A Randomized Phase 3 Study of Ivonescimab Plus Chemotherapy Versus Pembrolizumab Plus Chemotherapy for the First-line Treatment of Metastatic Non-small Cell Lung Cancer: HARMONi-3

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BACKGROUND

- A combination of platinum-based chemotherapy plus programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) is the most common treatment approach for patients with newly diagnosed Stage IV non-small cell lung cancer (NSCLC) regardless of tumor PD-L1 status[1]
- Ivonescimab is a first-in-class investigational bispecific antibody against PD-1 and vascular endothelial growth factor (VEGF; Figure 1)[2,3]
  - > By blocking both PD-1 and VEGF in the tumor microenvironment, ivonescimab has the potential to drive synergistic anti-tumor activity through higher binding affinity and increased activity of T cells
  - > In vitro studies have shown that the presence of VEGF increases PD-1 binding strength by more than 10-fold
- In Phase 3 studies, ivonescimab has yielded promising clinical outcomes in patients with advanced/metastatic NSCLC[4-6]
  - > In HARMONi-A, patients with relapsed advanced/metastatic epidermal growth factor receptor (EGFR)-mutated NSCLC (excluding patients with T790M variant) treated with ivonescimab plus chemotherapy had a median progression-free survival (mPFS) of 7.1 months (vs 4.8 months for the placebo plus chemotherapy group) and an overall response rate (ORR) of 50.6% (vs 35.4%)
  - > In HARMONi-2, patients with PD-L1–positive advanced NSCLC treated with ivonescimab experienced a longer mPFS compared with those treated with pembrolizumab (11.1 months vs 5.8 months, respectively)
    - The PFS benefit of ivonescimab was consistent across patients with PD-L1 tumor proportion scores of 1%-49% (hazard ratio [HR] 0.54) and >50% (HR 0.48)
  - > In the Phase 3 trial, HARMONi-6, patients with squamous NSCLC treated first-line (1L) with ivonescimab plus chemotherapy achieved superior PFS vs patients treated with tislelizumab (anti–PD-1) plus chemotherapy regardless of PD-L1 status making it the first known regimen to achieve clinically meaningful benefit over an anti–PD-(L)1 antibody-chemotherapy combination
- HARMONi-3 is the first global study to investigate the efficacy and safety of ivonescimab plus chemotherapy in patients with metastatic (Stage IV) NSCLC with no prior systemic treatment history[7]

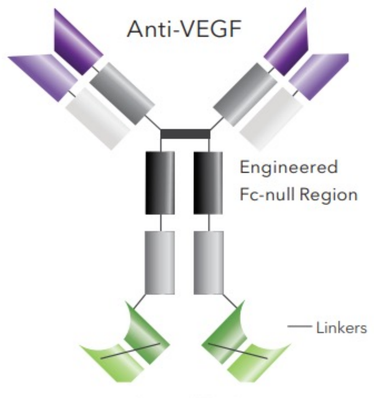


Figure 1. Ivonescimab PD-1/VEGF Bispecific Antibody. Anti–PD-1 scFv attaches to the C-terminus of each anti–VEGF-A antibody heavy chain. Ivonescimab has a heterotetrameric structure consisting of 2 heavy chains of the IgG1 subclass and 2 light chains of the kappa subclass, which are covalently linked through disulfide bonds.[2]

Fc, fragment crystallized; IgG1, immunoglobulin G1; PD-1, programmed cell death protein 1; scFv, single-chain variable fragment; VEGF, vascular endothelial growth factor.

KEY ELIGIBILITY CRITERIA[3,7]

Key Inclusion Criteria

- ≥18 years of age at time of enrollment
- ECOG Performance Status score of 0 or 1
- Metastatic (Stage IV) NSCLC with histologically or cytologically confirmed squamous or non-squamous NSCLC
- Tumor proportion score for PD-L1 expression, irrespective of the PD-L1 expression, prior to randomization
- ≥1 measurable noncerebral lesion according to RECIST v1.1
- No prior systemic treatment for metastatic NSCLC[a]

Key Exclusion Criteria

- Histologic or cytopathologic evidence of the presence of small cell lung carcinoma
- Known actionable genomic alterations (EGFR, ALK, ROS1, and BRAF V600E) for which 1L approved therapies are available
- Has received any prior therapy for NSCLC in the metastatic setting
- Radiologically documented evidence of major blood vessel invasion or tumor invading organs or there is a risk of esophagotracheal or esophagopleural fistula in the opinion of the investigator
- Symptomatic central nervous system (CNS) metastases or CNS metastasis ≥1.5 cm
- History of bleeding tendencies or coagulopathy and/or clinically significant bleeding symptoms or risk within 4 weeks (including gastrointestinal bleeding, hemoptysis)

[a] Patients receiving adjuvant or neoadjuvant chemotherapy or curative-intent chemoradiotherapy with or without PD-(L)1 inhibitors are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the development of metastatic disease.

TRIAL ENDPOINTS[3,7]

Primary Endpoints

- Overall survival
- PFS as assessed by investigator based on RECIST v1.1[b]

Secondary Endpoints

- ORR,[b] disease control rate, and duration of response as assessed by investigator based on RECIST v1.1
- Safety assessment: incidence and severity of adverse events and clinically significant abnormal laboratory test results
- Pharmacokinetics: ivonescimab serum drug concentration profiles
- Immunogenicity: number of patients with detectable anti-ivonescimab antibody at baseline and post treatment

[b] Images will be collected for blind review by the IRRC as a sensitivity analysis.

TRIAL DESIGN[3,7]

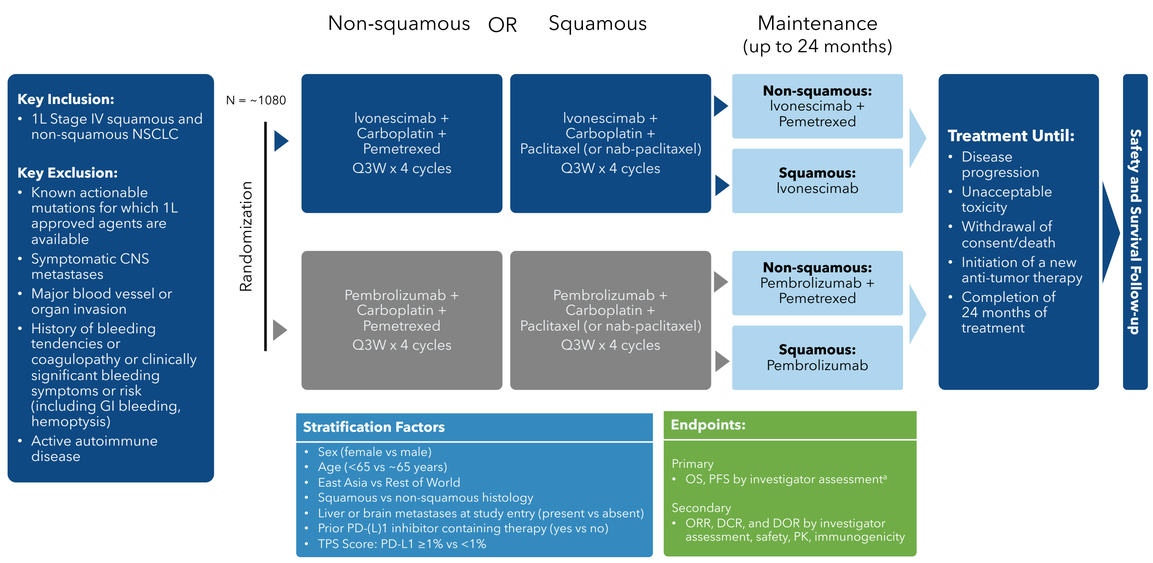


Figure 2. HARMONi-3 Trial Design. HARMONi-3 is a global, randomized, double-blind, phase 3 study to compare the efficacy and safety of ivonescimab or pembrolizumab, combined with platinum-doublet chemotherapy in patients with metastatic NSCLC without activating mutations who have not previously received systemic therapy for metastatic disease. Approximately 1080 patients will be randomized (1:1) to receive 4 cycles of ivonescimab (20 mg/kg) or pembrolizumab (200 mg) combined with platinum-doublet chemotherapy as an IV injection Q3W followed by ivonescimab or pembrolizumab +/- pemetrexed maintenance therapy Q3W as determined by histology.

[a] A PFS sensitivity analysis will be performed based on IRRC's assessment.

1L, first-line; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; GI, gastrointestinal; IRRC, Independent Radiologic Review Committee; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, once every 3 weeks; TPS, tumor proportion score.

TRIAL STATUS[7]

- This study is expected to enroll participants at 174 locations across North America, Europe, and Asia (Figure 3)
- The latest information on this study can be found at ClinicalTrials.gov, reference number NCT05899608

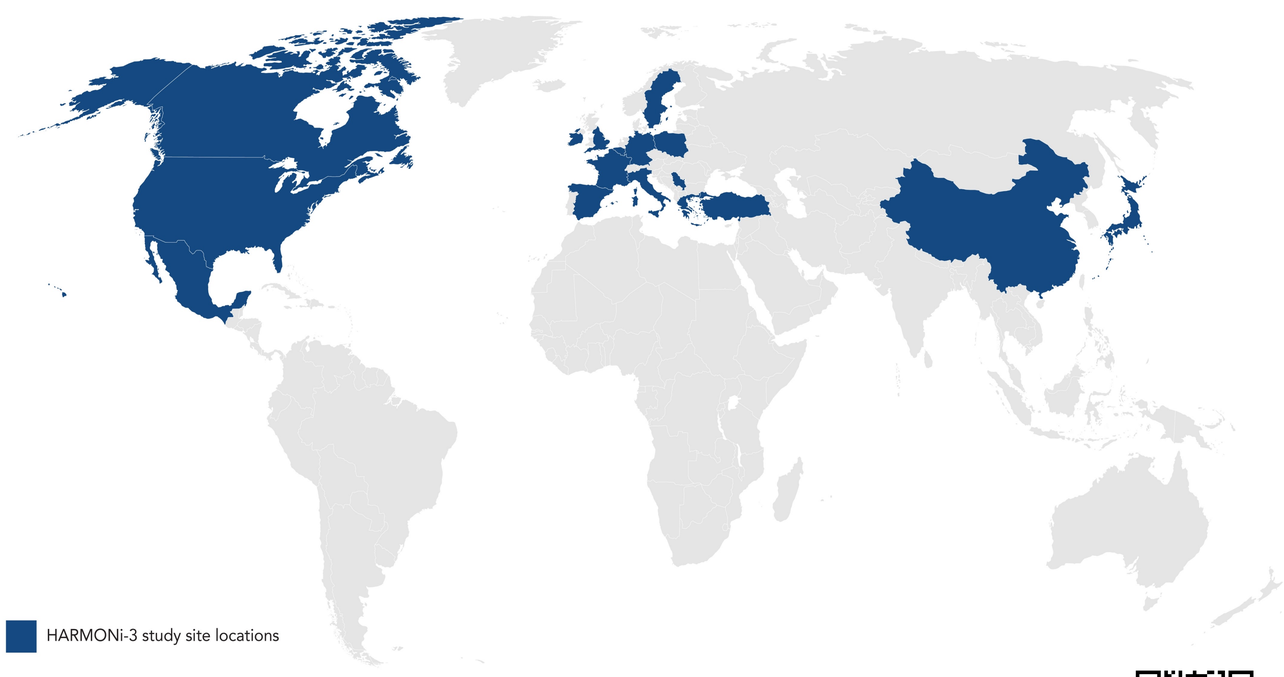


Figure 3. HARMONi-3 Study Locations.

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