



Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

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Summary

Background Oncogenic alterations in *RET* represent important therapeutic targets in thyroid cancer. We aimed to assess the safety and antitumour activity of pralsetinib, a highly potent, selective *RET* inhibitor, in patients with *RET*-altered thyroid cancers.

Methods ARROW, a phase 1/2, open-label study done in 13 countries across 71 sites in community and hospital settings, enrolled patients 18 years or older with *RET*-altered locally advanced or metastatic solid tumours, including *RET*-mutant medullary thyroid and *RET* fusion-positive thyroid cancers, and an Eastern Co-operative Oncology Group performance status of 0–2 (later limited to 0–1 in a protocol amendment). Phase 2 primary endpoints assessed for patients who received 400 mg once-daily oral pralsetinib until disease progression, intolerance, withdrawal of consent, or investigator decision, were overall response rate (Response Evaluation Criteria in Solid Tumours version 1.1; masked independent central review) and safety. Tumour response was assessed for patients with *RET*-mutant medullary thyroid cancer who had received previous cabozantinib or vandetanib, or both, or were ineligible for standard therapy and patients with previously treated *RET* fusion-positive thyroid cancer; safety was assessed for all patients with *RET*-altered thyroid cancer. This ongoing study is registered with clinicaltrials.gov, NCT03037385, and enrolment of patients with *RET* fusion-positive thyroid cancer was ongoing at the time of this interim analysis.

Findings Between Mar 17, 2017, and May 22, 2020, 122 patients with *RET*-mutant medullary and 20 with *RET* fusion-positive thyroid cancers were enrolled. Among patients with baseline measurable disease who received pralsetinib by July 11, 2019 (enrolment cutoff for efficacy analysis), overall response rates were 15 (71%) of 21 (95% CI 48–89) in patients with treatment-naïve *RET*-mutant medullary thyroid cancer and 33 (60%) of 55 (95% CI 46–73) in patients who had previously received cabozantinib or vandetanib, or both, and eight (89%) of nine (95% CI 52–100) in patients with *RET* fusion-positive thyroid cancer (all responses confirmed for each group). Common ($\geq 10\%$) grade 3 and above treatment-related adverse events among patients with *RET*-altered thyroid cancer enrolled by May 22, 2020, were hypertension (24 patients [17%] of 142), neutropenia (19 [13%]), lymphopenia (17 [12%]), and anaemia (14 [10%]). Serious treatment-related adverse events were reported in 21 patients (15%), the most frequent ($\geq 2\%$) of which was pneumonitis (five patients [4%]). Five patients [4%] discontinued owing to treatment-related events. One (1%) patient died owing to a treatment-related adverse event.

Interpretation Pralsetinib is a new, well-tolerated, potent once-daily oral treatment option for patients with *RET*-altered thyroid cancer.

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Introduction

The incidence of thyroid cancer has increased over the past decade, with medullary thyroid cancer representing 15% of all thyroid cancer cases (75% sporadic and 25% hereditary) and papillary thyroid cancer accounting for 80–85% of all differentiated thyroid cancer.^{1–3} Despite its low prevalence, medullary thyroid cancer accounts for almost 14% of all thyroid cancer-related deaths.⁴ Activating alterations in the *RET* proto-oncogene (*RET*), which encodes a transmembrane receptor tyrosine kinase

(proto-oncogene tyrosine-protein kinase receptor *RET*), are known oncogenic drivers in both medullary thyroid cancer and differentiated thyroid cancer, and represent a promising therapeutic target.^{5,6} Medullary thyroid cancer originates from parafollicular C cells and can be hereditary, associated with two subtypes of multiple endocrine neoplasia syndrome type 2 (MEN2; MEN2A and MEN2B), or sporadic.⁷ *RET* mutations occur in more than 95% of hereditary and approximately 50% of sporadic medullary thyroid cancer.⁸ In the hereditary form, these include

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Research in context

Evidence before this study

We searched PubMed for studies published in English between Jan 1, 2015, and July 31, 2020, investigating targeted treatment of *RET*-altered thyroid cancer. Search terms included “*RET*” plus “thyroid” and were filtered for clinical trials. Of the 16 entries returned, there were no clinical trials specifically done in patients with *RET*-altered thyroid cancer. In clinical trials enrolling patients with medullary thyroid cancer not limited to *RET*-alterations, the response rate with the standard-of-care multikinase inhibitor cabozantinib was 32% and with vandetanib was 46%. Furthermore, in clinical trials of patients with radioiodine-refractory differentiated thyroid cancer, response rates with the standard-of-care multikinase inhibitor lenvatinib was 65% and with sorafenib was 12%. Although these multikinase inhibitors have shown clinical activity in the respective indications, rates of adverse events leading to dose reduction and treatment discontinuation were generally high owing to their broad activity against many kinases.

Added value of this study

To the best of our knowledge, ARROW is the first prospective study to investigate treatment of *RET*-altered solid tumours, including *RET*-mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer, with pralsetinib. Our data show that pralsetinib has clinical activity in patients with *RET*-mutant medullary thyroid cancer, including in patients

who were treatment naive or had previously received cabozantinib or vandetanib, or both, as well as in patients with previously treated *RET* fusion-positive thyroid cancer (response rates of 71%, 60%, and 89%, respectively). In patients with *RET*-altered thyroid cancer who received the recommended phase 2 dose of 400 mg once daily, pralsetinib was well tolerated with a predictable safety profile, and rates of dose reductions and treatment discontinuations because of treatment-related adverse events were low when compared with available multikinase inhibitors. Overall, pralsetinib had a manageable safety profile in patients with *RET*-altered thyroid cancer and provided meaningful clinical activity in patients irrespective of previous treatment history.

Implications of all the available evidence

Patients with *RET*-altered thyroid cancer have few safe and effective treatment options outside of standard of care available for tumours without targetable oncogenic drivers. Findings from our study show that *RET*-targeted treatment with pralsetinib has antitumour activity in *RET*-altered thyroid cancer and a manageable safety profile. The utility of *RET*-targeted therapies is also validated by outcomes with selipratinib, another targeted *RET* inhibitor, which were reported following the data cutoff for the present study. Approval of both of these agents in the USA provides new treatment options in this patient population.

extracellular domain mutations (most commonly at the C634 codon), which promote ligand-independent activation of *RET*, and kinase domain mutations (primarily M918T, A883F, or V804L/M), which promote *RET* auto-activation and consequent oncogenic signalling.^{9,10} In the sporadic form, the M918T mutation accounts for more than 75% of the *RET* alterations and might be associated with a worse prognosis.^{11,12} In differentiated thyroid cancer, which originates from follicular cells, *RET* fusions are present in approximately 10–20% of papillary thyroid cancer,⁸ and less common (<10%) in other thyroid cancer subtypes such as follicular, Hürthle-cell, poorly differentiated, and anaplastic.^{13,14} Among patients with papillary thyroid cancer, the most common *RET* fusion partners are *CCDC6* (59%) and *NCOA4* (36%).^{10,15}

Multikinase inhibitors were in the past standard of care for advanced medullary thyroid cancer (cabozantinib and vandetanib) and radioiodine-refractory differentiated thyroid cancer (lenvatinib and sorafenib).¹⁶ Although these multikinase inhibitors have shown clinical activity in the respective indications,^{17–20} they are associated with significant dermatological, cardiovascular, and gastrointestinal side-effects owing to their broad activity against many kinases, including vascular endothelial growth factor receptors.^{17–21} These toxicities frequently lead to dose reductions and discontinuations, which might affect the quality of life and outcomes of patients.^{17–21}

Pralsetinib (formerly BLU-667, Blueprint Medicines) is an oral, once daily, selective *RET* inhibitor that potently targets *RET*-altered kinases, including V804L/M gate-keeper mutations associated with resistance to other tyrosine kinase inhibitors.^{22,23} Here, we report on the safety and efficacy of pralsetinib in patients with *RET*-altered thyroid cancer from the registrational phase 1/2 study (ARROW), which formed the basis of approval in the USA for treatment of advanced or metastatic *RET*-mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer.²⁴

Methods

Study design and participants

ARROW is a multicentre, open-label, first-in-human phase 1/2 study of pralsetinib. The study is being done in 13 countries globally across 71 sites in community and hospital settings. The phase 1 study portion established the maximum tolerated dose and recommended phase 2 dose.²⁵ The ongoing phase 2 portion of the study consists of multiple expansion groups (figure 1).

Patients aged 18 years or over with unresectable, locally advanced or metastatic solid tumours were enrolled into each phase 2 expansion group as defined by disease type and previous therapy status (appendix p 10). For inclusion in medullary thyroid cancer enrolment groups, patients were required to have a diagnosis of medullary thyroid with

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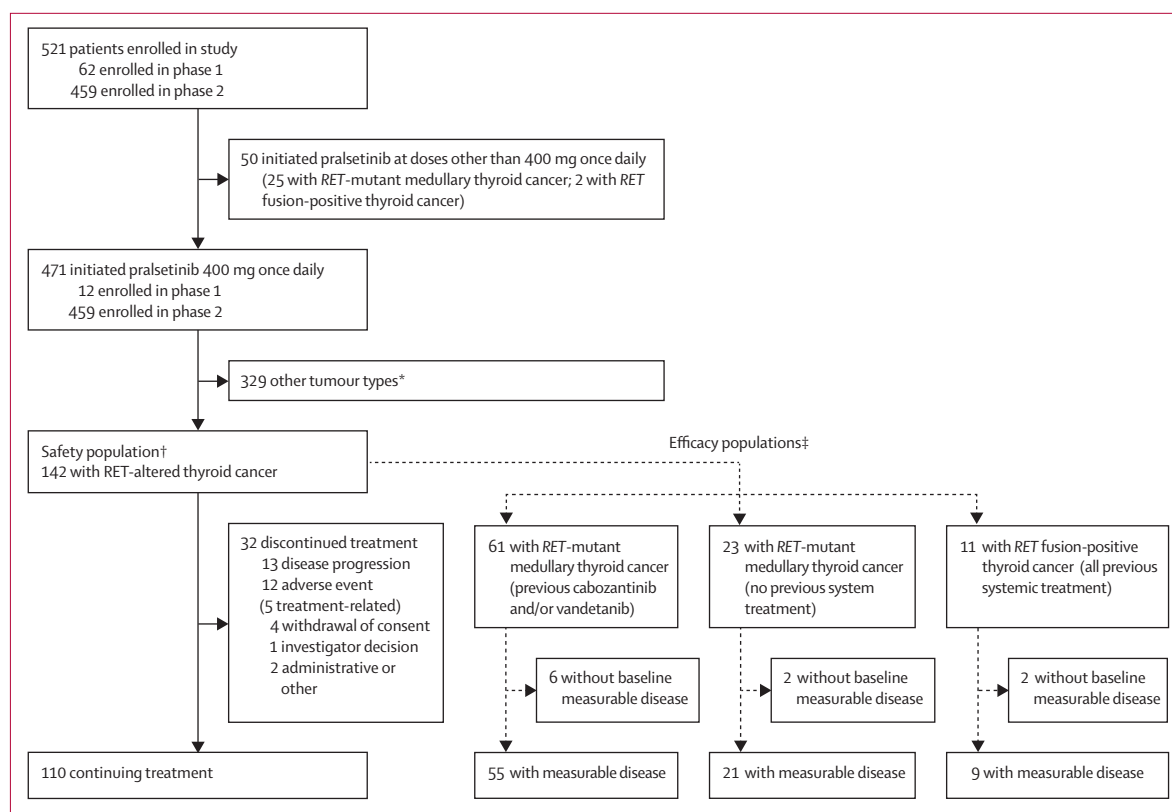


Figure 1: Trial profile

*Includes patients with RET fusion-positive NSCLC or other solid tumours outside of thyroid cancer, patients with medullary thyroid cancer with no documented RET mutation, patients with RET-mutant solid tumours outside of thyroid, and patients who had previous treatment with a selective RET inhibitor (selpercatinib).

†Patients who received ≥ 1 dose of 400 mg pralsetinib by May 22, 2020. ‡Patients who enrolled by July 11, 2019.

progression within 14 months before the screening visit; for inclusion in the RET fusion-positive solid tumour group (from which patients with RET fusion-positive thyroid cancer were included in the analyses presented herein), patients were required to have a diagnosis of an advanced solid tumour (excluding non-small-cell lung cancer with an oncogenic RET fusion (per local testing) and previously received standard of care for tumour type (if any) if deemed appropriate by the local investigator. Before July 11, 2019 (the enrolment cutoff date for presented efficacy analyses), eligibility was limited to patients who had previously received standard-of-care treatments or those who were not candidates for available standard therapies. Subsequently, the protocol was amended to allow first-line patients in the phase 2 treatment-naïve expansion groups regardless of eligibility for standard therapies. Additional eligibility criteria included adequate organ function, Eastern Cooperative Oncology Group performance status of 0–2 (later limited to 0–1 in a protocol amendment after July 25, 2018), and measurable disease by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with central nervous system metastases were permitted if neurologically stable without increasing corticosteroid doses. Radioactive iodine

refractory was defined as at least 1 of a cumulative dose of at least 600 mCi; no iodine uptake on post-radioactive iodine treatment scan; or at least one measurable lesion that has progressed (per RECIST version 1.1) within 12 months of radioactive iodine treatment (even if radioactive iodine avidity was shown at the time of pretreatment or post-treatment scan). Full eligibility criteria are provided in the protocol (appendix).

This study was done in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki and based on the International Council for Harmonisation E6 requirements. The protocol was approved by the institutional review boards at all sites and all patients provided signed informed consent. Safety was initially monitored by a safety review committee consisting of investigators and sponsor representatives.

Procedures

In the dose-escalation portion of the study, patients received pralsetinib orally at doses of 30–600 mg once daily. In the phase 2 dose expansion, patients initiated pralsetinib at the recommended phase 2 dose of 400 mg once daily. All patients received pralsetinib until disease progression, intolerance, withdrawal of consent, or investigator decision.

Dose reductions (in 100 mg increments) for study drug-related toxicities were permitted, with treatment to be discontinued if a dose reduction below 100 mg was required; doses could be interrupted for study drug-related toxicities for up to 28 days. Specific guidelines on dose modification are provided in the protocol.

Tumour assessments per RECIST version 1.1 were done by masked independent central review. The reviewers (radiologists) were masked to treatment cohorts and individual patient treatment status, as well as results generated by other radiologists. *RET* alterations were identified via local testing methods, including sequencing of DNA or RNA in tumour tissue or circulating in blood, or by fluorescent in situ hybridisation in tumour tissue. CT or magnetic resonance imaging of all known sites of disease was done at screening and approximately every 8 weeks during treatment. For patients with medullary thyroid cancer, serum calcitonin, carcinoembryonic antigen concentrations and disease-related diarrhoea, as reported by bowel movement history, were followed longitudinally. Adverse events were graded according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). Clinical laboratory evaluations for safety were done at local laboratories according to the schedules specified in the protocol.

Outcomes

The phase 2 primary endpoints were the proportion of patients achieving an objective tumour response (a complete or partial response per RECIST version 1.1), as established by masked independent central review, and safety. Key secondary endpoints included duration of response (defined as the time from first tumour response until disease progression or death, whichever occurred first), clinical benefit rate (proportion of patients with a confirmed complete or partial response or stable disease of ≥ 16 weeks), disease control rate (proportion of patients with a complete or partial response or stable disease), progression-free survival (defined as the time from first pralsetinib dose to disease progression or death, whichever occurred first), and overall survival. Medullary thyroid cancer-specific endpoints included biochemical response rates for serum calcitonin and carcinoembryonic antigen concentrations, defined as the proportion of patients with normalisation of serum concentrations following treatment confirmed a minimum of 4 weeks later (complete response) or at least a 50% decrease from baseline serum concentrations maintained for at least 4 weeks (partial response), and resolution of baseline disease-related diarrhoea. Concentrations of thyroglobulin and anti-thyroglobulin antibodies were not systematically collected at all study sites. Pharmacokinetic parameters of pralsetinib, a secondary endpoint of ARROW, will be presented in a later publication. Electrocardiogram assessments are described in a companion publication describing outcomes in patients with *RET* fusion-positive non-small cell lung cancer enrolled in ARROW.²⁶

Statistical analysis

Patients with *RET*-altered thyroid cancer who initiated pralsetinib at the recommended phase 2 dose of 400 mg once daily including those enrolled in the phase 1 dose escalation by the enrolment cutoff date (July 11, 2019) were

| | RET-mutant medullary thyroid cancer | | RET fusion-positive thyroid cancer |
|---|--|---|------------------------------------|
| | Previous cabozantinib or vandetanib, or both, treatment group (n=61) | No previous systemic treatment group (n=23) | All (n=11) |
| Median age (rIQR), years | 58 (49–64) | 61 (54–70) | 61 (54–70) |
| Age ≥ 65 years | 15 (25%) | 10 (43%) | 4 (36%) |
| Sex | | | |
| Female | 20 (33%) | 6 (26%) | 5 (45%) |
| Male | 41 (67%) | 17 (74%) | 6 (55%) |
| Race | | | |
| White | 49 (80%) | 17 (74%) | 9 (82%) |
| Asian | 3 (5%) | 5 (22%) | 2 (18%) |
| Black | 0 | 1 (4%) | 0 |
| Unknown or other | 9 (15%) | 0 | 0 |
| Eastern Cooperative Oncology Group performance status | | | |
| 0 | 17 (28%) | 15 (65%) | 4 (36%) |
| 1 | 41 (67%) | 8 (35%) | 7 (64%) |
| 2† | 3 (5%) | 0 | 0 |
| Disease stage at screening | | | |
| III | 0 | 0 | 0 |
| IV | 27 (44%) | 5 (22%) | 7 (64%) |
| IVA | 5 (8%) | 5 (22%) | 1 (9%) |
| IVB | 10 (16%) | 5 (22%) | 1 (9%) |
| IVC | 19 (31%) | 8 (35%) | 2 (18%) |
| CNS or brain metastases | 5 (8%) | 4 (17%) | 5 (45%) |
| Number of previous therapies | 2 (1–2) | 0 (0–0) | 2 (2–3) |
| Any previous systemic therapy | 61 (100%) | 0 | 11 (100%) |
| Radioactive iodine | .. | .. | 11 (100%) |
| Multikinase inhibitor | 61 (100%) | 0 | 6 (55%) |
| Cabozantinib only | 13 (21%) | 0 | 0 |
| Vandetanib only | 26 (43%) | 0 | 1 (9%) |
| Cabozantinib and vandetanib | 22 (36%) | 0 | 1 (9%) |
| Lenvatinib or sorafenib, or both | 5 (8%) | 0 | 6 (55%) |
| Chemotherapy | 6 (10%) | 0 | 0 |
| Immunotherapy | 3 (5%) | 0 | 0 |
| Other anticancer therapy | 6 (10%) | 0 | 11 (100%) |
| Primary <i>RET</i> mutation | 61 (100%) | 23 (100) | .. |
| M918T | 41 (67%)‡ | 8 (35%) | .. |
| Cysteine rich domain§ | 14 (23%) | 12 (52%) | .. |
| V804L/M | 2 (3%) | 1 (4%) | .. |
| Other | 4 (7%) | 2 (9%) | .. |
| Hereditary <i>RET</i> mutation | 10 (16%) | 11 (48%) | .. |
| Sporadic <i>RET</i> mutation | 50 (82%) | 12 (52%) | .. |
| Hereditary vs sporadic <i>RET</i> mutation unknown | 1 (2%) | 0 | .. |

(Table 1 continues on next page)

included in phase 2 efficacy analyses. Separate analyses were done for patients with *RET*-mutant medullary thyroid cancer who previously received cabozantinib or vandetanib, or were treatment naive, and had *RET* fusion-positive thyroid cancer. The findings presented herein represent interim analyses done in support of regulatory filings. Tumour response endpoints (overall response rate, duration of response, clinical benefit rate, and disease control rate) were assessed for the *RET*-altered measurable disease populations, which consisted of the subset of patients in the efficacy populations with baseline measurable disease confirmed by masked central review. Time-to-event endpoints (progression-free survival and overall survival) were assessed in each population for all patients enrolled by July 11, 2019. The enrolment cutoff date and definition for measurable disease population were defined by agreement with the US Food and Drug Administration in order to ensure adequate follow-up time for the registrational dataset and to provide an adequate assessment of efficacy in relevant populations. Safety is presented for all patients with *RET*-mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer who initiated pralsetinib at 400 mg once daily by the data cutoff date (May 22, 2020).

Two-sided 95% CIs were based on exact binomial distributions via the Clopper-Pearson method. Duration of response, progression-free survival, and overall survival were established by means of the Kaplan-Meier method. Estimates of duration of follow-up for duration of response, progression-free survival, and overall survival were based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula. Sample size determinations were made independently for each phase 2 enrolment group and are provided in the protocol; briefly, sample size and null hypothesis for group 3 (medullary thyroid cancer with previous cabozantinib or vandetanib, or both, treatment) were based on FDA guidance on estimation of best response rate with available standard-of-care treatments; group 4 (medullary thyroid cancer without previous cabozantinib or vandetanib treatment) was enrolled for exploratory analyses and no power or sample size determinations were made; for group 5 (other *RET* fusion-positive solid tumours outside of non-small-cell lung cancer; includes patients with *RET* fusion-positive thyroid cancer) sample size and null hypothesis were based on the assumption of no appropriate therapies for *RET* mutation-positive solid tumours outside of non-small-cell lung cancer. All statistical analyses were done with SAS version 9.4. The data cutoff date for all analyses was May 22, 2020. During phase 2, an independent data monitoring committee was established. This study is registered with ClinicalTrials.gov, NCT03037385.

Role of the funding source

The study was designed by the funder in collaboration with the investigators. The funder had a role in data

| | RET-mutant medullary thyroid cancer | | RET fusion-positive thyroid cancer |
|--------------------------------|--|---|------------------------------------|
| | Previous cabozantinib or vandetanib, or both, treatment group (n=61) | No previous systemic treatment group (n=23) | All (n=11) |
| (Continued from previous page) | | | |
| RET fusion | .. | .. | 11 (100%) |
| Fusion partners | | | |
| CCDC6 | .. | .. | 6 (55%) |
| KIF5B | .. | .. | 0 |
| NCOA4 | .. | .. | 2 (18%) |
| Other¶ | .. | .. | 3 (27%) |

Data are n (%) or median (IQR). rIQR=relative IQR. *Includes patients enrolled by July 11, 2019. †Eastern Cooperative Oncology Group performance status of 2 was permitted before a protocol amendment. ‡Three patients classified with M918T as the primary mutation also had a V804L or V804M mutation. §Includes C609, C611, C618, C620, C630, or C634. ||Includes D898_E901del (1), L790F (1), A883F (2), K666E (1), and R844W (1). ¶Includes ACBD5, DLG5, and SNRNP70.

Table 1: Demographics and baseline characteristics*

| Summary of tumour response to pralsetinib 400 mg* | | | |
|---|--|---|--|
| | RET-mutant medullary thyroid cancer group | | RET fusion-positive thyroid cancer group |
| | Previous cabozantinib or vandetanib, or both, treatment group (n=55) | No previous systemic treatment group (n=21) | All (n=9) |
| Overall response rate | 33 (60%); (46–73) | 15 (71%); (48–89) | 8 (89%); (52–100) |
| Best overall response | | | |
| Complete response | 1 (2%) | 1 (5%) | 0 |
| Partial response | 32 (58%) | 14 (67%) | 8 (89%) |
| Stable disease | 18 (33%) | 6 (29%) | 1 (11%) |
| Progressive disease | 2 (4%) | 0 | 0 |
| Disease control rate† | 51 (93%); (82–98) | 21 (100%); (84–100) | 9 (100%); (66–100) |
| Clinical benefit rate‡ | 44 (80); (67–90) | 21 (100%); (84–100) | 8 (89%); (52–100) |
| Median time to first response,§ months | 3.7 (IQR 1.9–5.6) | 5.6 (IQR 3.5–9.2) | 1.9 (IQR 1.8–2.8) |
| Median duration of response,§ months | NR (15.1–NE) | NR (NE–NE) | NR (NE–NE) |
| 6 months | 96% (90–100) | 93% (81–100) | 100% (100–100) |
| 12 months | 92% (82–100) | 84% (63–100) | 86% (60–100) |

Data are n (%), % (95% CI), or median (IQR). NE=not estimable. NR=not reached. *Blinded independent central review of tumour response; includes patients with measurable disease confirmed on central review and enrolled by July 11, 2019; data cutoff, May 22, 2020. †Proportion of patients with best overall response, complete response, partial response, or stable disease. ‡Proportion of patients with confirmed complete response, partial response, or stable disease lasting ≥16 weeks from first dose date. §Patients with complete response or partial response are included in the analysis.

Table 2: Summary of tumour response*

collection, data analysis, and data interpretation in conjunction with the authors, who all had access to all data.

Results

Between March 17, 2017, and the data cutoff date of May 22, 2020 (at which time the study was ongoing), 587 patients were screened and 521 were enrolled, of whom 147 had *RET*-mutant medullary thyroid cancer and

22 had *RET* fusion-positive thyroid cancer. A total of 142 patients with *RET*-mutant medullary thyroid cancer (n=122) or *RET* fusion-positive thyroid cancer (n=20) initiated the recommended phase 2 pralsetinib dose of 400 mg once daily and were included in the safety analyses (figure 1). Of these, 61 patients with *RET*-mutant medullary thyroid cancer who had previously received cabozantinib or vandetanib, or both, 23 treatment-naïve patients with *RET*-mutant medullary thyroid cancer, and 11 patients with *RET* fusion-positive thyroid cancer (all with previous systemic treatment) initiated treatment by the enrolment cutoff for efficacy analyses. As some patients did not have baseline measurable disease confirmed by masked central review, 55, 21, and 9 patients were included in the measurable

disease populations for each of these subgroups, respectively.

Responses among patients with *RET*-altered thyroid cancer at each dose amount and dose-limiting toxicities per the Bayesian optimal interval design (irrespective of tumour type) in the phase 1 portion of ARROW are shown in the appendix (pp 2, 10). Two patients treated with 600 mg once daily had dose-limiting toxicities (hypertension and hyponatraemia, both grade 3) across all tumour types, and the maximum tolerated dose of pralsetinib was determined to be 400 mg once-daily (appendix p 10). The 400 mg once-daily dose was selected as the recommended phase 2 dose based on safety and pharmacokinetic outcomes from previously presented phase 1 findings.²⁵

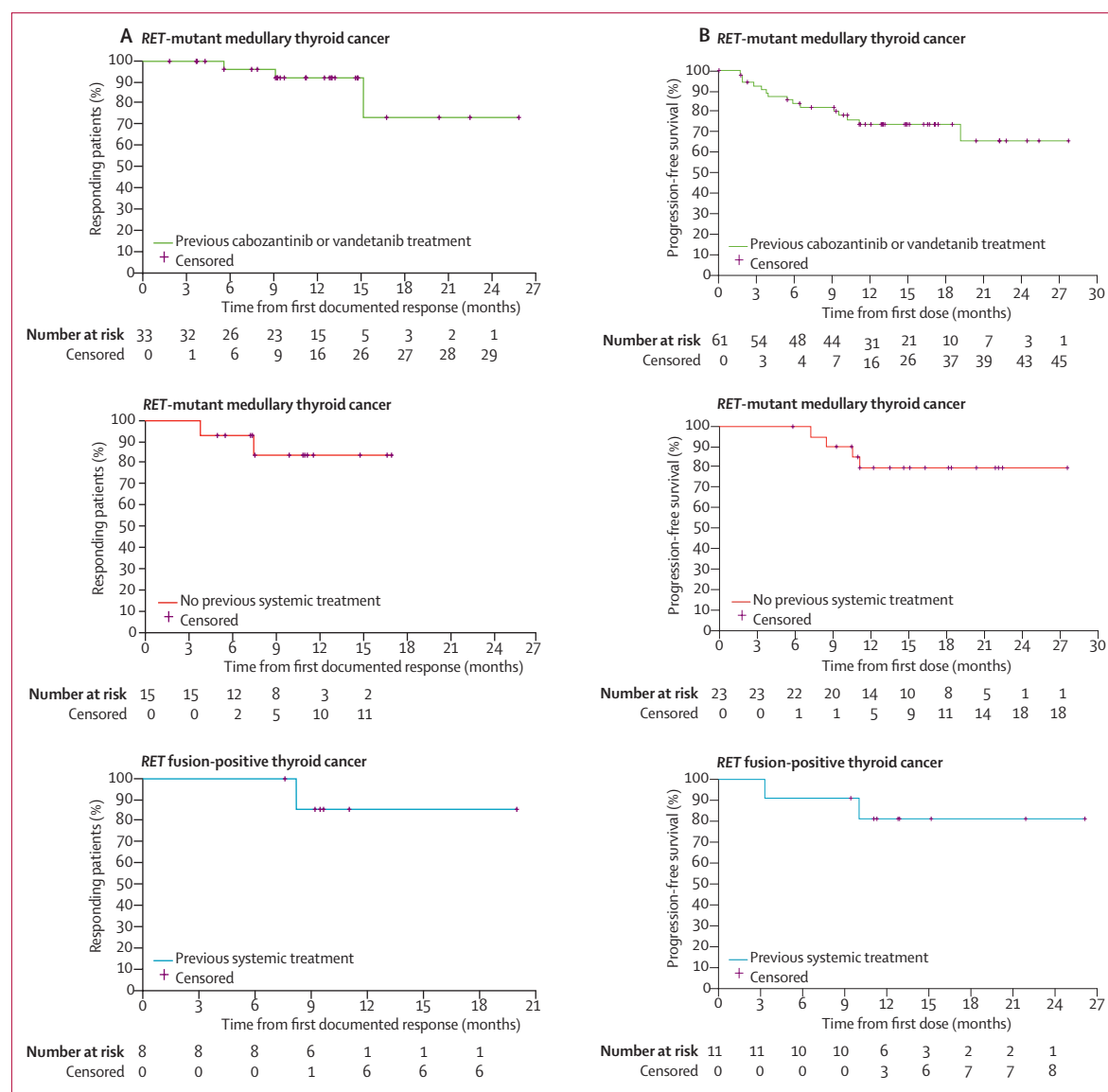


Figure 2: (A) Duration of response (measurable disease) and (B) progression-free survival (intention-to-treat) in patients who initiated 400 mg pralsetinib. RET=rearranged during transfection.

Patients with *RET*-mutant medullary thyroid cancer who previously received cabozantinib or vandetanib ($n=61$), had a median age of 58 (IQR 49–64) years and all had stage IV disease. The majority (41 [67%] of 61) had primary *M918T* mutations (of these, three patients also had a *V804L/M* non-primary mutation), 14 (23%) of 61 had primary mutations in the cysteine rich domain, two (3%) of 61 had primary *V804L/M* mutations, and four (7%) of 61 had other mutations. Baseline characteristics for patients who were treatment-naïve ($n=23$) were generally similar to patients who previously received cabozantinib or vandetanib, or both (table 1). In patients with *RET* fusion-positive thyroid cancer ($n=11$), median age was 61 (IQR 54–70) years, six (55%) of 11 had received a previous multikinase inhibitor, and all 11 patients had radioactive iodine-refractory disease. The most frequent *RET* fusion partners were *CCDC6* (6 [55%] of 11) and *NCOA4* (2 [18%] of 11).

In patients with *RET*-mutant medullary thyroid cancer previously treated with cabozantinib or vandetanib, or both, the overall response rate was 33 (60%) of 55 (95% CI 46–73), with a complete response rate of one (2%) of 55 (table 2). Median time to first response (complete response or partial response) was 3.7 months (IQR 1.9–5.6). Median duration of response was not reached with median follow-up of 11.2 months (IQR 7.9–14.6). The Kaplan-Meier estimate of the probability of ongoing response at 6 months was 96% (95% CI 90–100) and at 12 months was 92% (95% CI 82–100; figure 2A). Responses were observed regardless of *RET* mutation genotype, including all five patients with medullary thyroid cancer harbouring *RET V804L/M* gatekeeper mutations that were previously treated with cabozantinib or vandetanib, or both, three of whom also had *M918T* (figure 3A). Tumour shrinkage was observed in 52 (98%) of 53 (95% CI 90–100) patients with baseline and post-baseline assessments. Median progression-free survival was not reached (95% CI 19.1–not estimable) with an estimated 1-year progression-free survival rate of 75% (95% CI 63–86) after a median follow-up of 14.9 months (IQR 11.1–17.1; figure 2B). Median overall survival was not reached (95% CI not estimable) and the estimated 1-year overall survival rate was 89% (95% CI 81–97) after median follow-up of 16.5 (IQR 13.4–20.8; appendix p 11).

Among treatment-naïve patients with *RET*-mutant medullary thyroid cancer, the overall response rate was 15 (71%) of 21 (95% CI 48–89), with a complete response rate of one (5%) of 21 (table 2). Median time to first response was 5.6 months (IQR 3.5–9.2), and median duration of response was not reached with median follow-up of 10.8 months (IQR 7.3–11.5). Kaplan-Meier estimates of the probability of ongoing response at 6 months was 93% (95% CI 81–100) and 12 months was 84% (63–100; figure 2A). Tumour shrinkage was observed in 21 (100%) of 21 (95% CI 84–100) treatment-naïve patients. Median progression-free survival was not reached (95% CI not estimable) with estimated 1-year

progression-free survival rate of 81% (95% CI 63–98) after a median follow-up of 15.1 months (IQR 12.2–21.8; figure 2B). Median overall survival was not reached (95% CI not estimable) and the estimated 1-year overall survival rate was 91% (95% CI 78–100) after median follow-up of 18.5 months (IQR 14.2–23.3; appendix p 11).

In patients with *RET*-mutant medullary thyroid cancer who had disease-related diarrhoea at baseline, 14 (93%) of 15 had resolution of symptoms by the end of the second cycle. Additionally, in patients with *RET*-mutant medullary thyroid cancer with detectable calcitonin concentrations ($n=83$) and carcinoembryonic antigen ($n=79$) at baseline, circulating plasma concentrations decreased over time, with biochemical response rates of 72 (87%) of 83 (95% CI 78–93) and 52 (66%) of 79 (95% CI 54–76), respectively (appendix p 12).

In patients with *RET* fusion-positive thyroid cancer, the overall response rate was eight (89%) of nine (95% CI 52–100; all partial responses; table 2). Median time to first response was 1.9 months (IQR 1.8–2.8). Duration of response was not reached with median follow-up of 9.5 months (IQR 9.2–11.1); Kaplan-Meier estimates of the probability of ongoing response at 6 months were 100% (95% CI 100–100) and at 12 months were 86% (60–100; figure 2A). Tumour shrinkage was observed in nine (100%) of nine patients (66–100). Median progression-free survival was not reached (95% CI not estimable) with an estimated 1-year progression-free survival rate of 81% after a median follow-up of 12.9 months (IQR 11.3–15.1; figure 2B). Median overall survival was also not reached (95% CI not estimable) with an estimated 1-year overall survival rate of 91% (95% CI 74–100), after a median follow-up of 15.8 months (IQR 13.5–17.6; appendix p 11).

Mean treatment duration in the safety population ($n=142$) was 12.3 months (SD 7.3); the median daily dose was 383 mg (IQR 311–400) with a median relative dose intensity (the percentage of the planned 400-mg once-daily dosage received) of 85% (IQR 70–99). Treatment-related adverse events occurring in patients with *RET*-altered thyroid cancer who received at least one dose of pralsetinib 400 mg ($n=142$) are shown in table 3. The most frequent all-cause adverse events (appendix p 5) of any grade ($\geq 40\%$ of patients) were anaemia (64 patients [45%]), musculoskeletal pain (64 [45%]), constipation (62 [44%]), increased aspartate aminotransferase (60 [42%]), and hypertension (57 [40%]). Serious treatment-related adverse events were reported in 21 patients (15%), the most frequent ($\geq 2\%$) of which was pneumonitis (five patients [4%]). Dose reduction owing to treatment-related adverse events occurred in 66 (46%) patients, most commonly owing to neutropenia (13 [9%]), lymphopenia (11 [8%]), anaemia (8 [6%]), and hypertension (8 [6%]). Dose interruptions owing to treatment-related adverse events were observed in 76 (54%) patients, most commonly due to neutropenia (13 [9%]), asthenia (13 [8%]), hypertension (11 [8%]), anaemia (9 [6%]), diarrhoea (8 [6%]), and lymphopenia

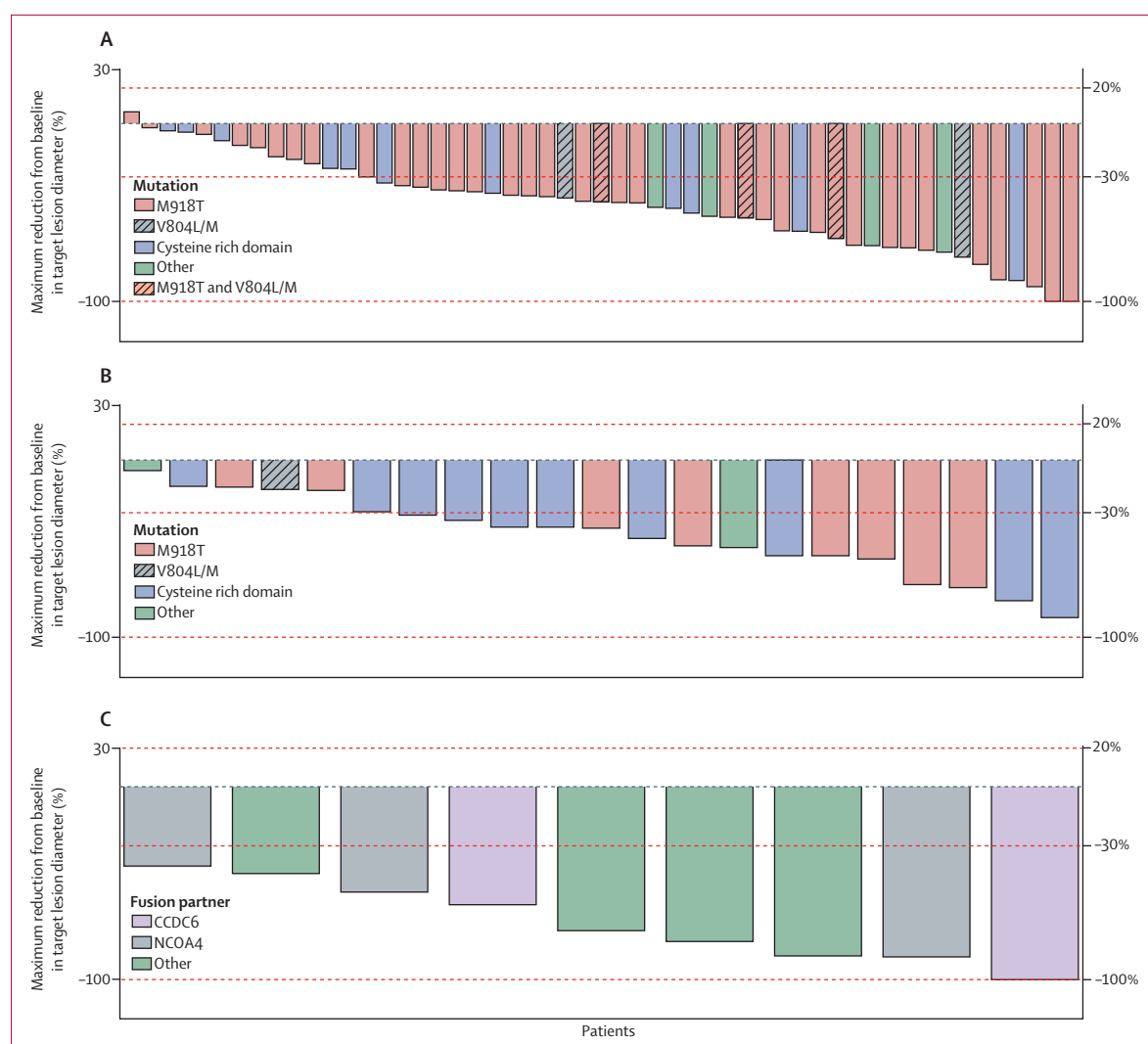


Figure 3: Maximum reduction in target lesion diameter* in patients with RET-mutant medullary thyroid cancer

(A) previously treated with vandetanib or cabozantinib, or both, or (B) treatment-naïve, and (C) RET fusion-positive thyroid cancer. RET=rearranged during transfection. *By central review. Each bar represents an individual patient.

(8 [6%]). Treatment-related adverse events leading to treatment discontinuation occurred in five (4%) patients: anaemia in two patients, pneumonia in one patient, blood creatinine phosphokinase increased in one patient, and acute respiratory distress syndrome and pneumonitis in one patient. There were eight (6%) deaths due to adverse events on study (appendix p 5), three (2%) due to disease progression, three (2%) due to pneumonia, one (1%) due to jugular vein thrombosis, and one (1%) due to respiratory failure. One patient died owing to a treatment-related adverse event; this patient was diagnosed with interstitial pneumonitis on day 44 and later discontinued pralsetinib after two cycles owing to treatment-related pneumocystis jirovecii pneumonia. Grade 3 and above pneumonia of any cause occurred in 17 (12%) patients, with a median time to resolution of 1.3 weeks (95% CI 0.9–1.7).

Discussion

In this phase 1/2 study in patients with advanced or metastatic RET-mutant medullary thyroid cancer or RET fusion-positive thyroid cancer, pralsetinib 400 mg administered as an oral dose once daily showed potent and durable clinical activity. Efficacy was maintained regardless of RET genotype or previous treatment history, and pralsetinib treatment was associated with a manageable safety profile.

The results of this study with pralsetinib in patients with RET-mutant medullary thyroid cancer compare favourably with previously reported outcomes in patients treated with frontline standard-of-care multikinase inhibitors: overall response rates were 32% with cabozantinib (actively progressing disease)¹⁷ and 46% with vandetanib (with or without actively progressing disease).¹⁸ The selective RET inhibitor selpercatinib was approved in patients with

RET-altered thyroid cancers following the data cutoff of the present study.²⁷ The response rate of 71% with pralsetinib in patients with treatment-naïve *RET*-mutant medullary thyroid cancer is consistent with outcomes reported for selpercatinib in patients not previously treated with vandetanib or cabozantinib²⁸ and suggest that *RET* inhibitors might have a therapeutic advantage over available first-line multikinase inhibitors in this *RET*-altered population.

To our knowledge, before this study, there were no standard systemic therapies for patients whose disease progressed on cabozantinib or vandetanib, or both, a population with high unmet need. Here, we show that pralsetinib was highly active in patients who previously received cabozantinib or vandetanib, or both (overall response rate 60%), including in patients with the gatekeeper *V804L/M* mutation, which confers resistance to both therapies. Alongside findings with selpercatinib,²⁸ these findings indicate targeted *RET* inhibition is of benefit in patients with previously treated *RET*-mutant medullary thyroid cancer.

Among patients with *RET* fusion-positive thyroid cancer who previously received radioactive iodine, the high overall response rate (89%) compared favourably with rates reported in patients with radioiodine-refractory thyroid cancer treated with sorafenib (12%)²⁰ and lenvatinib (65%)¹⁹; selpercatinib has also shown activity in *RET* fusion-positive thyroid cancer,²⁸ illustrating the utility of targeted *RET* inhibition in this population.

Pralsetinib 400 mg once daily was well tolerated with a manageable safety profile from a clinical perspective. Adverse events were readily managed through supportive medications, dose interruptions, and dose reductions. There were low rates of adverse events associated with vascular endothelial growth factor receptors and fibroblast growth factor receptor 1 inhibition by multikinase inhibitors, including fatigue, diarrhoea, hypertension, and hyperphosphataemia.^{8,21,29,30} Rates of dose reductions owing to treatment-related adverse events were high in phase 3 trials of cabozantinib (79%),¹⁷ lenvatinib (68%),¹⁹ and sorafenib (64%)²⁰; whereas the rate was lower at 35% with vandetanib, the patient population in that trial included patients with potentially less severe, more indolent disease.¹⁸ These rates, along with discontinuation rates of 12–16% owing to (any-cause) adverse events^{17–20} compromise the long-term effective use of multikinase inhibitors in thyroid cancers.¹⁰ Although cross-trial comparisons are problematic owing to population and eligibility differences, with pralsetinib, rates of treatment-related dose reductions were 46% and of discontinuations were 4% in patients with advanced thyroid cancers. These findings, which are also consistent with those reported for selpercatinib,²⁸ suggest selective *RET* inhibition with pralsetinib represents a tolerable treatment option in *RET*-altered thyroid cancers.

It should be noted that although the populations evaluated in this study formed the basis for regulatory

| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
|--|-----------|----------|---------|---------|
| Any treatment-related adverse event | 61 (43%) | 67 (47%) | 8 (6%) | 1 (1%) |
| Increased aspartate aminotransferase | 47 (33%) | 2 (1%) | 0 | 0 |
| Constipation | 38 (27%) | 1 (1%) | 0 | 0 |
| Decreased white blood cell count* | 37 (26%) | 12 (8%) | 0 | 0 |
| Increased alanine aminotransferase | 31 (22%) | 2 (1%) | 0 | 0 |
| Hyperphosphataemia | 31 (22%) | 0 | 0 | 0 |
| Asthenia* | 31 (22%) | 6 (4%) | 0 | 0 |
| Neutropenia* | 28 (20%) | 18 (13%) | 1 (1%) | 0 |
| Anaemia* | 27 (19%) | 14 (10%) | 0 | 0 |
| Increased blood creatinine | 25 (18%) | 0 | 0 | 0 |
| Musculoskeletal pain* | 25 (18%) | 0 | 0 | 0 |
| Dysgeusia | 23 (16%) | 0 | 0 | 0 |
| Hypertension* | 23 (16%) | 24 (17%) | 0 | 0 |
| Oedema* | 22 (15%) | 0 | 0 | 0 |
| Diarrhoea | 20 (14%) | 3 (2%) | 0 | 0 |
| Headache* | 19 (13%) | 0 | 0 | 0 |
| Thrombocytopenia* | 18 (13%) | 2 (1%) | 2 (1%) | 0 |
| Dry mouth | 17 (12%) | 0 | 0 | 0 |
| Lymphopenia* | 12 (8%) | 15 (11%) | 2 (1%) | 0 |
| Hypocalcaemia | 10 (7%) | 1 (1%) | 0 | 0 |
| Pneumonitis* | 9 (6%) | 4 (3%) | 0 | 0 |
| Stomatitis | 8 (6%) | 1 (1%) | 0 | 0 |
| Increased blood creatine phosphokinase | 7 (5%) | 6 (4%) | 2 (1%) | 0 |
| Electrocardiogram QT prolonged | 6 (4%) | 1 (1%) | 0 | 0 |
| Increased transaminases | 3 (2%) | 1 (1%) | 0 | 0 |
| Cough* | 3 (2%) | 1 (1%) | 0 | 0 |
| General physical health deterioration | 2 (1%) | 2 (1%) | 0 | 0 |
| Urinary tract infection | 2 (1%) | 2 (1%) | 0 | 0 |
| Pneumonia* | 2 (1%) | 0 | 0 | 1 (1%) |
| Cell death | 1 (1%) | 1 (1%) | 0 | 0 |
| Hypotension | 1 (1%) | 1 (1%) | 0 | 0 |
| Granulocytopenia | 0 | 1 (1%) | 0 | 0 |
| Hyponatraemia* | 0 | 1 (1%) | 0 | 0 |
| Syncope | 0 | 1 (1%) | 0 | 0 |
| Haematuria | 0 | 1 (1%) | 0 | 0 |
| Acute respiratory distress syndrome | 0 | 0 | 1 (1%) | 0 |
| Respiratory failure | 0 | 1 (1%) | 0 | 0 |
| Myositis | 0 | 1 (1%) | 0 | 0 |
| Bicytopenia | 0 | 1 (1%) | 0 | 0 |
| Bone marrow failure | 0 | 1 (1%) | 0 | 0 |

Data are n (%). *RET*=rearranged during transfection. Grade 1–2 treatment-related adverse events reported at least 10% of patients and all grade 3–5 events are shown. *Grouped terms.

Table 3: Treatment-related adverse events in patients with *RET*-altered thyroid cancer who received pralsetinib 400 mg (n=142)

approval, the findings presented here are interim analyses. As such, medians for duration of response (median follow-up, approximately 9–11 months), progression-free survival (median follow-up approximately 13–15 months), and overall survival (median follow-up approximately 16–19 months) were not reached for any of the reported groups at the time of data cutoff. However, there were high probabilities of ongoing response ($\geq 84\%$), progression-free survival ($\geq 75\%$), and overall survival ($\geq 89\%$) at 12 months in each group, suggesting that pralsetinib has durable clinical activity. The key strength of our study is that results are based on masked independent central radiology review of tumour assessments, thereby eliminating potential bias associated with investigator assessments. A limitation of our study is that determination of *RET* genotype for enrolment of patients with *RET* fusion-positive tumour types could be based on local testing and was not restricted to central analysis by next generation sequencing of plasma (ctDNA) or tumour tissue. Nonetheless, the high response rates observed despite the use of a range of local genotyping techniques are suggestive of the potential generalisability of our findings and highlight the need for broad implementation of molecular screening to identify patients with *RET*-altered thyroid tumours.

In conclusion, pralsetinib showed potent efficacy in patients with *RET*-altered thyroid cancers and was well-tolerated. On the basis of these data, pralsetinib has been approved in the USA as a once-daily oral treatment for *RET*-mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer. Taken together, our findings suggest that pralsetinib has the potential to transform the existing treatment paradigm for patients with *RET*-altered thyroid cancer and represents a valuable addition to the armamentarium of selective targeted therapies for oncogene-driven cancers.

Contributors

The study was designed by the funder in collaboration with all the authors. All authors contributed to data collection, which were analysed by HZ and the funder in conjunction with all the other authors. All authors had access to all the data reported in the study and contributed to data interpretation. The first draft of the manuscript was written by VS, MH, and MHT, with editorial assistance from a medical writer paid for by the funder. All authors reviewed and edited the manuscript, and agreed to submit the manuscript for publication. HZ and CDT accessed and verified the underlying data.

Declaration of interests

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Data sharing

The anonymised derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years after this article's publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to Blueprint Medicines medinfo@blueprintmedicines.com. The trial protocol will also be made available, as will a data fields dictionary.

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