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

Background
- Rearranged during transfection (RET) gene fusions have been identified as oncogenic drivers in 1–2% of non-small-cell lung cancer (NSCLC) patients.
- 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.
- Pralsetinib is an investigational RET inhibitor that selectively targets RET fusions and mutations, with greater potency than multikinase inhibitors.
- 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).
- Across the entire safety population in the ARROW study, the most common treatment-related adverse events were grade 1–2 per the Common Terminology Criteria for Adverse Events (CTCAE).

Study objective
- AcceleRET Lung, an international, open-label, randomized, phase 3 study (NCT04075601), 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.

Table 1: Key eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Adult patients aged ≥18 years</td>
<td>Prior systemic treatment for metastatic disease</td>
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<td>Pathologically confirmed advanced or metastatic NSCLC</td>
<td>Prior treatment with a selective RET inhibitor</td>
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<td>Measurable disease (RECIST 1.1)</td>
<td>CNS metastases or primary CNS tumor associated with progressive neurological symptoms</td>
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<td>Determined by local site</td>
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<td>Investigator or central radiographic imaging review assessment</td>
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<td>RET fusions assessed by next generation in situ hybridization and circulating tumor DNA methods</td>
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<td>ECOG performance status of 0–1</td>
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<td>Prior therapy in the neoadjuvant setting is allowed if recurrence assessed by local site upon disease progression from completion of treatment.</td>
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Study design

- Eligible patients: adult patients aged ≥18 years with metastatic non-small-cell lung cancer (NSCLC) with a RET gene fusion who have not received prior systemic treatment for metastatic disease (N=250) will be randomized 1:1 to pralsetinib treatment (450 mg QD) ± pembrolizumab or investigator’s choice of SOC treatment: 
  - Platinum/gemcitabine or 
  - Platinum/gemcitabine ± pembrolizumab.
- Secondary endpoints: overall survival, safety/tolerability, clinical benefit rate, duration of response, plasma concentration of pralsetinib at specified timepoints.
- No prior systemic treatment for metastatic disease is allowed.

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

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).

References

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