocrine	<i>TP53</i> R248W
Patient 2^b	Cholangiocarcinoma	<i>ALK</i> E1433* <i>BRAF</i> V600E <i>BRCA1</i> N997S <i>EGFR</i> G588S <i>TP53</i> P190T
Patient 3	Pancreatic	<i>ATM</i> R2854C <i>CTNNB1</i> S45F
Patient 4	Unknown primary	<i>KRAS</i> Q61L <i>NTRK1</i> V341M <i>RNF43</i> D442V
Patient 5	Gastric	<i>CDKN2A</i> N71S <i>CDKN2A</i> A68_P70del <i>TP53</i> R248Q
Patient 6	Sarcoma	<i>BRCA1</i> N550H <i>BRCA1</i> F486L
Patient 7	Colorectal	<i>ERBB2</i> T273I <i>ALK</i> A877T <i>POLE</i> E327K <i>PTEN</i> I8N
Patient 8^b	Colorectal	<i>BRCA2</i> C1573* <i>ERBB2</i> L1109Q <i>KIT</i> V845E <i>KRAS</i> Q61H <i>MET</i> V1305E <i>MTOR</i> T2390S <i>POLD1</i> Y467F <i>PTCH1</i> H1215L <i>RNF43</i> D442V <i>TP53</i> Q100*
Patient 9	Ovarian	<i>CD274</i> Amplification <i>ROS1</i> Amplification <i>BRCA1</i> V920D <i>BRCA1</i> V764E <i>BRCA2</i> C1591* <i>EGFR</i> H1111Qfs*55 <i>RET</i> F150Lfs*60 <i>TP53</i> A161Gfs*6
Patient 10^b	Colorectal	<i>CCND2</i> Amplification <i>MYC</i> Amplification <i>TSC2</i> P878S <i>GNAS</i> R201H <i>PIK3CB</i> E1051G <i>TP53</i> R282W
Patient 11	Pancreatic	<i>NTRK3</i> Q673*
Patient 12	Head and neck	<i>NTRK1</i> R692C <i>TP53</i> R175H
Patient 13	SCLC	<i>CD274</i> Amplification <i>RNF43</i> S693F
Patient 14	Cholangiocarcinoma	<i>EGFR</i> A1118T <i>MYCN</i> P237L

Extended Data Fig. 2 | See next page for caption.

Extended Data Fig. 2 | Co-occurring alterations in patients with *RET* fusions in the ARROW trial at study entry. ^a12 patients from the efficacy population did not have any genomics carried out except CRF before the first treatment and were therefore not included. ^bTwo patients with colorectal cancer and one patient with cholangiocarcinoma were excluded from efficacy analyses due to additional co-occurring driver alterations of *PIK3CB* E1051G, *KRAS* Q61H and *BRAF* V600E, respectively. After enrollment, although the patients were allowed to continue on-study, considering concurrent activating events the sponsor later excluded these patients from the efficacy cohort as the concurrent drivers were adjudicated centrally.

Therapy, n (%)	<i>RET</i> fusion–positive solid tumors	
	Efficacy-evaluable population ^a (n = 23)	Safety population ^b (N = 29)
Prior antineoplastic therapy	20 (87)	26 (90)
Prior lines of therapy		
0	3 (13)	3 (10)
1–2	13 (57)	17 (59)
≥3	7 (30)	9 (31)
Prior systemic therapy		
Targeted therapy	6 (26)	8 (28)
Chemotherapy	19 (83)	25 (86)
PD-1/PD-L1 inhibitors	2 (9)	2 (7)
Other	6 (26)	10 (34)
Prior radiation therapy	9 (39)	10 (34)
Prior cancer-related surgery	16 (70)	20 (69)

Extended Data Fig. 3 | Phase 2 study design. ^aEnrollment as of 18 February 2021 and data cutoff date 18 October 2021. ^bEnrollment and data cutoff date as of 18 October 2021. PD-1, programmed death-1; PD-L1, programmed death ligand-1.



Extended Data Fig. 4 | a, Duration of response in 13 patients with *RET* fusion-positive tumors in the efficacy-evaluable population with a confirmed CR or PR. **b**, Progression-free survival in 23 patients with *RET* fusion-positive tumors in the efficacy-evaluable population. **c**, Overall survival in 23 patients with *RET* fusion-positive tumors in the efficacy-evaluable population.

Preferred term, n (%)	<i>RET</i> fusion–positive solid tumors (N = 29) ^a	
	All grades	Grade ≥3
Patients with treatment-emergent AE	29 (100)	21 (72)
AST increased	15 (52)	3 (10)
Asthenia	15 (52)	0
ALT increased	14 (48)	2 (7)
Anemia	13 (45)	7 (24)
Neutropenia	11 (38)	9 (31)
Constipation	11 (38)	0
Abdominal pain	9 (31)	3 (10)
Hypertension	7 (24)	2 (7)
Musculoskeletal pain	7 (24)	1 (3)
Diarrhoea	7 (24)	0
White blood cell count decreased	6 (21)	2 (7)
Thrombocytopenia	6 (21)	2 (7)
Hypophosphatemia	6 (21)	2 (7)
Blood creatinine increased	6 (21)	1 (3)
Pyrexia	6 (21)	1 (3)
Dyspnoea	6 (21)	0
Nausea	6 (21)	0
Cough	5 (17)	0
Vomiting	5 (17)	0

Extended Data Fig. 5 | Treatment-emergent adverse events occurring in ≥15% of patients. ^aEnrollment and data cutoff date as of 18 October 2021.

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Consistent with expectations of good scientific practice, researchers can request access to our studies by providing a data request with a commitment to publish their findings. The data request is reviewed by an independent review panel. This is a team of external independent experts who were appointed by the Wellcome Trust. Considering the commitment to publish, i.e. releasing some of the data obtained through the data request into the public domain, the following considerations apply:

- A legitimate commercial interest in light of the data being part of a registrational study where data have not yet been submitted to regulatory agencies for review (Roche releases data after the medicine studied has been approved by regulators for the indication in both the US and EU or terminated from development (all indications) and usually 18 months after completion of the study report (to enable a publication to be submitted). It would for example be in our interest to publish the regulatory filing data set prior to making data available to researchers.
- Patient confidentiality: it needs to be considered whether the data can be properly anonymized in light of the rarity of the alteration and the low patient numbers so that the privacy and confidentiality of research participants is not compromised in any way.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	587 patients were enrolled across all groups by the data cut-off. For Group 5, which excluded patients with RET fusion-positive NSCLC but included patients with RET fusion-positive thyroid cancer, a total sample size of 100 patients with solid tumors harboring a RET fusion was intended to allow >90% power at the 2-sided significance level of 0.05 for testing the assumption of null hypothesis of ORR = 0.1 versus the alternative ORR = 0.3. Findings for patients with RET fusion-positive thyroid cancer have been reported previously so were excluded from this interim analysis.
Data exclusions	3 patients were excluded from the efficacy evaluable population due to additional oncogenic driver mutations in addition to RET. This was a prespecified exclusion criterion.
Replication	N/A - This was an interim analysis of a non-randomized Phase 1/2 clinical study in a subset of patients from the ARROW trial with RET fusion-positive solid tumors.
Randomization	This is a single-arm study with no randomization.
Blinding	This is a single-arm study with no blinding.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

Methods

n/a	Involvement	n/a	Involvement
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines	<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology	<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern		

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	N/A - no covariate analyses conducted. The median age (range) of the response-evaluable population was 53 years (31-71), with 14 (61%) female patients. Sixty-five percent were white, 30% were asian, and 4% were black.
Recruitment	Patients were recruited by participating investigators. The Investigator at each center ensured that the patients were given

Recruitment

full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients were also notified that they were free to discontinue from the study at any time. Patients were given the opportunity to ask questions and allowed time to consider the information provided. Patients were recruited strictly abiding to the inclusion and exclusion criteria which are defined in full in the manuscript Supplementary Information (Protocol). All patients provided written informed consent. Participants were not compensated, except for the reimbursement of reasonable travel expenses.

Patients were enrolled across 23 study centers in 10 countries worldwide. Due to the geographical distribution of the study centers, participants may not represent the global general population. No other bias emerging from recruitment is expected.

Ethics oversight

The full protocol was approved by the institutional review board or independent ethics committee of each participating site. The name of each participating institute/organization/site in this study whose ethical committee approved the protocol is provided in the supplementary information.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

NCT03037385

Study protocol

Provided with submission

Data collection

Patients recruited and data collected at hospitals and medical centers between March 2017 and November 2020 (data cut-off)

Outcomes

Primary endpoints were objective tumor response rate (confirmed complete response [CR] or partial response [PR]) per Response Evaluation Criteria in Solid Tumors version 1.1) and safety. Key secondary endpoints included clinical benefit rate, disease control rate, duration of response, progression-free survival, and overall survival. Tumor response per RECIST v1.1 was assessed by blinded independent central review (BICR). Computed tomography or magnetic resonance imaging of all known disease sites was performed at screening and approximately every 8 weeks during treatment. Adverse events were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and terms were pooled. DOR, PFS, and OS were analyzed using the Kaplan–Meier method. Estimates of follow-up duration for DOR, PFS, and OS were based on the inverse Kaplan–Meier method with 95% CIs based on the Greenwood formula.