AcceleRET Lung: A Phase 3 Study of First-Line Pralsetinib in Patients with *RET* Fusion+ Advanced/Metastatic Non-Small-Cell Lung Cancer (NSCLC)

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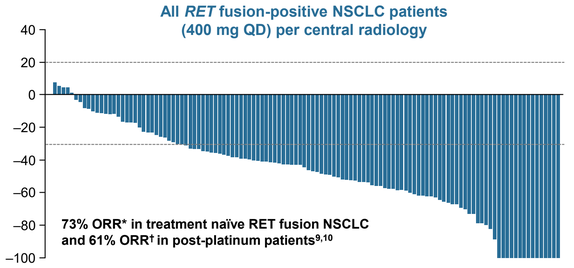
Background

- 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 an investigational RET inhibitor that selectively targets *RET* fusions and mutations, with greater potency than multikinase inhibitors[8]
- In a registration-enabling phase 1/2 clinical study (ARROW; NCT03037385), pralsetinib demonstrated an overall response rate of 61% in patients with *RET* fusion-positive metastatic NSCLC who were previously exposed to platinum treatment (n=80) (Figure 1)[9,10]
- Preliminary data from the ARROW study in first-line treatment of patients with *RET* fusion-positive NSCLC (n=26) demonstrated an overall response rate of 73% with a 12% complete response rate, suggesting high clinical efficacy (Figure 1)[9,10]
- Across the entire safety population 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]

Figure 1: Pralsetinib has substantial anti-tumor activity in *RET* fusion-positive metastatic NSCLC[9,10]



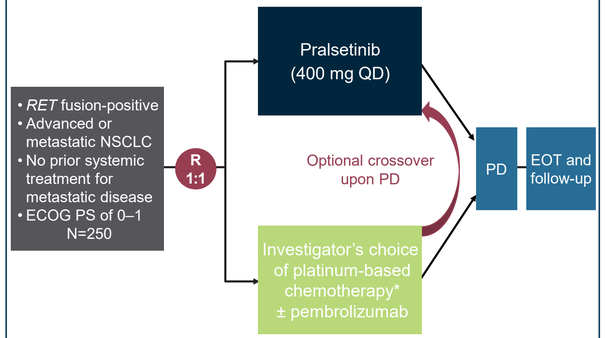
*All responses confirmed. †Two responses pending confirmation
NSCLC, non-small-cell lung cancer; ORR, overall response rate; QD, once daily; RET, rearranged during transfection; SD, stable disease.

Study objective

- 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

Study design

Figure 2: AcceleRET Lung study design



*Patients with non-squamous histology will receive platinum/pemetrexed with or without pembrolizumab; patients with squamous histology will receive platinum/gemcitabine
ECOG PS, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS); EOT, end of treatment; NSCLC, non-small-cell lung cancer; PD, progressive disease; QD, once daily; R, randomized; RET, rearranged during transfection.

- 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 pembrolizumab use if randomized to the SOC arm, history of brain metastases, and Eastern Cooperative Oncology Group performance status
- Crossover to receive pralsetinib will be allowed for patients randomized to SOC upon disease progression confirmed by central review assessment

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Adult patients aged ≥18 years • Pathologically confirmed advanced or metastatic NSCLC • Measurable disease (RECIST 1.1) determined by local site investigator or central radiographic imaging review assessment • *RET* fusions assessed by next generation in situ hybridization and circulating tumor DNA methods • ECOG performance status of 0–1 • Prior therapy in the neo/adjuvant setting is allowed if recurrence occurred after ≥6 months from completion of treatment	• 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; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiation therapy.

Study endpoints

Primary endpoint

- Progression-free survival compared to investigator's choice of SOC treatment according to a blinded independent central review (RECIST 1.1)
  - Sample size (N=250) determined based on the assumption of a 0.57 hazard ratio for pralsetinib vs investigator's choice of SOC treatment

Secondary endpoints

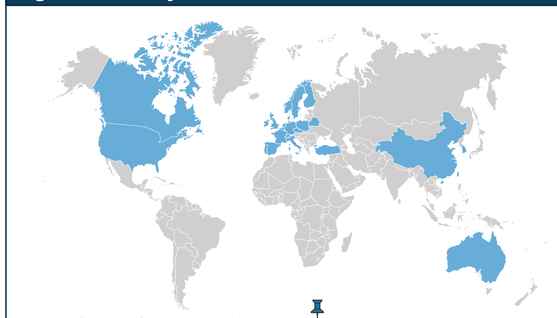
- Overall response rate (RECIST 1.1)
- Overall survival
- Safety/tolerability
- Clinical benefit rate
- Duration of response
- Disease control rate
- Time to intracranial progression (RECIST 1.1)
- Intracranial response rate (RECIST 1.1)
- Quality-of-life measurements* Plasma concentration of pralsetinib at specified timepoints

*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 5 Dimension (EQ-5D-5L) questionnaires
RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care; vs, versus.

Enrollment and current status

- The target enrollment is 250 patients
- Enrollment in this international multicenter is planned/has begun in 128 sites in 26 countries including centers in North America, Europe, Asia, and Australia (Figure 3)

Figure 3: Study sites



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