Phase I Dose-finding Study of MIW815 (ADU-S100), an Intratumoral STING Agonist, in Patients With Advanced Solid Tumors or Lymphomas

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Introduction

The ST-Ignitor of Nonspecific Genes (STING) pathway plays a crucial role in the innate immune response to immunogenic tumors.

- Activation of the STING pathway increases interferon (IFN)-β production and induces the recruitment and priming of plasmacytoid dendritic cells (pDCs) to produce IFN-β.
- MIW815 (ADU-S100) is a novel synthetic cyclic dinucleotide that activates the STING pathway.

Methods

Study design

- Thia-igor, multicenter, open-label, 1:1-humain Phase I trial of MIW815 (ADU-S100) in patients with advanced solid tumors and lymphoma in dose escalation.
- MIW815 (ADU-S100) treatment: weekly intratumoral injections of 50–3200 µg MIW815 (ADU-S100; 3-weeks-on/1-week-off).

Patient population

- Key inclusion criteria:
  - Adult patients with advanced solid tumors or lymphomas who have progressed, despite standard therapy, or in whom standard therapy is not an option or is not effective.

- Key exclusion criteria:
  - Symptomatic central nervous system (CNS) metastases or CNS resection requiring local CNS-directed therapy.

Assessments

- Adverse events (AEs) were assessed via a diary visit according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- Tumor response was determined locally, according to RECIST v1.1, and in a central review of tumors in 2016: Stage I/II (1/100), stage III/IV (1/20), and stage IV (100).

Results

Patient characteristics and disposition

- Of the 41 patients who received MIW815 (ADU-S100) at 65% of patients were continuing treatment. Treatment was discontinued in 37% (20/65) of patients due to disease progression, 25% (16/65) patient decision, 9% (6/65) death, and 7% (5/65) adverse event.

Safety and tolerability

- AEs were observed in 100% of patients (n=41).

- The most common AEs were injection site reactions (88%), fatigue (61%), and cytokine release syndrome (27%).

- No patients experienced grade 5 AEs.

- Three patients experienced grade 5 AEs: one patient died due to immune-related adrenocortical crisis, one patient had respiratory failure due to respiratory insufficiency, and one patient had multiorgan failure due to respiratory insufficiency.

Pharmacokinetics

- The apparent clearance of MIW815 (ADU-S100) from systemic circulation was rapid, with a mean plasma clearance of 7.92 L/h.

- MIW815 (ADU-S100) binding to the STING receptor resulted in a >2-fold increase in expression of the PD-L1 programmed death ligand (PD-L1), CD80, and PD-L1, and the nuclear factor (NF)-κB gene set in the treated lesion.

- An increase in CD8-positive tumor-infiltrating lymphocytes (TILs) and PD-L1 staining on pre-treatment immunohistochemistry (IHC) was observed.

Conclusions

- MIW815 (ADU-S100) is well tolerated and is active in patients with advanced solid tumors and lymphomas.

- Further research is needed to determine the optimal dose and regimen for clinical trials.