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REPOLARIZATION OF T CELLS BY AMV564 IN PATIENTS PROGRESSING ON CHECKPOINT BLOCKADE

Victoria Smith*, Sterling Eckard, Bianca Rojo, Patrick Chun. *Amphivena Therapeutics, Inc., South San Francisco, CA, USA*

Background MDSC produce numerous immune-suppressive factors and are associated with poor outcomes across different cancers. They are frequently elevated in patients experiencing inadequate benefit from checkpoint blockade and there is a crucial need for therapies for this patient population. MDSC are recruited from bone marrow in response to both tumor signaling and T cell activation, and their accumulation in tumors and lymphatics can limit the potential benefits of immunostimulatory therapies. AMV564 is a bivalent T cell engager that selectively depletes MDSC. In a phase 1 study, pharmacodynamic analyses revealed significant depletion of MDSC, T cell activation, expansion of the T cell repertoire and an IFN-gamma-dominant cytokine profile with comparatively limited IL6 induction.¹ Monotherapy activity including a confirmed RECIST complete response was observed. The clinical and pharmacodynamic profiles of AMV564 are being further evaluated in specific patient cohorts, including patients progressing on checkpoint blockade.

M-MDSC after T Cell Activation

Abstract 887 Figure 1

Significantly higher induction of M-MDSC is apparent in patients previously receiving checkpoint blockade (CPB) after T cell activation by AMV564.

Abstract 887 Figure 2

Treatment with AMV564 promotes increases in effector CD8 and CD4 T cells in patients previously treated with CPB (examples shown are Merkel cell carcinoma (MCC) and head and neck squamous cell carcinoma (HNSCC)).

Abstract 887 Figure 3

Th-1 like repolarization of Treg is apparent in patients previously treated with CPB (MCC, HNSCC examples) after treatment with AMV564 (a). Example CD25 low and T-Bet high cells in HNSCC patient (arrow, b).

Methods In a phase 1b expansion study (NCT04128423), patient cohorts with cancers more likely to include actionable tumor antigens were selected for treatment with AMV564, with most patients representing checkpoint treatment failures. An additional cohort of patients included heterogeneous tumor types stratified by tumor mutation burden (TMB) score from circulating tumor DNA. Pharmacodynamic analyses including direct immunophenotyping (flow cytometry) of T and myeloid cell compartments in peripheral blood were performed on patients treated with AMV564 (15 µg daily for 10 of 21 days by subcutaneous injection).

Results Changes in myeloid and T cell profiles consistent with the pharmacodynamic signature of AMV564 were observed in patients receiving AMV564 despite one or more prior lines of checkpoint blockade therapy. Notably, both high baseline MDSC and elevated induction of MDSC after T cell activation were apparent (figure 1). Control of MDSC by AMV564 was associated with increases in both effector CD8 and CD4 T cells (figure 2). Extremely elevated levels of regulatory T cells were often observed: after treatment with AMV564, a Th-1-like repolarization of these cells was apparent, often associated with reduction in CD25 (figure 3).

Conclusions Treatment with AMV564 yielded substantial reductions in MDSC and favorable polarization of CD8 and

CD4 T cells, including Th1-like polarization of Treg. This signature was apparent in patients previously treated with checkpoint inhibitors, despite strong induction of MDSC in response to T cell activation, and high baseline levels (>20%) of Treg.

Trial Registration NCT04128423

REFERENCES

1. Smith V, Eckard S, Rettig MP, *et al.* AMV564, a bivalent, bispecific T-cell engager, depletes myeloid derived suppressor cells and activates T cells in cancer patients. *Cancer Res* 2020;**80**(16 Supplement):5699.

Ethics Approval This study was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each participating institution (including Ohio State University, MD Anderson Cancer Center, Duke University, University of California Los Angeles, Advent Health, Christ Hospital). All participants gave informed consent for samples used to generate pharmacodynamic data. No sensitive or identifiable information is included.

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