P10763

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 STimulator of INterferon 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 cluster of differentiation 8 (CD8)-positive T cells against tumor antigens.[1]

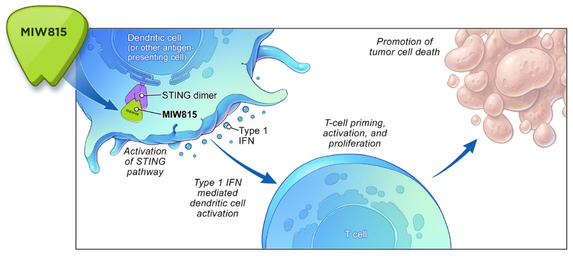
MIW815 (ADU-S100) is a novel synthetic cyclic dinucleotide that activates the STING pathway *in vitro* (**Figure 1**).[2]

In preclinical tumor mouse models, intratumoral injection of MIW815 (ADU-S100) resulted in tumor regression in both injected and non-injected lesions.[3]

This first-in-human Phase I study was designed to evaluate the safety and efficacy of MIW815 (ADU-S100) in patients with advanced solid tumors or lymphomas.

- In addition, MIW815 (ADU-S100) is currently being investigated in combination with anti-programmed cell death protein 1 (PD-1; NCT03172936) or anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4; NCT02675439) antibodies in Phase I clinical trials in patients with advanced solid tumors and lymphomas.

Figure 1. MIW815 (ADU-S100) Mechanism of Action



IFN, interferon; STING, stimulator of interferon genes.

Methods

Study design

This is a multicenter, open-label, first-in-human, Phase I study of MIW815 (ADU-S100) in patients with advanced solid tumors or lymphomas currently in dose escalation (**Figure 2**; NCT02675439; EudraCT 2015-005245-31).

Primary objectives

- Safety and tolerability of MIW815 (ADU-S100).
- Recommended dose for future studies.

Secondary objectives

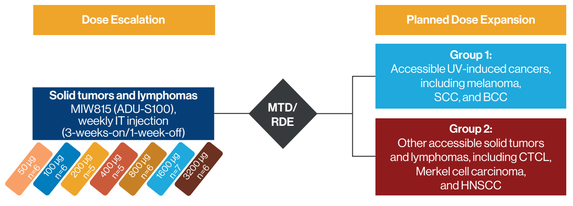
- Preliminary antitumor activity of MIW815 (ADU-S100).
- Pharmacokinetics (PK) and pharmacodynamics (PD) of MIW815 (ADU-S100).

Exploratory objective

- Biomarkers of response to MIW815 (ADU-S100).

Patients are treated with weekly intratumoral injections of MIW815 (ADU-S100; 50–3200 µg) on a 3-weeks-on/1-week-off schedule until they experience unacceptable toxicity, disease progression per immune-related response criteria (irRC) for solid tumors, or confirmed progressive disease in lymphoma, and/or patient/investigator decision.

Figure 2. MIW815X2101 Study Design



BCC, basal cell carcinoma; CTCL, cutaneous T-cell lymphoma; HNSCC, head and neck squamous cell carcinoma; IT, intratumoral; MTD, maximum tolerated dose; RDE, recommended dose for expansion; SCC, squamous cell carcinoma; UV, ultraviolet.

Patient population

Key inclusion criteria

Adult patients with advanced/metastatic solid tumors or lymphomas who have progressed despite standard therapy, are intolerant to standard therapy, or for whom standard therapy is not reasonably effective or does not exist.

Measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or Cheson 2014 criteria.[4]

- At least two distinct lesions are required; both accessible for baseline and on-treatment biopsies, with patient consent.
- Lesion 1 must measure ≥10 to <100 mm in longest diameter, and be accessible for repeated intratumoral injection.

Eastern Cooperative Oncology Group performance status of ≤1.

Prior immunotherapy is permitted.

Key exclusion criteria

Symptomatic central nervous system (CNS) metastases or CNS metastases requiring local CNS-directed therapy.

Systemic anticancer therapy within 4 weeks of the first dose of study treatment.

Treatment with systemic steroid therapy, other than replacement-dose steroids in the setting of adrenal insufficiency.

Systemic treatment with any immunosuppressive medication.

History of, or active, autoimmune disease with the exception of vitiligo or resolved childhood asthma/atopy.

Assessments

Adverse events (AEs) were assessed at every visit according to the Common Terminology Criteria for Adverse Events v4.03.

Tumor response was determined locally according to irRC, RECIST v1.1, and Cheson 2014 criteria[4] for lymphoma, at screening and on Day (D) 1 of Cycle (C) 3, every 8 weeks up to C11, and then every 12 weeks until disease progression or patient withdrawal.

Blood samples were collected for PK analysis on C1D1, C1D15, and C3D1, and for PD assessment of cytokine levels on C1D1, C1D8, C1D15, and C3D1.

Results

Patient characteristics and disposition

As of August 16, 2018, 41 patients received MIW815 (ADU-S100) and 4 (9.8%) patients were continuing on treatment. Treatment was discontinued in 37 (90.2%) patients due to disease progression (n=29; 70.7%), physician decision (n=4; 9.8%), patient decision (n=3; 7.3%), and death (n=1; 2.4%).

Baseline patient demographics are shown in **Table 1**. The number of patients treated at each MIW815 (ADU-S100) dose level is shown in **Figure 2**.

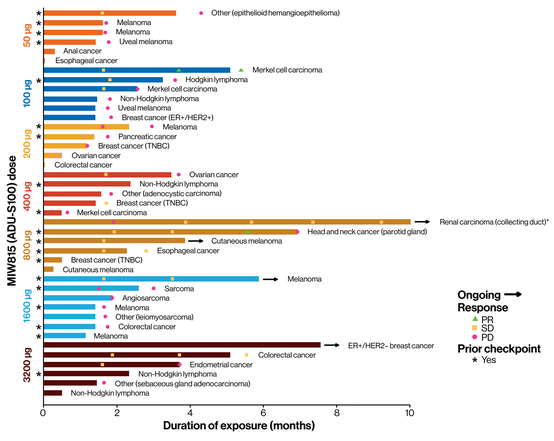
A summary of the time on MIW815 (ADU-S100) treatment and patient response is shown in **Figure 3**.

Table 1. Baseline Patient Demographics

Characteristic	All Patients (N=41)
Median age, years (range)	62 (26–80)
Sex, n (%)	
Male	18 (43.9)
Female	23 (56.1)
Race, n (%)	
Caucasian	27 (65.9)
Black	6 (14.6)
Asian	2 (4.9)
Other/unknown	6 (14.6)
ECOG PS, n (%)	
0	11 (26.8)
1	30 (73.2)
Prior therapy with a checkpoint inhibitor, n (%)	
Yes	22 (53.7)
No	19 (46.3)
Number of prior regimens, n (%)	
0	3 (7.3)
1	4 (9.8)
≥2	34 (82.9)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Figure 3. Time on MIW815 (ADU-S100) Treatment and Response Evaluation



Data cut-off: August 16, 2018.
*Patient ongoing treatment at 14 months.
ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; HER2+, HER2-positive; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Safety and tolerability

AEs suspected to be related to MIW815 (ADU-S100) treatment were reported in 78.0% of patients; 12.2% of patients experienced Grade 3/4 AEs.

- The most common suspected related AEs (in ≥10% of all patients) were headache, injection site pain, and pyrexia (in 14.6% of patients each).
- Elevated lipase was the only Grade 3/4 suspected related AE reported in >1 patient (n=2; 4.9%).

Treatment-emergent serious AEs were reported in 1 patient (Grade 3 dyspnea and Grade 4 respiratory failure; dose level: 1600 µg); this was related to underlying disease progression.

There were no dose-limiting toxicities (DLTs) observed during the first cycle of treatment and no patients discontinued treatment due to an AE.

Pharmacokinetics

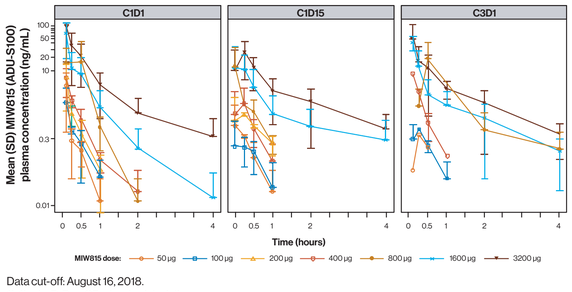
The mean plasma concentration–time profiles for MIW815 (ADU-S100) on C1D1, C1D15, and C3D1 are shown in **Figure 4**.

MIW815 (ADU-S100) absorption from the intratumoral injection site was rapid, reaching maximal plasma concentration within minutes of dosing.

MIW815 (ADU-S100) exposure generally increased in a dose-dependent manner.

The apparent clearance of the MIW815 (ADU-S100) from systemic circulation was rapid with an observed terminal half-life of approximately 10–23 minutes.

Figure 4. Concentration–Time Profiles for MIW815 (ADU-S100) on C1D1, C1D15, and C3D1



Data cut-off: August 16, 2018.
C, Cycle; D, Day; SD, standard deviation.

Patient vignette – Case example 1

Patient and disease characteristics

63-year-old male with Stage IV collecting duct carcinoma with metastases to the left supraclavicular lymph node (LN) and left neck.

Treatment history: antineoplastic therapy with an investigational mouse double minute 2 homolog (MDM2) inhibitor and prior right radical nephrectomy and retroperitoneal LN dissection.

Experience on study

Treatment: weekly intratumoral injections of 800 µg MIW815 (ADU-S100; 3-weeks-on/1-week-off).

Reported toxicities: Grade 1 headache, nausea, and hyperthyroidism/Graves' disease.

Best overall response (BOR): stable disease (SD); patient remains on study at C14.

On-study pharmacodynamics

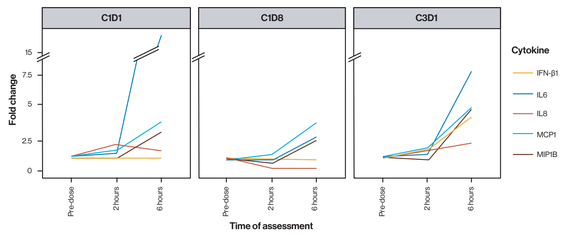
Increases in systemic cytokine levels, including interleukin 6 (IL6), were observed following MIW815 (ADU-S100) injection on C1D1, C1D8, and C3D1 (**Figure 5A**).

Treatment with MIW815 (ADU-S100) resulted in a >2-fold increase in expression of the *IFN-γ*, programmed death-ligand 1 (*PD-L1*), and *CD8A* genes, and the natural killer (NK) cell gene set in the injected lesion (**Figure 5B**).

An increase in CD8-positive tumor-infiltrating lymphocytes (TILs) and PD-L1 stromal staining was observed in the injected lesion following MIW815 (ADU-S100) treatment (**Figure 5C**).

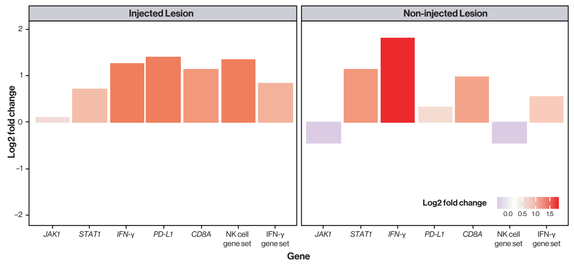
Figure 5. Case Example 1: Pre- and Post-MIW815 (ADU-S100) Therapy Cytokine Levels, RNA, and IHC in a Patient With Collecting Duct Carcinoma

A. Fold Change in Systemic Cytokine Levels on C1D1, C1D8, and C3D1



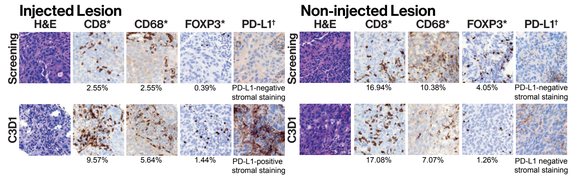
C, Cycle; D, Day; IFN, interferon; IHC, immunohistochemistry; IL6, interleukin 6; IL8, interleukin 8; MCP1, monocyte chemoattractant protein 1; MIP1B, macrophage inflammatory protein 1 beta.

B. Fold Change in Intratumoral RNA Expression in the Injected and Non-injected Lesion From Screening to C3D1 (Pre-dose)



*NK cell gene set includes: *IL12A, IL12B, KIR3DL1, KIR3DL2, KIR3DL3, KLRB1, KLRC1, KLRC2, KLRD1, KLRF1, KLRG1, KLRK1*, and *NCR1*; †IFN-γ gene set includes: *TBK1, IRF3, IFNAR1, JAK1, JAK2, TYK2, STAT1, STAT2, STAT3, IFNG, IFNGR1, IDO1, IL15RAm CXCL9, CXCL10, CXCL11*, and *CD274*.
C, Cycle; *CD8A*, cluster of differentiation 8A; D, Day; IFN, interferon; *JAK1*, Janus kinase 1; NK, natural killer; *PD-L1*, programmed death-ligand 1; *STAT1*, signal transducer and activator of transcription 1.

C. IHC Micrographs of the MIW815 (ADU-S100) Injected and Non-injected Lesion at Screening and C3D1 (Pre-dose)



*Biomarker area % per image analysis; †Tumor positive score % per pathologist analysis; PD-L1 measured using the IHC 22C3 pharmDx assay.
C, Cycle; CD, cluster of differentiation; D, Day; FOXP3, forkhead box P3; H&E, hematoxylin and eosin; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

Patient vignette – Case example 2

Patient and disease characteristics

68-year-old male with esophageal cancer and metastases to the mediastinal LN, supraclavicular LN, and adrenal gland.

Treatment history: neoadjuvant paclitaxel, carboplatin, and radiation therapy followed by tumor resection, adjuvant 5-fluorouracil and oxaliplatin chemotherapy, and for metastatic disease cisplatin/irinotecan, nivolumab, and investigational anti-matrix metallopeptidase-9 antibody therapy.

Experience on study

Treatment: weekly intratumoral injections of 800 µg MIW815 (ADU-S100; 3-weeks-on/1-week-off).

Reported toxicities: Grade 1 injection site reaction and exertional dyspnea; patient also experienced an incarcerated bowel (unrelated to study drug).

BOR: SD for 3 cycles.

On-study pharmacodynamics

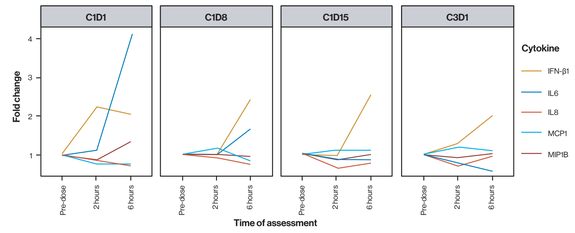
IFN-β1 levels increased following MIW815 (ADU-S100) injection on C1D1, C1D8, C1D15, and C3D1 (**Figure 6A**).

Expression of the T-cell differentiation antigen *CD8A* gene and the NK cell gene set were increased >2-fold in the injected lesion as a result of MIW815 (ADU-S100) treatment (**Figure 6B**).

Following MIW815 (ADU-S100) injection, an increase in the staining of CD8-positive TILs and PD-L1 stromal staining was observed in the injected lesion (**Figure 6C**).

Figure 6. Case Example 2: Pre- and Post-MIW815 (ADU-S100) Therapy Cytokine Levels, RNA, and IHC in a Patient With Esophageal Cancer

A. Fold Change in Systemic Cytokine Levels on C1D1, C1D8, C1D15, and C3D1



C, Cycle; D, Day; IFN, interferon; IHC, immunohistochemistry; IL6, interleukin 6; IL8, interleukin 8; MCP1, monocyte chemoattractant protein 1; MIP1B, macrophage inflammatory protein 1 beta.

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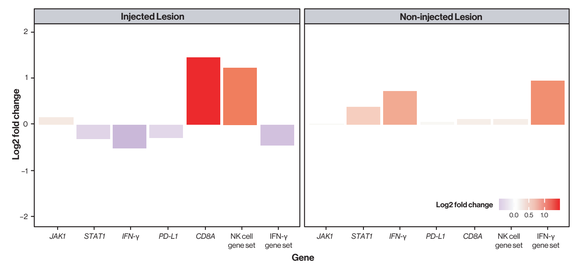
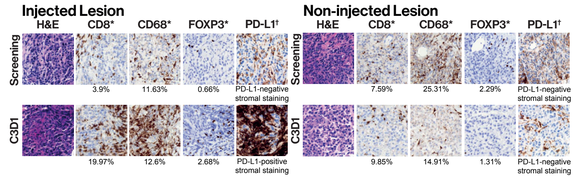


*NK cell gene set includes: *IL12A, IL12B, KIR3DL1, KIR3DL2, KIR3DL3, KLRB1, KLRC1, KLRC2, KLRD1, KLRF1, KLRG1, KLRK1*, and *NCR1*; †IFN-γ gene set includes: *TBK1, IRF3, IFNAR1, JAK1, JAK2, TYK2, STAT1, STAT2, STAT3, IFNG, IFNGR1, IDO1, IL15RAm CXCL9, CXCL10, CXCL11*, and *CD274*.
C, Cycle; *CD8A*, cluster of differentiation 8A; D, Day; IFN, interferon; *JAK1*, Janus kinase 1; NK, natural killer; *PD-L1*, programmed death-ligand 1; *STAT1*, signal transducer and activator of transcription 1.

C. IHC Micrographs of the MIW815 (ADU-S100) Injected and Non-injected Lesion at Screening and C3D1 (Pre-dose)



*Biomarker area % per image analysis; †Tumor positive score % per pathologist analysis; PD-L1 measured using the IHC 22C3 pharmDx assay.
C, Cycle; CD, cluster of differentiation; D, Day; FOXP3, forkhead box P3; H&E, hematoxylin and eosin; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

Conclusions

Single-agent MIW815 (ADU-S100) was well tolerated at doses ranging from 50 to 3200 µg in patients with advanced solid tumors and lymphoma with no DLTs noted. Dose escalation is ongoing.

Preliminary signs of MIW815 (ADU-S100) biological activity were observed in patients with advanced solid tumors and lymphoma, including those who had previously received treatment with a checkpoint inhibitor.

In the highlighted patient cases, the ability of MIW518 (ADU-S100) to activate the antitumor immune response is suggested by observed increases in CD8-positive TILs, genes involved in the antitumor immune response, and systemic cytokines following MIW815 (ADU-S100) injection.

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