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

TPS9633

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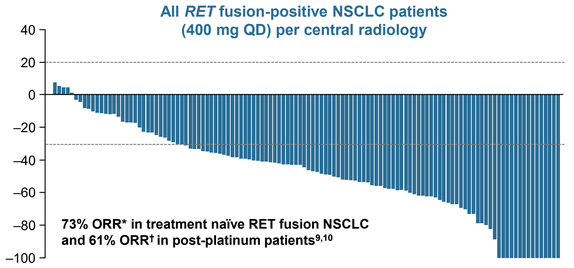
Background

- 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]



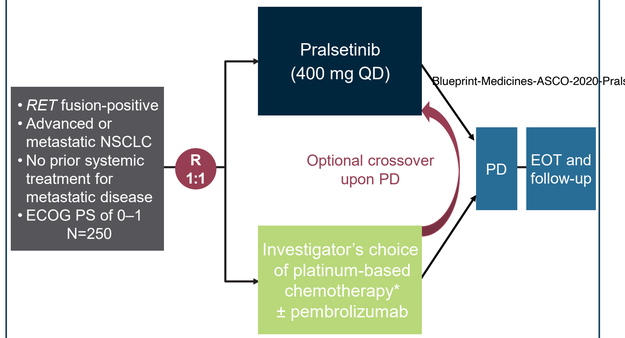
*All responses confirmed. †Two responses pending confirmation
NSCLC, non-small-cell lung cancer; ORR, overall response rate; QD, once daily; RET, rearranged during transfection; SD, stable disease.

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 occured 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 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

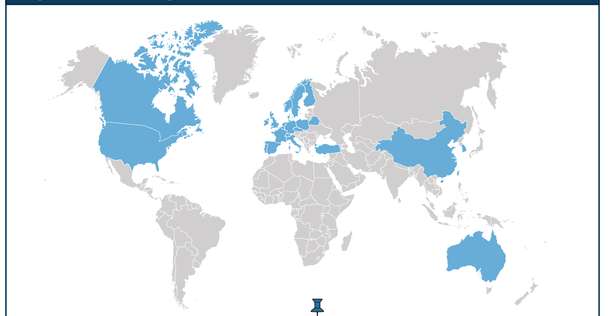
- Overall response rate (RECIST 1.1)
- Overall survival
- Safety/tolerability
- Clinical benefit rate
- Duration of response
- Disease control rate
- Time to intracranial progression (RECIST 1.1)
- Intracranial response rate (RECIST 1.1)
- Quality-of-life measurements* Plasma concentration of pralsetinib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

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support was provided by Miriam Cohen, PhD, Manoshi Nath, MSc, and editorial support was provided by Sinead Stewart, all of Paragon, Knutsford, UK, supported by Blueprint Medicines, Cambridge, MA according to Good Publication Practice guidelines.

Disclosures

Study sponsored by Blueprint Medicines. BB received research funding from AstraZeneca, Pfizer, Eli Lily, Onxeo, Bristol-Myers Squibb, Inivata, Abbvie, Amgen, Blueprint Medicines, Clegene, GlaxoSmithKline, Ignyta, Ipsen, Merck KGaA, MSD Oncology, Nektar, PharmaMar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Therapeutics, Cristal Therapeutics, Daiichi Sankyo, Janssen Oncology, OSE Immunotherapeutics, BeiGene, Boehringer Ingelheim, Roche/Genentech, Servier andTolero Pharmaceuticals. EP consulted for and served on speaker's bureaus for Pfizer, Roche, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Guardant Health, Novartis, Takeda, Abbvie, Blueprint Medicines, Eli Lily, Merck KGaA, Merck Sharp & Dohme, Janssen, Samsung, Medscape, Prime Oncology, Touchtime; received research funding from Merck, and other relationships include Grifols. CC, MG, CT are employees of and own stock or other ownership in Blueprint Medicines. JG is an employee of and owns stock or other ownership in Celldex; and has consulted for Blueprint Medicines. SP consulted for Boehringer Ingelheim, Roche, Novartis, Pfizer, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Guardant Health, Abbvie, EMD Serono, Takeda, Paradox Therapeutics, Incyte; received travel and accommodation expenses from Boehringer Ingelheim, Merck Sharp & Dohme and Roche; received honoraria from Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Chugai Pharma; and research funding from Boehringer Ingelheim, Epizyme, Bristol-Myers Squibb, Clovis Oncology, Roche, Eli Lily and Takeda.

Presented at ASCO 2020, May 29 – June 2, 2020, Virtual Format.