TiP Poster 2023

Poster

#C030

HARMONi-3: A Randomized, Controlled, Multiregional Phase 3 Study of Ivonescimab Combined with Chemotherapy Versus Pembrolizumab Combined with Chemotherapy for the First-line Treatment of Metastatic Squamous Non-Small Cell Lung Cancer

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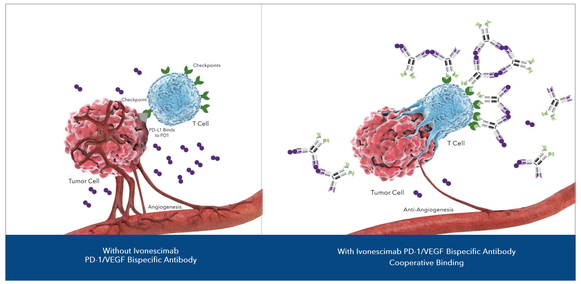
BACKGROUND

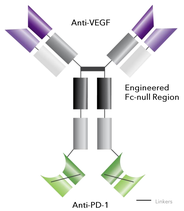
- For first-line metastatic squamous non-small cell lung cancer (NSCLC), treatment with the combination of a programmed cell death protein 1 (PD-1) checkpoint inhibitor plus platinum doublet chemotherapy has become standard of care.[1,2] The addition of antiangiogenic agents to immunotherapy has emerged as a promising strategy for cancer treatment[3,4,5]
- Ivonescimab (SMT112/AK112) is a novel tetravalent bispecific antibody with an engineered Fc-null region targeting PD-1 and vascular endothelial growth factor (VEGF). Given the correlation between VEGF and PD-1 expression in the tumor microenvironment,[6,7,8] simultaneous, cooperative blockade of these 2 targets by ivonescimab may drive enhanced antitumor activity[9,10]
- Previously reported Phase 2 trial data included 63 first-line advanced or metastatic squamous NSCLC patients without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations treated with ivonescimab plus paclitaxel and carboplatin demonstrated that these patients had an objective response rate of 67% with a median duration of response (DoR) of 15 months, and a 9-month overall survival (OS) estimate of 93% (median OS not reached). Notably, 38% of these patient's tumors had a PD-L1 TPS of <1%[11]
- Furthermore, ivonescimab was well tolerated in patients with squamous cell carcinoma histology in combination with platinum doublet chemotherapy with a treatment emergent adverse event discontinuation rate of 11% and one grade ≥ 3 bleeding event (1.6%).[11]

MECHANISM OF ACTION

Ivonescimab: First-in-Class PD-1/VEGF Bispecific Antibody in Clinical Development

Brings two validated mechanisms in oncology[9,11,12] into ONE novel tetravalent molecule.





Designed to Optimize the Balance of Anti-tumor Activity and Safety[7,8]

Cooperative Binding

- Presence of VEGF increases binding of PD-1 by >10-fold in-vitro[6]

Potential to accumulate higher levels of ivonescimab in the tumor microenvironment (TME) vs. healthy tissue

Simultaneous interaction of PD-1 & VEGF blockades have the potential to drive synergistic anti-tumor activity[7,9,10]

Engineered Fc-null region could lead to reduced adverse events

- Via reduction of antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC) in-vitro[10,12] and no meaningful infusional cytokine release (IL-6 and TNF-α) in patients[10]

Half-life ($T_{1/2}$) of 6-7 days[11] of ivonescimab provides blockade of both targets and with its affiliated clearance, could potentially lead to a favorable safety profile[7,8]

STUDY DESIGN

Phase 3 randomized, parallel-group, blinded, multiregional study comparing the efficacy and safety of ivonescimab or pembrolizumab, combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy in patients with metastatic squamous NSCLC who have not previously received systemic therapy for metastatic disease. Approximately 400 patients will be randomized in this study.

Key Inclusion:

- Metastatic Stage IV squamous NSCLC
- Adequate hematologic and organ function

Key Exclusion:

- Known actionable mutations for which 1L approved agents are available
- Prior systemic treatment for metastatic NSCLC
- Symptomatic central nervous system (CNS) metastases
- Major blood vessel invasion or encasement by cancer; intratumor cavitation
- History of bleeding tendencies or coagulopathy or clinically significant bleeding symptoms or risk (including GI bleeding, hemoptysis)
- Active autoimmune disease

Randomization 1:1

- Ivonescimab 20 mg/kg q3w + carboplatin AUC 5 or 6 q3w + paclitaxel 175 or 200 mg/m² q3w (or nab-paclitaxel 100 mg/m² q3w) x 4 cycles → Ivonescimab (maintenance up to 24 months)
- Pembrolizumab 200 mg q3w + carboplatin AUC 5 or 6 q3w + paclitaxel 175 or 200 mg/m² q3w (or nab-paclitaxel 100 mg/m² q3w) x 4 cycles → Pembrolizumab (maintenance up to 24 months)

Stratification factors:

- Sex (female vs male)
- Age (<65 vs ≥65 years)
- Geographical region: East Asia vs Rest of the world (ROW)
- Liver or brain metastases at study entry (present vs absent)

Treatment until:

- Disease progression
- Unacceptable toxicity
- Withdrawal of consent/death

Primary Endpoints

- Overall survival

Secondary Endpoints

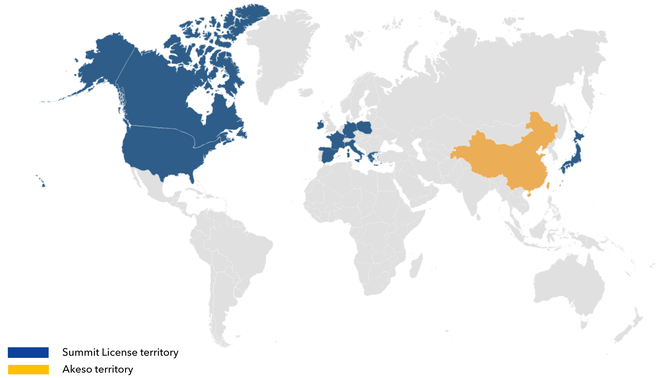
- Progression free survival assessed by investigator based on RECIST v1.1
- Overall response rate (including DoR) assessed by investigator based on RECIST v1.1
- Safety assessment: incidence and severity of adverse events (AEs) and clinically significant abnormal laboratory test results
- Pharmacokinetic (PK) characteristics: ivonescimab serum drug concentrations profiles
- Immunogenicity: number and percentage of patients with detectable anti-ivonescimab antibody (ADA) at baseline and post treatment

Exploratory Endpoints

- Potential biomarkers in tumor tissue and peripheral blood
- CNS metastases response using the Response Assessment in Neuro-Oncology (RANO) criteria in patients with CNS metastasis at baseline
- Health Related Quality of Life (HRQoL) assessment

STUDY STATUS

- This study is expected to enroll in US, Canada, France, Germany, Greece, Ireland, Italy, Poland, Spain, Japan (noted in blue which are in Summit Therapeutics' license territory) and China (noted in orange which is Akeso's territory)
- Please visit ClinicalTrials.gov to find out the latest information on this study and reference NCT05899608



ACKNOWLEDGEMENT

- We are grateful to the patients and their families, study investigators, and the staff at all sites who have and are participating in the HARMONi-3 study
- This study is sponsored by Summit Therapeutics, Inc., (US, Canada, Europe) and Akeso Biopharma Co Ltd (China)

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Ivonescimab is an investigational therapy that is not approved by any regulatory authority.

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