

LIBRA: A Phase 2, Open-Label Platform Study Evaluating Novel Agent-Based Combinations in Locally Advanced or Metastatic NSCLC

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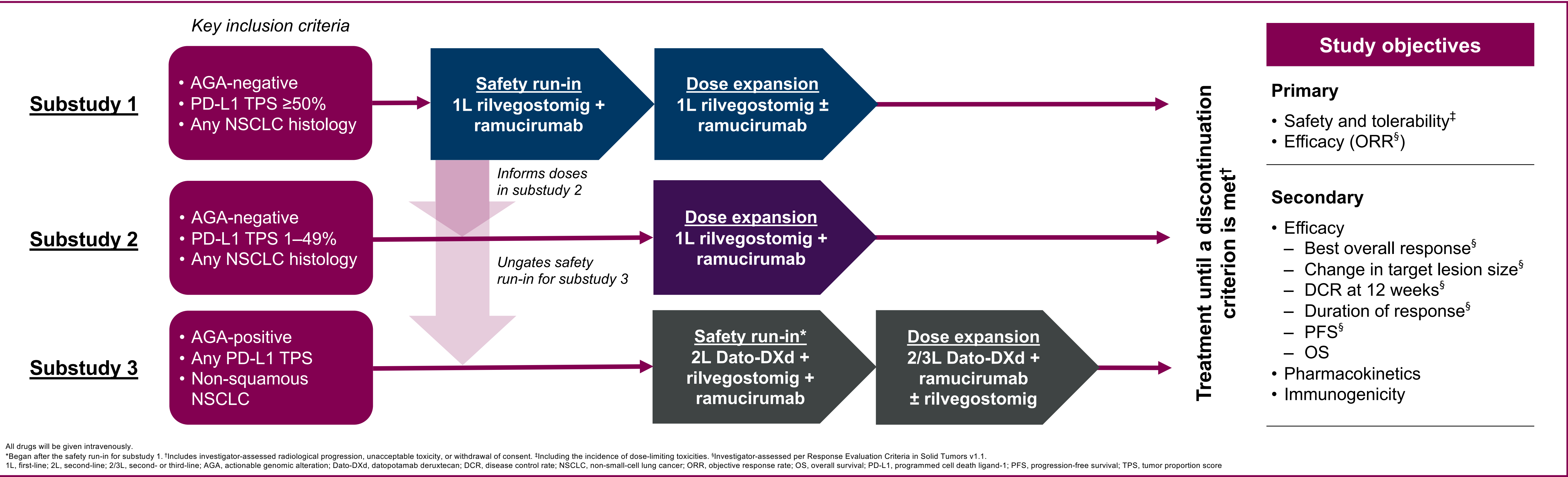
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Background

- Immunotherapies and targeted agents have improved treatment outcomes for patients with actionable genomic alteration (AGA)-negative or AGA-positive advanced non-small-cell lung cancer (NSCLC).
 - Immunotherapy targeting the PD-1/PD-L1 axis, with or without chemotherapy, has transformed the first-line treatment of AGA-negative NSCLC,^{1,2} but many patients still do not derive durable clinical benefit from these treatments.³
 - First-line treatment for AGA-positive NSCLC is biomarker-driven, and most subsequent therapies comprise chemotherapy with or without targeted agents.⁴
- Approaches simultaneously targeting angiogenesis and the PD-1/PD-L1 axis, with or without chemotherapy, have demonstrated survival benefits in AGA-negative^{5–7} and AGA-positive advanced or metastatic NSCLC.^{8–11}
- Rilvegostomig is a monovalent, Fc-reduced, dual checkpoint bispecific IgG1 monoclonal antibody against PD-1 and T cell immunoreceptor with Ig and ITIM domains (TIGIT) receptors.
 - Rilvegostomig demonstrated encouraging preliminary efficacy and a manageable safety profile in immune checkpoint inhibitor-naïve, AGA-negative metastatic NSCLC in the first-in-human ARTEMIDE-01 study.^{12,13}
- Ramucirumab is an anti-VEGFR2 antibody approved to treat multiple tumor types.¹⁴
 - Ramucirumab plus erlotinib is approved as first-line therapy for *EGFR*-mutated metastatic NSCLC.¹⁵
 - Ramucirumab plus docetaxel is approved for metastatic NSCLC previously treated with platinum-based chemotherapy and, if appropriate, EGFR- or ALK-directed therapies.¹⁶
- Datopotamab deruxtecan (Dato-DXd), a trophoblast cell surface antigen 2 (TROP2)-directed antibody-drug conjugate, has demonstrated notable clinical activity with a manageable safety profile in previously treated, *EGFR*-mutated locally advanced or metastatic NSCLC.^{17,18}
 - In the USA, Dato-DXd is approved for use after receipt of EGFR-directed therapy and platinum-based chemotherapy based on the outcomes of the TROPION-Lung 01 and TROPION-Lung05 studies.^{17–19}
- Rilvegostomig plus ramucirumab may provide clinical benefit for patients with AGA-negative, previously untreated advanced or metastatic NSCLC; in addition, Dato-DXd plus ramucirumab and rilvegostomig may provide clinical benefit for patients with AGA-positive NSCLC that has progressed while receiving prior targeted therapies.

Here we describe substudies 1–3 of **LIBRA (NCT07098338)**, a Phase 2, multicenter, open-label platform study evaluating novel treatment combinations in patients with locally advanced or metastatic NSCLC.

Figure 1. Study Design



Study design

- LIBRA currently comprises three substudies (**Figure 1**).
 - Substudy 1 is evaluating rilvegostomig with or without ramucirumab as first-line therapy for AGA-negative NSCLC with a PD-L1 tumor proportion score (TPS) ≥50%.
 - Substudy 2 is evaluating rilvegostomig plus ramucirumab as first-line therapy for AGA-negative NSCLC with a PD-L1 TPS 1–49%.
 - Substudy 3 is evaluating Dato-DXd plus ramucirumab with or without rilvegostomig as second- or third-line therapy for AGA-positive non-squamous NSCLC.
- Substudies 1 and 3 both comprise safety run-in and dose expansion components.
 - Safety run-in data from substudy 1 informs dose expansion in substudies 1 and 2.
 - The safety run-in for substudy 3 began after completion of the safety run-in for substudy 1.
- Progression to dose expansion and the doses used is determined by the safety review committee for each substudy based on safety run-in data.
- Additional dose-expansion cohorts may be initiated in each substudy to assess additional doses or patient subgroups.

Inclusion and exclusion criteria

Key inclusion criteria (all substudies)

- Aged ≥18 years.
- Eastern Cooperative Oncology Group performance status 0 or 1.
- Has ≥1 target lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Adequate organ and bone marrow function.
- Life expectancy ≥12 weeks.
- Provision of fresh or archival tumor tissue at screening in expansion parts.

Key inclusion criteria (substudies 1 and 2)

- Histologically or cytologically documented locally advanced or metastatic NSCLC (any histology).
- PD-L1 TPS ≥1% (≥50% for substudy 1 and 1–49% for substudy 2).
- AGA-negative.
- No prior systemic therapy for locally advanced or metastatic disease.

Key inclusion criteria (substudy 3)

- Histologically or cytologically documented locally advanced or metastatic non-squamous NSCLC.
- AGA-positive.
- Experienced disease progression while receiving prior targeted therapies for locally advanced or metastatic disease.

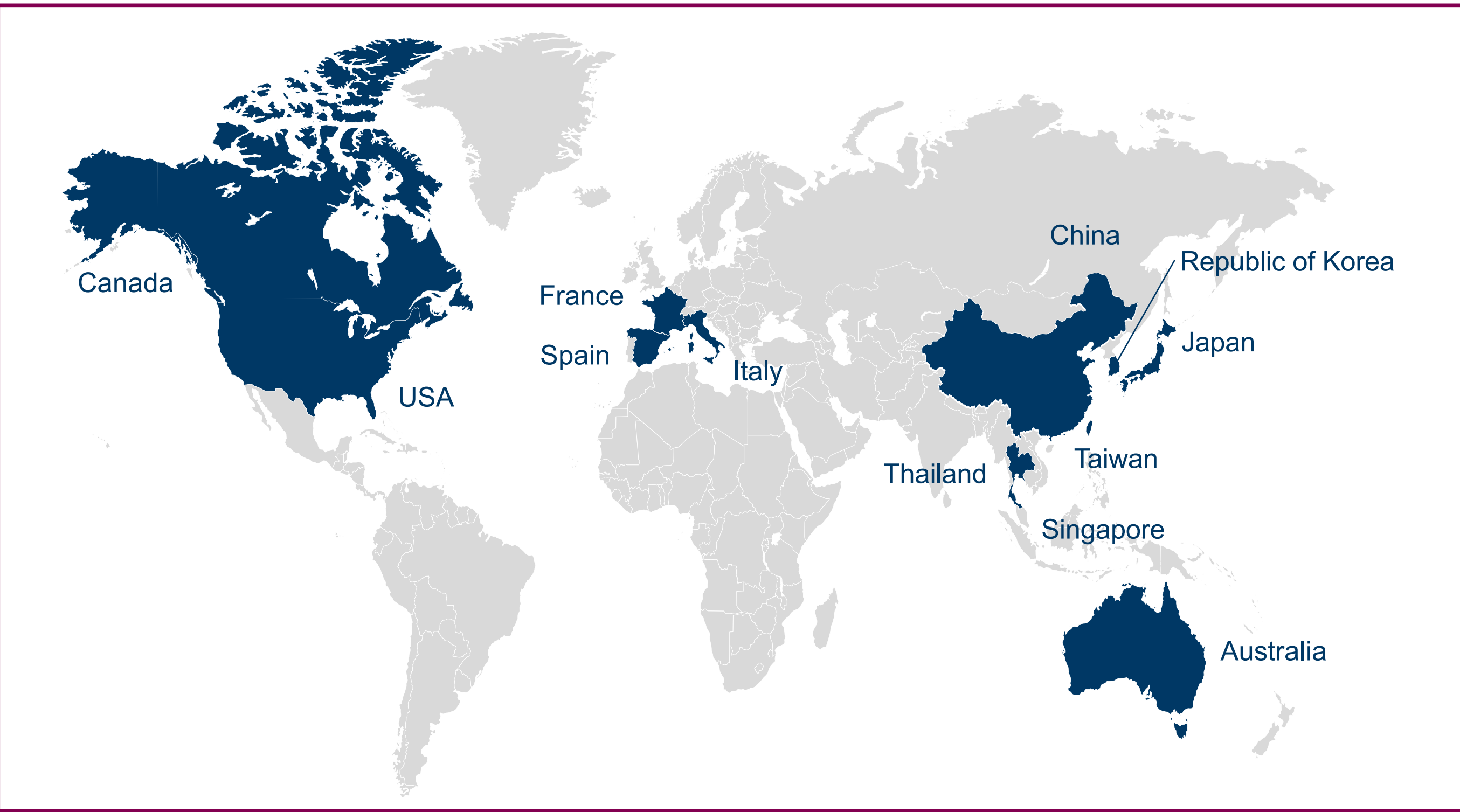
Key exclusion criteria (all substudies)

- Severe or uncontrolled systemic diseases with the capacity to jeopardize study participation.
- Active or prior documented autoimmune or inflammatory disorders.
- Active infections.
- Unstable brain metastases.
- History of another primary malignancy.
- History of uncontrolled hypertension.
- Uncontrolled or significant cardiac disease.
- High risk of bleeding or disorders of coagulation, including gross hemoptysis within two months prior to receiving the first dose of study treatment.
- Prior immune-mediated therapy.
- Receipt of live, attenuated vaccine ≤30 days prior to the first dose of study treatment.
- Persistent Grade ≥2 toxicities from prior anticancer therapy.

Study status

- Study locations at the time of presentation are shown in **Figure 2**.
- Enrollment began in August 2025 and primary completion is anticipated in April 2029.
- As of July 20, 2026, recruitment of patients to dose-expansion cohorts had started for all current substudies.
- More substudies may be added in the future to assess additional treatment combinations.

Figure 2. Study Locations



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Disclosures of conflicts of interest

Jonathan W. Goldman reports advisory board or committee roles for AbbVie, AstraZeneca, Bristol Myers Squibb, Genentech, Jazz, Lilly, Pfizer, and Summit; receiving consulting fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Genentech, Jazz, Lilly, Pfizer, and Summit; and receiving grants/funds from AbbVie, Advaxis, AstraZeneca/MedImmune, Bristol Myers Squibb, Corvus Pharmaceuticals, Genentech/Roche, Lilly, Lyell, Pfizer, and Spectrum Pharmaceuticals.

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