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HARMONi: A Randomized, Double-Blind, Multi-Center, Phase III Study of AK112 or Placebo Combined With Pemetrexed and Carboplatin in Patients with *EGFR*-mutant Locally Advanced or Metastatic Non-Squamous NSCLC Who Have Failed to *EGFR*-TKI Treatment

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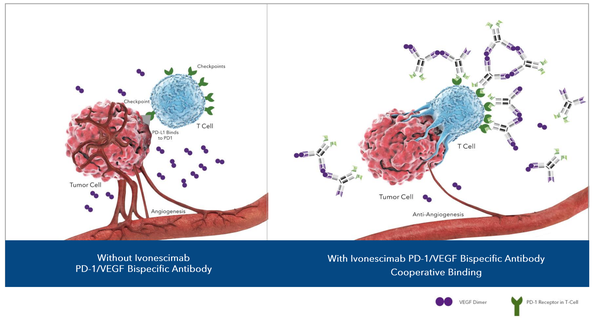
BACKGROUND / INTRODUCTION

- For patients (pts) with *EGFR*-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard, drug resistance remains a challenge, and an effective therapy after progression is needed
- Ivonescimab (SMT112/AK112) is a novel tetravalent bispecific antibody (2 binding sites for PD-1 and 2 binding sites for VEGF) with an engineered Fc-null region and a half-life of 6-7 days.[6,9] In the presence of VEGF, binding affinity to PD-1 increases more than 10-fold.[6,9] Given the correlation between VEGF and PD-1 expression in the tumor microenvironment,[4-6] simultaneous blockade of these 2 targets by ivonescimab drives antitumor activity[1,4,7]
- The highly engineered Fc-null region of ivonescimab in combination with a shorter half-life could potentially lead to reduced adverse events, compared to co-administration of individual anti-PD-(L)1 and anti-VEGF agents[4,6]
- For previously reported Phase 2 trial data, which included 19 pts with *EGFR* mutated NSCLC who progressed following TKI therapy, the response rate to ivonescimab plus pemetrexed and carboplatin was 68.4% (13/19)[4] with a tolerable safety profile in the total population (N=174) treated with ivonescimab plus chemotherapy[9]
- Here, we describe a Phase 3 study of ivonescimab combined with chemotherapy for locally advanced or metastatic non-squamous NSCLC harboring *EGFR* mutations who had failed prior *EGFR*-TKI therapy (NCT05184712)

MECHANISM OF ACTION

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

Brings two validated mechanisms in oncology[1,2,3] into ONE novel tetravalent molecule.



Designed to Optimize the Balance of Anti-tumor Activity and Safety[4,5]

Cooperative Binding
- Presence of VEGF increases binding of PD-1 by >10-fold in-vitro[6]
- VEGF dimer leads to potential interconnection of multiple ivonescimab molecules, which may lead to increased binding of T-cells in-vitro[6]

Potential to accumulate higher levels of ivonescimab in the tumor microenvironment vs. healthy tissue
- Higher levels of PD-1 & VEGF expression in the TME[4-6]

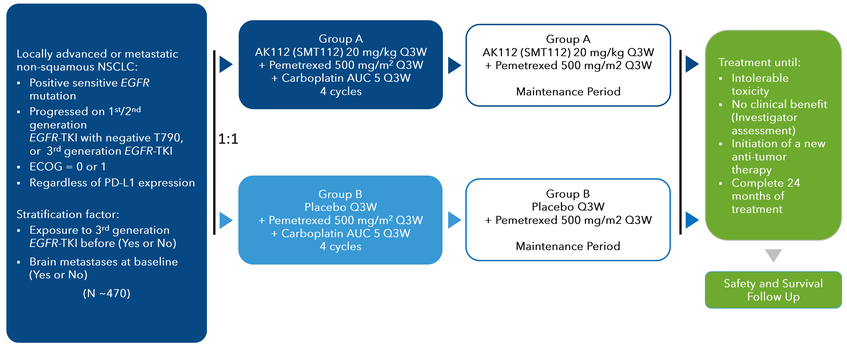
Simultaneous interaction of PD-1 & VEGF blockades have the potential to drive synergistic anti-tumor activity[1,4,7]
- Inhibiting VEGF can help improve the effect of immunotherapy by modulating the tumor microenvironment[4]
- Enhancing the PD-1 blockade helps activate T-cells[2]

Engineered Fc-null region could lead to reduced adverse events
- Via reduction of ADCC, ADCP, and CDC in-vitro[7,8] and no meaningful infusional cytokine release (IL-6 and TNF-α) in patients[7]
- Humanized IgG1 bispecific antibody[4]

$T_{1/2}$ of 6-7 days[9] of ivonescimab provides blockade of both targets and with its affiliated clearance, could potentially lead to a favorable safety profile[4,5]

STUDY DESIGN

Phase 3 randomized, double-blind, multiregional study evaluating the efficacy and safety of ivonescimab combined with pemetrexed and carboplatin chemotherapy in patients with locally advanced or metastatic non-squamous NSCLC who have progressed on *EGFR*-TKI treatment.



Primary Endpoints
- Overall survival
- PFS assessed by IRRC based on RECIST v1.1

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

KEY ELIGIBILITY CRITERIA

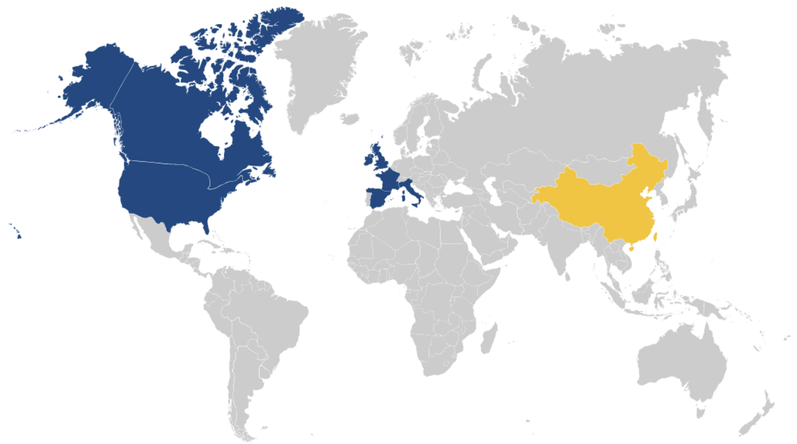
Key Inclusion Criteria
- Locally advanced (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC
- *EGFR* Mutation
- Progression after prior treatment with a third generation *EGFR*-TKI (i.e. osimertinib, lazertinib, ametinib, vometinib)
- At least one measurable noncerebral lesion according to RECIST 1.1

Key Exclusion Criteria
- Prior immunotherapy or systemic treatment for advanced stage (IIIB to IV) NSCLC. Patients receiving adjuvant or neoadjuvant chemotherapy for nonmetastatic disease are eligible if disease progression occurs at least 6 months after the end of the last chemotherapy
- Radiologically documented evidence of major blood vessel invasion, encasement by cancer, or evidence of intratumor cavitation
- Symptomatic 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
- Patients with >30 Gy of chest radiation therapy within 6 months prior to the first dose
- Major surgical procedures or serious trauma within 4 weeks prior to the first dose, or major surgical plans within 4 weeks after the first dose
- Presence of pleural effusions, pericardial effusions, or ascites that is clinically symptomatic or requires repeated drainage

Assessments and Follow-up
- Responses will be assessed by imaging of the chest, abdomen, and pelvis ever 6 weeks through 54 weeks and every 12 weeks thereafter by IRRC per RECIST v1.1 until disease progression, start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first
- Adverse events (AEs) will be monitored throughout the study and for 30 days during the follow-up period (90 days for serious or immune related AEs) and will be graded according to the Common Terminology Criteria for Adverse Events, v5.0
- Patient-reported outcomes (EORTC QLQ C30) will be performed every odd cycle up to Cycle 7 (Cycles 1, 3, 5, 7) then every 4 cycles onward (Cycles 11, 15, 19, etc.)

STATUS

- Countries participating in the HARMONi study in Summit Therapeutics license territory include the United States, Canada, Spain, France Italy, and the UK
- Enrollment for the HARMONi study in Akeso's territory in China is complete
- Please visit ClinicalTrials.gov to find out the latest information on this study and reference NCT05184712



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- Presenting author has no conflicts of interest to declare

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

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