Pralsetinib in patients with advanced or metastatic RET-altered thyroid cancer: updated data from the ARROW trial


BACKGROUND

- Oncogenic RET alterations are common in thyroid cancers and are therapeutically targetable.
- Current treatment options for patients with advanced thyroid cancer include the multitargeted tyrosine kinase inhibitors cabozantinib and vandetanib for metastatic thyroid cancer (MTC), and cabozantinib, lenvatinib and sorafenib for differentiated thyroid cancer; these are often associated with dose reduction or discontinuation of treatment due to adverse events.
- Pralsetinib is a highly potent, selective RET inhibitor.
- Pralsetinib at 400 mg once-daily (QD) has demonstrated clinical activity in RET-altered thyroid cancer safety population: 172 patients treated at 400 mg QD.

METHODS

- Adult patients with RET-altered locally advanced/metastatic thyroid cancer, who had enrolled in ARROW and initiated oral pralsetinib at 400 mg QD.
- Phase II primary endpoints: ORR by bIRC per RECIST v1.1, and safety; key secondary endpoints include: duration of response (DoR), progression-free survival (PFS), and overall survival (OS).
- ORR and DoR evaluated in both the measurable disease population and the ITT populations (PFS and OS assessed only in the ITT population).
- Safety was evaluated in all patients with RET-altered thyroid cancer who initiated pralsetinib at 400 mg QD prior to the data cut-off.

RESULTS

Patient characteristics
- At data cut-off (12 April 2021), the ITT population comprised 145 patients with RET-mutant MTC (with/without prior systemic therapy, including C/V, and 22 patients with RET-TP TC, of which 21 had received prior systemic therapy, including radioactive iodine (Table 1)
- Treatment-naive patients had received no prior systemic therapy.

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Pralsetinib (MK-0642, 400 mg QD) was approved in April 2021 by the US Food and Drug Administration for the treatment of adult patients with advanced or metastatic RET-altered thyroid cancer (TC).

- Pralsetinib has demonstrated clinical activity in RET-altered thyroid cancer safety population: 172 patients treated at 400 mg QD.
- In this updated analysis including more patients, pralsetinib showed clinical activity in RET-altered thyroid cancer.
- Overall response rate (ORR) (95% CI): 22/145 (15.2% [11.2–20.3%]) in patients with RET-mutant MTC.
- In the same patient cohort, the ORR was 22/21 (105.8% [77.0–99.3%]) in patients with treatment-naive RET-mutant MTC.

Efficacy: ORR
- In the ITT population, the ORR was (Table 2):
  - 51% in patients with RET-mutant MTC who had received prior C/V
  - 72% in treatment-naive patients with RET-mutant MTC
- 86% in patients with previously treated RET-TP TC

Similar results were observed in the measurable disease population (Table 2).
- Responses were observed regardless of the RET mutation genotype or RET fusion partner (Figure 1).

Efficacy: time-to-event endpoints
- In the ITT population, median DoR was (Table 2):
  - 25.8 months in patients with RET-mutant MTC who had received prior C/V
  - Not reached (NR) in treatment-naive patients with RET-mutant MTC
  - 17.5 months in patients with previously treated RET-TP TC

DoR remains immature, with fewer than 50% of events having occurred by the data cut-off.
- Median PFS: 24.9 months (95% CI 19.7–31.2) in patients with RET-mutant MTC who had received prior C/V;
  - NR (95% CI 27.5–not estimable [NE]) in treatment-naive patients with RET-mutant MTC; 19.4 months (95% CI 13.0–NE) in patients with previously treated RET-TP TC (Figures 2 and 3).
- Median OS was NR for all three cohorts.

CONCLUSIONS

In this updated analysis including more patients, pralsetinib continues to show high efficacy and a manageable safety profile in patients with RET-T halted thyroid cancer, regardless of mutation genotype or fusion partner.

SUMMARY

Ongoing studies (ORR) (ITT):
- 91%: RET-mutant MTC with prior C/V
- 72%: treatment-naive RET-mutant MTC
- 86%: previously treated RET-TP TC

Acceptable safety profile

Physicians should be aware of the signs and symptoms of pneumoconiosis (e.g., shortness of breath, coughing, chest pain) and consider prophylactic treatment with pneumocystis jirovecii pneumonia (PJP) prophylaxis.

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