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]
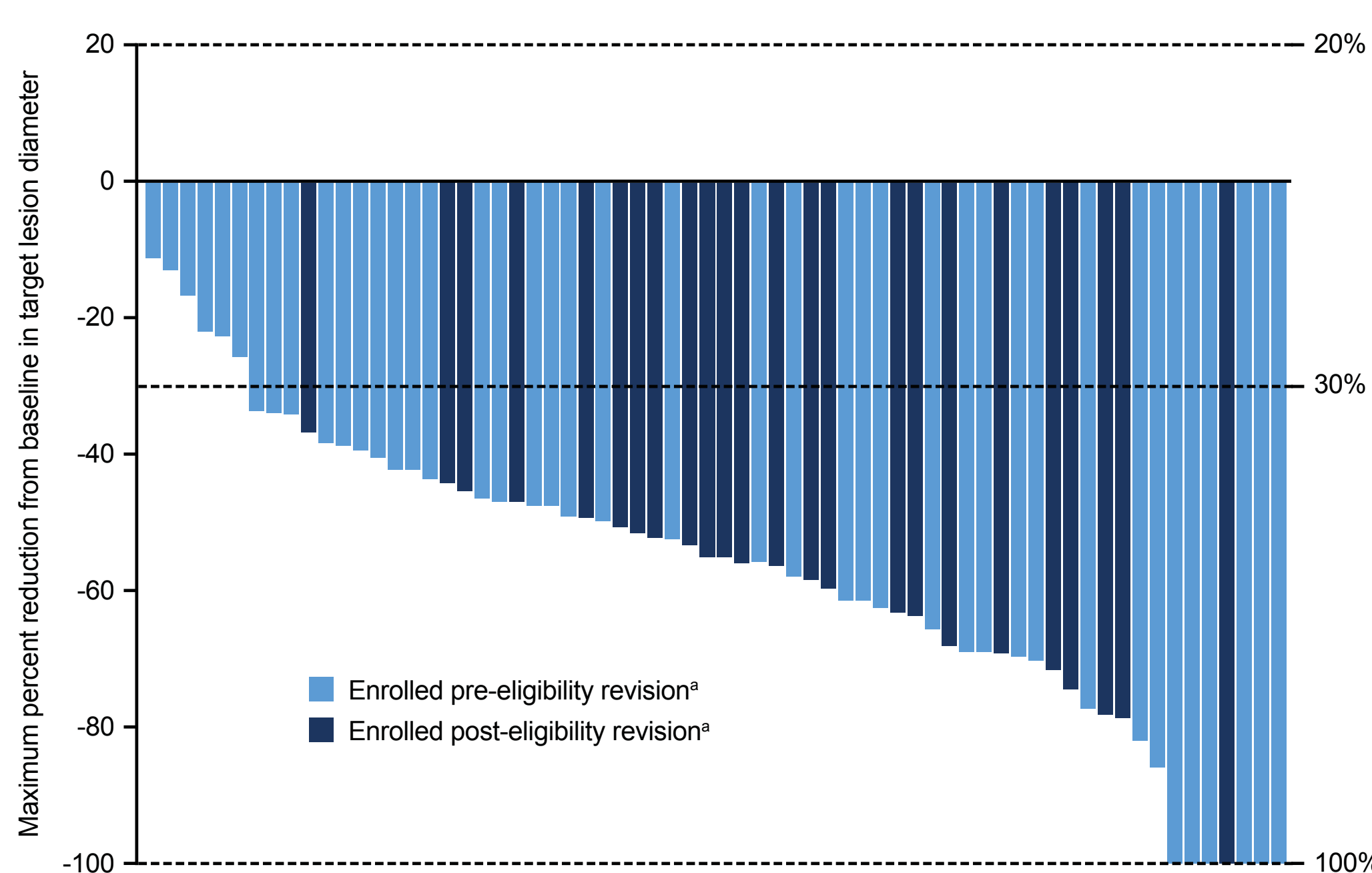
METHODS

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

Key eligibility criteria
- *RET* fusion–positive metastatic NSCLC
- ECOG PS 0–1
- No prior systemic treatment
n=226

R 1:1

Arm A: pralsetinib → PD by INV or BICR
Arm B: SOC → PD by INV and BICR → Optional crossover to pralsetinib → PD by INV
EOT survival follow-up

Stratification factors
- History of brain metastasis (yes/no)
- ECOG PS (0/1)
- Intended use of pembrolizumab if participant is randomized to the control arm (yes/no)

Investigator's choice of SOC platinum-based anticancer treatment regimens:
Non-squamous histology:
a) Carboplatin/cisplatin and pemetrexed or
b) Pembrolizumab, carboplatin/cisplatin and pemetrexed
Squamous histology:
Carboplatin/cisplatin and gemcitabine or
Pembrolizumab, carboplatin and paclitaxel or non-paclitaxel

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

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

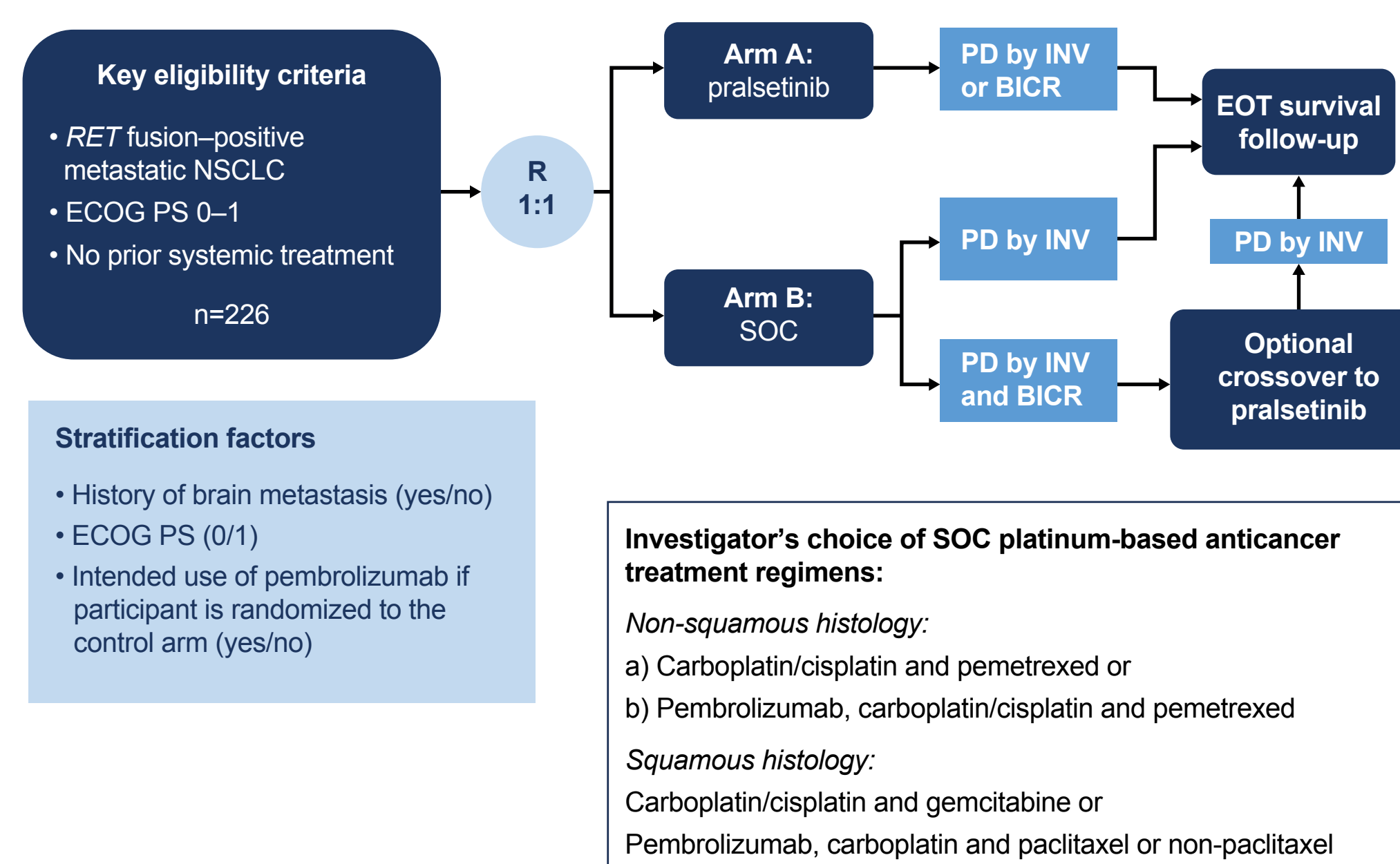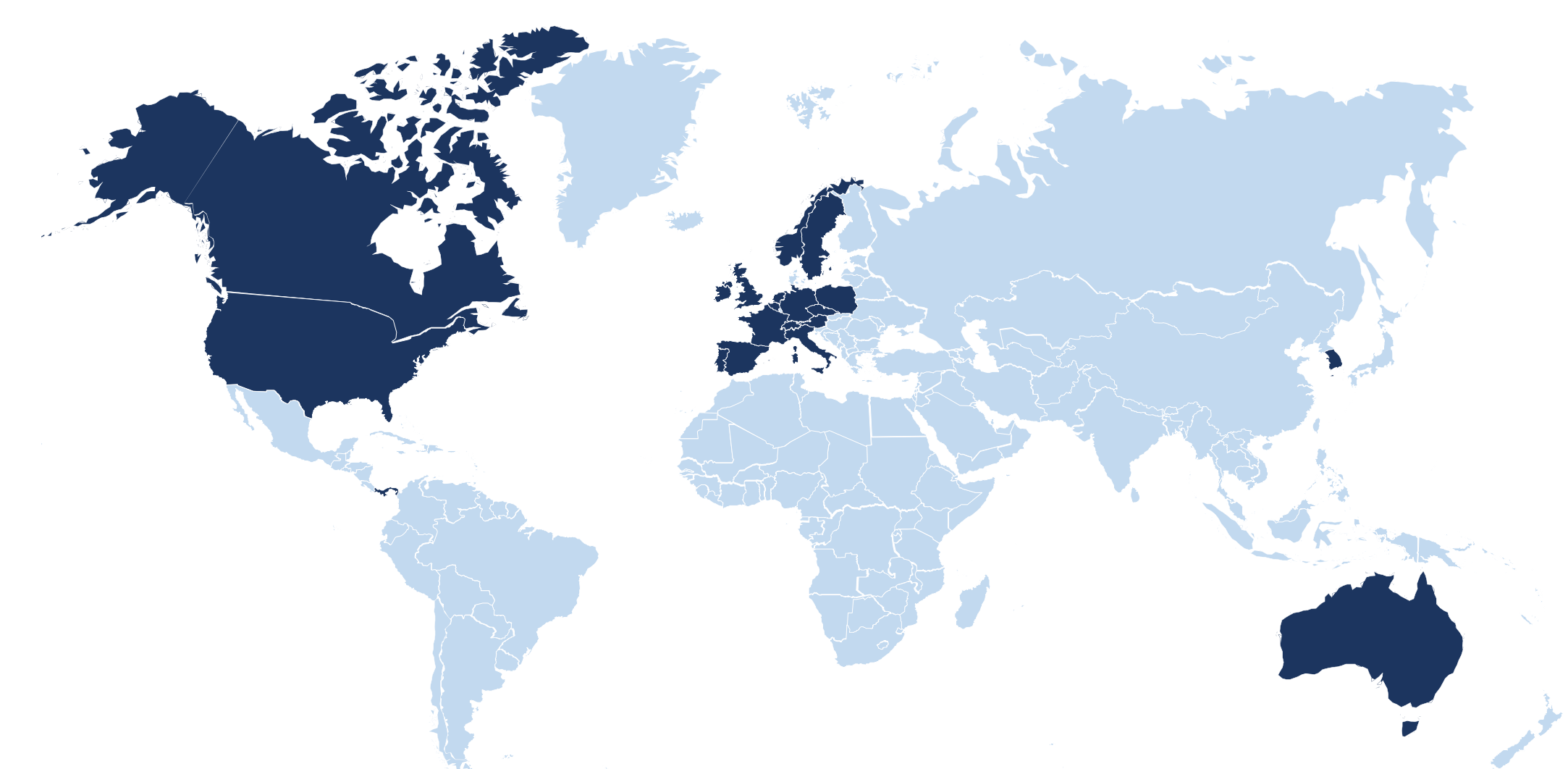Enrolled pre-eligibility revision[a]
Enrolled post-eligibility revision[a]

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

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.

Figure 3: Active study sites

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