Article published online: 2025-06-11

Ivonescimab: The Two Pronged Attack

Dilip Harindran Vallathol[1] Abhinav Menon[1] Arun R. Warrier[1]

[1] Department of Medical Oncology, Aster Medcity, Kochi, Kerala, India

Ind J Med Paediatr Oncol

Address for correspondence Dilip Harindran Vallathol, DM, Department of Medical Oncology, Aster Medcity, Kochi, Kerala 682 027, India (e-mail: dhdtraveller@gmail.com).

Abstract

Targeted therapy and immunotherapy have changed the landscape of treatment of cancers with respect to longevity and quality of life. Programmed death 1 (PD-1) and vascular endothelial growth factor (VEGF) are very salient targets of anticancer drugs. Dual blockade with bispecific antibodies is a novel mode of treatment of malignancies, which has already been successful in hematological malignancies. Ivonescimab, a novel bispecific antibody that targets PD-1 and VEGF, has been developed in China. It has been found to be beneficial in nonsmall cell lung cancer, biliary tract cancers, and breast cancers for which phase 3 clinical trials have already been discussed in various meetings and publications. The current drug review is regarding the parameters of this novel drug—the mechanism of action, clinical and preclinical trials, and approvals.

Keywords

- ivonescimab
- VEGF
- PD-1
- targeted therapy
- immunotherapy

Introduction

Targeted therapy and immunotherapy have been path breaking in cancer treatment. It has improved both survival and quality of life across malignancies. These events have become possible due to the advances made in the field of precision and personalized oncology. It has paved the way for the identification of novel targets and treatment modalities.[1]

Vascular endothelial growth factor (VEGF) and programmed death 1 (PD-1) are significant targets of anticancer drugs across various malignancies. PD-1 and VEGF are upregulated and coexpressed frequently in several solid tumors.[2] VEGF and PD-1 promote tumor angiogenesis and alter tumor milieu, respectively. Hence, combining immunotherapeutic and antiangiogenic agents against these targets has the potential to have a synergistic antitumor effect.[3] The synergistic action of ivonescimab is via the dual binding of the drug to PD-1 on immune cells and VEGF on tumor cells. This allows it to simultaneously activate the immune system to attack cancer cells and hinder the ability of neovascularization of cancer cells for survival. In a nutshell, it affects two important hallmarks of cancer. With this notion, the combination has been studied in various clinical trials including phase 3 trials including HARMONi-A and HARMONi-2.[4,5]

The current drug review is regarding ivonescimab which is an innovator bispecific drug targeting VEGF and PD-1 in unison.

Mechanism of Action and Discovery of Ivonescimab

Ivonescimab is a humanized immunoglobulin G1 (IgG1) bispecific antibody targeting PD-1 and VEGF in the tumor microenvironment. It is a first in class drug that has been developed for solid tumors. This medicine has a tetravalent structure that allows the formation of sizable complexes with dimeric VEGF, which leads to high avidity to PD-1. This results in cooperative binding that increases affinity of VEGF and PD-1 to tumor cells. This cooperative binding increases the binding affinity of the molecule by creating more binding sites. Therefore, the VEGF dimer also leads to the potential interconnection of multiple ivonescimab molecules that increases T cell activation and enhances tumor cell kill. These two targets (PD-1 and VEGF) in a single molecule enhance the potential to direct ivonescimab toward the tumor tissue than the healthy tissue. The efficacy of PD-1 binding is increased due to VEGF dimers by >18 times and for VEGF by >4 times.[2] Moreover, the safety profile will be improved

DOI https://doi.org/10.1055/s-0045-1809539.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

due to the Fc engineering, as compared with the combination of anti-PD-1 and anti-VEGF therapies.[3]

Preclinical trials have deciphered the soluble complexes formed by ivonescimab with VEGF dimers, which enhances the binding affinity of ivonescimab to PD-1 to more than 10-fold. Similarly, PD-1 increases ivonescimab binding to VEGF that ultimately leads to more VEGF blockade. Furthermore, treatment with ivonescimab has demonstrated dose-dependent antitumor response that is statistically significant (blocked the PD-1 signaling [$IC_{50} = 22.54$ nM] and VEGF signaling [IC50 = 3.13 nM], $p < 0.001$) in humanized murine tumor models.[3,6]

Clinical Trials of Ivonescimab

Phase 1 dose escalation study of ivonescimab was a multicenter trial done in advanced solid tumors that are refractory to standard therapies. The safety and efficacy was studied using an accelerated titration dose escalation design (0.3–30 mg/kg) administered intravenously every 2 weeks. The dose was determined to be 20 mg/kg every 2 weeks from this trial.[6]

The phase 2 trial was an open-label, multicenter trial conducted on 83 patients in China. The trial divided patients of nonsmall cell lung cancer (NSCLC) into three cohorts—cohort 1 included patients with previously untreated advanced NSCLC with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations; cohort 2 included patients with advanced NSCLC with *EGFR* mutations who failed previous tyrosine kinase inhibitor (TKI) therapy; and cohort 3 included patients with advanced NSCLC post-platinum-based chemotherapy and immunotherapy treatments. The results confirmed good overall response rates in all cohorts. In cohort 1, the median progression-free survival (PFS) was not reached and the 12-month PFS was 59.1%; in cohort 2, the median PFS was 8.5 months and the 12-month PFS was 35.5%; and in cohort 3, the median PFS was 7.5 months and the 12-month PFS was 44.5%.[7]

Using these results, the phase 3 HARMONi-A study was designed in 322 *EGFR* mutant NSCLC who had progressed on TKI. At a median follow-up time of 7.89 months, the median PFS was 7.1 months (95% confidence interval [CI], 5.9–8.7) in the ivonescimab group versus 4.8 months (95% CI, 4.2–5.6) in the placebo group (hazard ratio [HR], 0.46 [95% CI, 0.34–0.62]; $p < 0.001$), with an absolute difference of 2.3 months. All the prespecified subgroups showed PFS benefit favoring ivonescimab over placebo, including those with brain metastasis and who received third-generation TKI. The median overall survival data are not mature.[4]

Recently, the data of phase 3 HARMONi-2 study comparing ivonescimab to pembrolizumab in NSCLC were presented.[5] Subsequently, these results have been published. At a median follow-up of 8.67 months, the median PFS was 11.14 months among patients treated with ivonescimab ($n = 198$) versus 5.82 months for those treated with pembrolizumab ($n = 200$; stratified HR: 0.51; 95% CI, 0.38–0.69; $p < 0.0001$). The 9-month PFS rates with ivonescimab and pembrolizumab were 56 and 40%, respectively. The response was regardless of PDL-1 status or histology.[8]

Other than NSCLC, ivonescimab has also shown promise in other indications, which include triple-negative breast cancer,[9]small cell lung cancer, biliary tract cancer, and pancreatic cancer. The results of clinical trials for these indications are awaited.

Pharmacology and Adverse Events of Ivonescimab

Ivonescimab has been developed by Akeso, Inc—a biopharmaceutical company from China. The terminal half-life was determined to be around 7 days. Receptor occupancy was high at a dose level of 3.0 mg/kg every 2 weeks and higher. The maximum tolerated dose was determined to be 20 mg/kg every 2 weeks (as dose-limiting toxicities were observed at a dose of 30 mg/kg).[7]

The most common adverse events observed in clinical trials were hematological toxicities. The others include transaminitis and elevated serum creatinine. The most common immune-related adverse events included rash and hypothyroidism, while rare events were interstitial lung diseases and liver dysfunction. Common adverse events related to VEGF blockade included proteinuria and hypertension. Hence, there were no new safety signals and it was fairly well tolerated. Moreover, the adverse events (both immune-related and anti-VEGF- related) were less with ivonescimab when compared with usage of anti-VEGF and anti-PD-1 agents separately.[4,8]

Dose and Administration

Ivonescimab is administered at a dose of 20 mg/kg intravenously once every 3 weeks alone or along with chemotherapy as per indications. This dose was determined as per the phase 1a dose escalation trial as mentioned previously.

Ivonescimab Approval

The first fast track designation for the drug was obtained in 2022, for patients who had progressed on chemoimmunotherapy, in combination with docetaxel as second-line therapy. The Center of Drug Evaluation approved the drug in China in May 2024 for *EGFR*-mutant, nonsquamous NSCLC that progressed on any *EGFR* TKI therapy.[10] In August 2024, it was granted priority review for use as monotherapy for first-line treatment of PD-1 positive locally advanced or metastatic NSCLC. In the most recent update, it has received approval from the National Medical Products Administration (NMPA) for use as a monotherapy for the first-line treatment of PD-1 positive NSCLC patients who are negative for *EGFR/ALK* gene mutations.[11] The U.S. Food and Drug Administration has also granted fast track designation for the use of ivonescimab in combination with platinum-based chemotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with *EGFR* mutation, after disease progression following *EGFR*-TKI therapy.[12] Currently, approval from the Drug Controller General of India is not available for this drug.

Table 1 Selected ongoing clinical trials of Ivonescimab

Trial name	Arms	Indication
HARMONi-GI-01/AK112–309 study (Phase 3)	Ivonescimab versus durvalumab combined with chemotherapy	Biliary tract cancers
HARMONi-3 Clinical Trial (Phase 3)	Ivonescimab versus pembrolizumab combined with chemotherapy	Metastatic NSCLC
NCT05899608 (Phase 3)	Ivonescimab versus pembrolizumab combined with chemotherapy	Metastatic squamous NSCLC
NCT06672575 (Phase ½)	Ivonescimab	Recurrent glioblastoma
NCT05227664 (Phase 2)	Ivonescimab plus chemotherapy	Metastatic triple-negative breast cancers (preliminary results presented at ESMO 2024)[9]
HARMONi- 6 Clinical trial (Phase 3)	Ivonescimab versus tislelizumab combined with platinum-based chemotherapy	Squamous cell NSCLC

Abbreviations: ESMO, European Society of Medical Oncology; NCT, National Clinical Trial; NSCLC, nonsmall cell lung cancer.

Ongoing Clinical Trials

Ivonescimab is being studied for various indications in China, the results of which are highly anticipated. Selected ongoing clinical trials have been mentioned in ►**Table 1**.

Indian Perspective: Strengths, Limitations, and Future of Research

As the drug is not available or approved, the exact utility cannot be ascertained. Nonetheless, as with many other drugs, the arrival of this medicine to market has the potential to cause a change in practice. The strength of utilizing this drug in India is the availability of very suitable population and patient pool for clinical trials of ivonescimab for several indications. The diversity of the types of lung cancer that present to us in clinical practice is enormous. The limitation of this drug would be the penetrance of the clinical trials to our community in view of distinctive social and economic strata. Future research prospects for this drug have notable potential as this molecule will pave way for more research into bispecific therapy in solid tumors (similar to hematological malignancies). Further follow-up into the survival and toxicities with long-term utilization of ivonescimab needs to be investigated. Furthermore, the generalizability of these trial results to other populations (other than China) needs to be addressed. Real-world evidence of ivonescimab needs to be monitored to ascertain the HARMONi trial results.

Conclusion

PD-1/PD L1 interactions and VEGF are important targets in oncology therapeutics. Ivonescimab, which is a novel bispecific antibody, targets these in unison. The data which is currently available is very promising based on the current available evidence. Further follow-up on the clinical trials can shed more light on when to use it in clinical practice. Enrollment of Indian patients in clinical trials of ivonescimab is also strongly recommended.

Conflict of Interest
None declared.

References

1 Desai A, Reddy NK, Subbiah V. Top advances of the year: precision oncology. Cancer 2023;129(11):1634–1642
2 Dhillon S. Ivonescimab: first approval. Drugs 2024;84(09): 1135–1142
3 Zhong T, Huang Z, Pang X, et al. 1194 Mechanism of action of ivonescimab (AK112/SMT112): a first-in-class tetravalent Fc-silent bispecific antibody with dual blockade of PD-1 and VEGF that promotes cooperative biological effects. J Immunother Cancer 2023;11:x
4 Fang W, Zhao Y, Luo Y, et al; HARMONi-A Study Investigators. Ivonescimab plus chemotherapy in non-small cell lung cancer with EGFR variant: a randomized clinical trial. JAMA 2024;332 (07):561–570
5 Zhou C. Phase 3 study of ivonescimab (AK112) vs pembrolizumab as first-line treatment for PD-L1–positive advanced NSCLC: primary analysis of HARMONi-2. Paper presented at: World Conference on Lung Cancer, 2024; September 8, 2024; San Diego
6 Frentzas S, Austria Mislang AR, Lemech C, et al. Phase 1a dose escalation study of ivonescimab (AK112/SMT112), an anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors. J Immunother Cancer 2024;12(04):e008037
7 Zhao Y, Chen G, Chen J, et al. AK112, a novel PD-1/VEGF bispecific antibody, in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): an open-label, multicenter, phase II trial. EClinicalMedicine 2023;62:102106
8 Xiong A, Wang L, Chen J, et al. Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONi-2): a randomised, double-blind, phase 3 study in China. Lancet 2025; 405(10481):839–849
9 Ouyang Q, Wang X, Tian C, et al. The safety and efficacy of ivonescimab in combination with chemotherapy as first-line (1L) treatment for triple-negative breast cancer (TNBC). Ann Oncol 2024;35:S360–S361
10 Ivonescimab in combination with chemotherapy approved in China by NMPA for 2L+ EGFRm NSCLC based on HARMONi-A clinical trial: positive trend observed in overall survival towards ivonescimab plus chemotherapy; media release; PR Newswire. Published June 1, 2024. Accessed April 30, 2025 at: https://www.prnewswire.com/news-releases/ivonescimab-in-combination-with-chemotherapy-approved-in-china-by-nmpa-for-2l-egfrm-nsclc-based-on-harmoni-a-clinical-trial-positive-trend-observed-in-overall-survival-towards-ivonescimab-plus-chemotherapy-302161109.html

11 Ivonescimab receives NMPA approval for first-line treatment of PD-L1-positive NSCLC, based on breakthrough head to head phase III trial demonstrating superior efficacy over pembrolizumab. News release; PR Newswire. Published April 25, 2025. Accessed April 30, 2025 at: https://www.prnewswire.com/news-releases/ivonescimab-receives-nmpa-approval-for-first-line-treatment-of-pd-l1-positive-nsclc-based-on-breakthrough-head-to-head-phase-iii-trial-demonstrating-superior-efficacy-over-pembrolizumab-302438600.html

12 Oncology Drugs Fast-Tracked by the FDA in October 2024; media release, Oncology news central, Published November 1, 2024. Accessed April 30, 2025 at: https://www.oncologynewscentral.com/article/oncology-drugs-fast-tracked-by-the-fda-in-october-2024

