THE THERAPEUTIC POTENTIAL OF AMV564, A NOVEL BISPECIFIC BIVALENT (2 × 2) T-CELL ENGAGER, FOR THE TREATMENT OF CD30-EXPRESSING HEMATOLOGIC MALIGNANCIES
Tae H. Han¹, Jeannie Guenot², William S. Denney², Eric J. Feldman¹
¹Amphivena Therapeutics, South San Francisco, CA; ²Human Predictions, Cambridge, MA

ABSTRACT
Amphivena Therapeutics has discovered AMV564, a novel bispecific bivalent (2 × 2) T-cell engager targeting CD30, a co-stimulatory molecule expressed by several hematologic malignancies, including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL) and systemic anaplastic large cell lymphoma (sALCL). AMV564 engages and activates T-cells in both in vitro and in vivo models and is accompanied by rapid antitumor activity.

PHARMACOLOGY
In vivo Patient-tolerant Cytotoxicity
AMV564 has been evaluated in both healthy volunteers and patients with hematologic malignancies. AMV564 demonstrated potent in vivo antitumor activity with high levels of target engagement in patients with advanced hematologic malignancies treated with escalating doses of AMV564.

TRANSLATIONAL MEDICINE
Human Pharmacokinetic Prediction
AMV564 was designed and developed assuming that AMV564 disposition is similar to a protein-based macromolecule that is primarily eliminated by renal routes. A model for renal-based drug (RBD) AMV564 was used as a base model and described as a 3-compartment PK model with linear elimination. The clearance was increased to remove the effect of EEO (electrochemiluminescence) 0.3. A pharmacometric model of the T-cell engagement was also validated and predicted the concentration to achieve the IC50 was estimated to be 0.6 (RBD).

REFERENCES

ACKNOWLEDGMENTS
The authors acknowledge the support and contributions of Roland Walter, John DiPerna, Luis Gutierrez, Lilly Hsu, Jerry Sim, MAHFs, John Mould, PhD, and Marko Mihaljevic, MD, PhD. The authors also acknowledge the contributions of Stéphane Guesdon, Florian Ludwig, David Allen, and Steven Soriano.

C30 (Signs) is a clinically validating antigen target that is broadly expressed on the surface of malignant cells in both hematologic and solid malignant malignancies, as well as in cells that potentially support T-cell function, such as myeloid derived suppressor cells (MDSC).

AMV564 has been shown to eliminate MDSCs and restore hematopoietic, reduce potentiating polymorphonuclear cells in patient blotted and bone marrow samples, and produce robust antitumor activity when administered to patients.

In vitro studies, including co-cytotoxicity assays with C30 patient samples, human T-cell activation assays, and cytokine-release assays, as well as animal toxicity studies, were performed to characterize AMV564 activity.

AMV564 demonstrated potent in vitro antitumor activity with IC50 values of approximately 0.3 – 1 pM in patient samples. AMV564 was the first antibody to demonstrate that patients’ T-cells are more sensitive to T-cell engagement with AMV564 than similar bispecific monoclonal antibodies based on初步 enthusiasm.

In animal acute studies, AMV564 was tolerated at exposures that eliminated MDSCs in vivo, confirming the preclinical activity in both preclinical and clinical studies. Toxological findings noted in these studies were anticipated on the basis of the results in the pharmacodynamic studies and the human clinical trials.

A comprehensive set of preclinical data was evaluated for the evaluation of a T-cell engagement assay. The activity of AMV564 was assessed in human hematologic malignancy cell lines and primary patient samples. The mechanism of action was confirmed by clonal analysis and in vivo tumor growth. The activity of AMV564 was considered to be a direct cytotoxicity delivered to the tumor cells.

Clinical Trials/Efficacy for Predictive Antibody Activity
4. The human pharmacodynamic prediction was integrated with a pharmacokinetic model that describes the pharmacokinetics and pharmacodynamics of AMV564 exposure. A multiparametric model that assesses the relationship between the concentration of AMV564 and clinical outcomes was developed and validated. The results were used to guide the clinical trial design.

In the clinical trial, 116 patients were enrolled with a median age of 48 years (range 18–79), 60% were female, and 80% were Caucasian. The most common baseline disease was HL, with 55% of patients having HL.

In the ITT (intention-to-treat) population, 116 patients were evaluable for clinical activity. The clinical activity observed in the ITT population included both responses and stable disease.

The primary endpoint was the percentage of patients achieving responses in the clinical activity endpoint. In the ITT population, 116 patients were evaluable for clinical activity. The clinical activity observed in the ITT population included both responses and stable disease.

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The response rate was similar across a variety of subgroups, including age, gender, race, and baseline disease. The clinical activity observed in the ITT population included both responses and stable disease.

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In conclusion, AMV564 is a well tolerated bispecific (2 × 2) T-cell engager that targets CD30, a co-stimulatory molecule expressed by several hematologic malignancies, including HL, ALC, and sALCL. AMV564 demonstrates potent in vivo antitumor activity with high levels of target engagement in patients with advanced hematologic malignancies treated with escalating doses of AMV564. AMV564 is a potent, selective, and safe agent that has the potential to be a new therapeutic option for patients with hematologic malignancies.