AcceleRET Lung: a phase 3 study of first-line pralsetinib in patients with *RET* fusion–positive advanced/metastatic NSCLC

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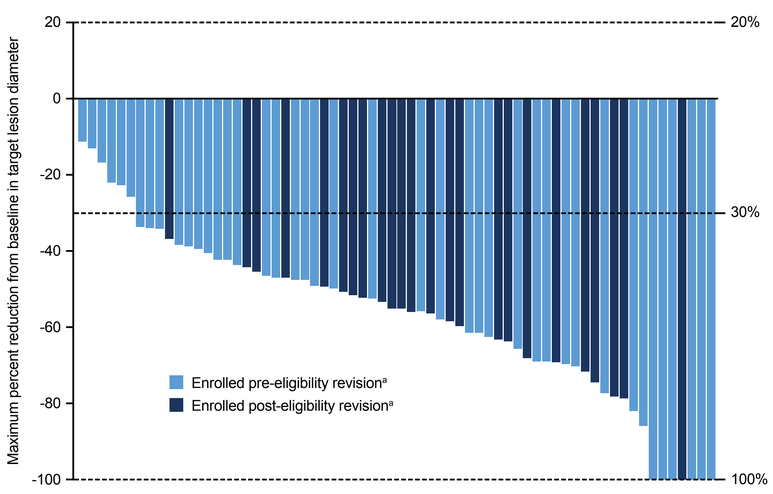
BACKGROUND

- Rearranged during transfection (*RET*) gene fusions have been identified as oncogenic drivers in multiple tumor types, including 1–2% of non-small-cell lung cancer (NSCLC)[1,2]
- Patients with *RET* alterations have poor response to immunotherapies, but those with NSCLC bearing certain driver mutations have shown improved outcomes with targeted therapy compared with standard of care (SOC) platinum-based chemotherapy[3–7]
- Pralsetinib is a RET inhibitor that selectively targets *RET* fusions and mutations, with greater potency than multikinase inhibitors[8]
- In the phase 1/2 ARROW study (NCT03037385; data cutoff: November 6, 2020), pralsetinib demonstrated an overall response rate of 79% in treatment-naive patients with *RET* fusion–positive metastatic NSCLC (n=68) and substantial antitumor activity (**Figure 1**)[9]
- Across the entire safety population (N=471) in the ARROW study, the most common treatment-related adverse events were of grade 1–2 per the Common Terminology Criteria for Adverse Events (CTCAE)[9]
- Pralsetinib was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with *RET* fusion–positive metastatic NSCLC as detected by an FDA-approved test, and by the European Commission for the treatment of adult patients with *RET* fusion–positive advanced NSCLC not previously treated with a RET inhibitor[10,11]

Figure 1: Pralsetinib demonstrated substantial antitumor activity in treatment-naive patients with *RET* fusion–positive metastatic NSCLC in the phase 1/2 ARROW study[9]



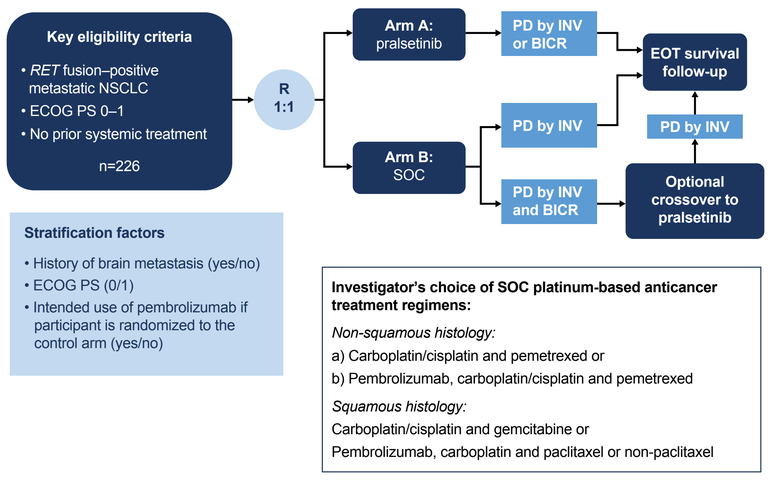
[a]ARROW (NCT03037385) protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

METHODS

Study objectives and design

- AcceleRET Lung, an international, open-label, randomized, phase 3 study (NCT04222972), will evaluate the efficacy and safety of pralsetinib compared with investigator's choice of platinum-based chemotherapy regimen as first-line treatment in patients with *RET* fusion–positive metastatic NSCLC
- Patients will be randomized 1:1 to receive pralsetinib 400 mg once daily or investigator's choice of SOC treatment (**Figure 2**)
- Stratification factors include intended presence of brain metastasis, Eastern Cooperative Oncology Group performance status, and intended use of pembrolizumab if randomized to the SOC arm
- Crossover to receive pralsetinib will be allowed for patients randomized to SOC upon disease progression confirmed by central review assessment

Figure 2: AcceleRET lung study design



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; PD, progressive disease; R, randomization.

Summary of key eligibility criteria

Key inclusion criteria

- Adult patients aged ≥18 years
- Pathologically confirmed advanced or metastatic NSCLC
- Measurable disease (RECIST 1.1) as determined by local site investigator or radiologic assessment
- Documented *RET* fusions as assessed by an accredited laboratory
- ECOG PS of 0–1
- Prior therapy in the neo/adjuvant setting is allowed if recurrence occurred after ≥6 months from completion of treatment

Key exclusion criteria

- Prior systemic treatment for metastatic disease
- Tumor has an additional primary targetable driver mutation
- Prior treatment with a selective RET inhibitor
- CNS metastases or primary CNS tumor associated with progressive neurological symptoms

CNS, central nervous system.

Study endpoints

Primary endpoint

- Progression-free survival compared to investigator's choice of SOC treatment according to a BICR (RECIST 1.1)
  - Sample size (N=226) determined based on the assumption of a 0.57 hazard ratio for pralsetinib versus investigator's choice of SOC treatment

Secondary endpoints

- Overall response rate (RECIST 1.1)
- Overall survival
- Safety/tolerability
- Clinical benefit rate
- Duration of response
- Disease control rate
- Quality-of-life measurements[a]

Exploratory endpoint

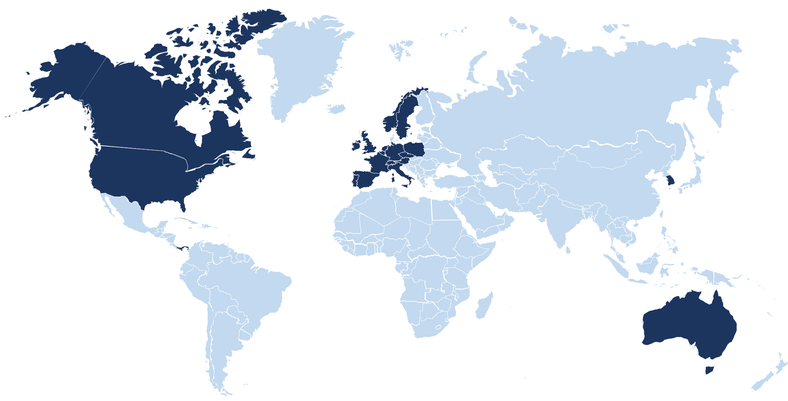
- Identification of potential biomarkers of antineoplastic activity and resistance
- Time to intracranial progression (RECIST 1.1)
- Intracranial response rate (RECIST 1.1)
- Plasma concentration of pralsetinib at specified timepoints

[a]European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-question (EORTC QLQ-C30), the EORTC Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13), and the EuroQoL Dimension (EQ-5D-5L) questionnaires.

ENROLLMENT AND CURRENT STATUS

- The target enrollment is 226 patients
- Enrollment in this international multicenter study is planned/has begun in 128 sites in 21 countries including North America, Europe, Asia, and Australia (**Figure 3**)

Figure 3: Active study sites



Disclosures

Study sponsored by F. Hoffmann-La Roche, Ltd. **S.P.** reports: honoraria for Amgen, AstraZeneca, Bayer, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Guardant Health, Guardant Health, Incyte, Janssen, Lilly, Merck KGaA, MSD, Novartis, Roche, and Takeda; consulting/advisory role for Amgen, AstraZeneca, Bayer, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Guardant Health, Incyte, Janssen, Lilly, Merck KGaA, MSD, Novartis, Pfizer, Roche, and Takeda; research funding for ARIAD (Inst), Boehringer Ingelheim (Inst), Bristol-Myers Squibb (Inst), Celgene (Inst), Clovis Oncology (Inst), Daiichi Sankyo (Inst), Epizyme (Inst), GlaxoSmithKline (Inst), Guardant Health (Inst), Janssen (Inst), Lilly (Inst), Mirati Therapeutics, MSD (Inst), Novartis (Inst), Roche (Inst), Takeda (Inst), Trizell, and Turning Point Therapeutics (Inst); travel, accommodation, or expenses for Boehringer Ingelheim, Merck Sharp & Dohme, and Roche.

For co-author disclosures please refer to the abstract: https://meetinglibrary.asco.org/

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