Phase Ib study of MIW815 (ADU-S100) in combination with spartalizumab (PDR001) in patients with advanced/metastatic solid tumors or lymphomas (NCT03172936)

Funda Meric-Bernstam,1 Shahneen Sandhu,2 Omid Hamid,3 Anna Spreafico,4 Stefan Kasper,5 Reinhard Dummer,6 Toshio Shimizu,7 Neeltje Steeghs,8 Nancy Lewis,9 Craig Talluto,10 Sinead Dolan,10 Andrew Bean,9 Robert J. Brown,11 Damian Trujillo,11 Nitya Nair,11 Jason J. Luke12

1Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX; 2Peter MacCallum Cancer Centre, Melbourne, Australia; 3The Angeles Clinic and Research Institute, Los Angeles, CA; 4Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Department of Medical Oncology, West German Cancer Centre, University Hospital Essen, Essen, Germany; 6University of Zurich, Zurich, Switzerland; 7National Cancer Center Hospital, Tokyo, Japan; 8Netherlands Cancer Institute, Amsterdam, The Netherlands; 9Novartis Pharmaceuticals Corporation, East Hanover, NJ; 10Novartis Institutes for BioMedical Research, Cambridge, MA; 11Aduro Biotech Inc., Berkeley, CA; 12The University of Chicago Medicine, Chicago, IL
Stimulator of Interferon Genes (STING) pathway

- STING pathway senses intracellular DNA, triggering an immediate production of type I IFN\(^1\)
- STING activation has wide-ranging impact on both the innate and adaptive immune response by inducing APC recruitment and priming and CD8+ T cells against tumor antigens\(^2\)
- MIW815 (ADU-S100) is a synthetic cyclic dinucleotide (CDN), a first-in-class STING agonist\(^3\)
- In mouse models, intratumoral injection of single-agent MIW815 (ADU-S100) resulted in tumor regression in both injected and non-injected lesions\(^4\)

APC, antigen-presenting cell; IFN, interferon.
MIW815 (ADU-S100) demonstrates combination efficacy with PD-1 checkpoint inhibitors in mouse models

• Blockade of PD-1 may restore adaptive immunity through effector T-cell signaling, function, and proliferation¹,²

• Combining the modulation of the tumor microenvironment provided by STING activation with the increase in T-cell activity provided by PD-1 blockade¹–³ may further improve anti-tumor immunity

• Spartalizumab (PDR001) is an investigational monoclonal antibody that blocks the interaction between PD-1 and PD-L1/2⁵

Figure reproduced with permission from Sivick KE, et al. Cell Rep 2018;25:3074–3085.

*p < 0.05, **p < 0.01, ***p < 0.001.
Ph Ib MIW815 (ADU-S100) + spartalizumab in patients with advanced solid tumors or lymphomas

Key inclusion criteria:
- Ability to undergo tumor biopsies of injected and non-injected lesions
  - Injectable lesions are cutaneous, subcutaneous, or nodal
- Prior immunotherapy is permitted

Data cut-off: April 5, 2019
Primary objective: Safety and tolerability
Secondary objectives: Preliminary anti-tumor activity, PK, and PD

MIW815 (ADU-S100) dose
- 50 µg
- 100 µg
- 200 µg
- 400 µg
- 800 µg
- 1600 µg

Patient population was enriched for TNBC and melanoma indications by allowing backfill of lower dose cohorts

NCT03172936
IV, intravenous; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; RDE, recommended dose for expansion; TNBC, triple negative breast cancer.
## Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>61 (27–93)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (50.6)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (49.4)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (24.1)</td>
</tr>
<tr>
<td>1</td>
<td>63 (75.9)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>1</td>
<td>10 (12.0)</td>
</tr>
<tr>
<td>2</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>52 (62.7)</td>
</tr>
<tr>
<td><strong>Prior immunotherapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60 (72.3)</td>
</tr>
<tr>
<td>No</td>
<td>23 (27.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Primary diagnosis, n (%)</strong></th>
<th>All patients (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>35 (42.2)</td>
</tr>
<tr>
<td>TNBC</td>
<td>11 (13.3)</td>
</tr>
<tr>
<td>Breast cancer (not TNBC)</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>9 (10.8)</td>
</tr>
</tbody>
</table>

Data cut-off: April 5, 2019
ECOG PS, Eastern Cooperative Oncology Group performance status.
## Patient disposition

<table>
<thead>
<tr>
<th>Disposition, n (%)</th>
<th>MIW815 weekly (3-weeks-on/1-week-off) + spartalizumab monthly</th>
<th>MIW815 monthly + spartalizumab monthly</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>n = 53</td>
<td>n = 30</td>
<td>N = 83</td>
</tr>
<tr>
<td></td>
<td>16 (30.2)</td>
<td>6 (20.0)</td>
<td>22 (26.5)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>37 (69.8)</td>
<td>24 (80.0)</td>
<td>61 (73.5)</td>
</tr>
<tr>
<td>Primary reason for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>20 (37.7)</td>
<td>16 (53.3)</td>
<td>36 (43.4)</td>
</tr>
<tr>
<td>Physician decision*</td>
<td>12 (22.6)</td>
<td>4 (13.3)</td>
<td>16 (19.3)</td>
</tr>
<tr>
<td>Patient decision</td>
<td>3 (5.7)</td>
<td>3 (10.0)</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>AEs</td>
<td>1 (1.9)</td>
<td>1 (3.3)</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

Data cut-off: April 5, 2019

*For patients with progressive disease that was not confirmed by imaging, sites were asked to enter the reason for discontinuation as physician decision.
Safety of MIW815 (ADU-S100) + spartalizumab

Most common (≥5% of patients) treatment-related AEs of any grade

<table>
<thead>
<tr>
<th>AE</th>
<th>Patients (N = 83)</th>
<th>Any grade, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>48 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>11 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (6.0)</td>
<td></td>
</tr>
</tbody>
</table>

- No dose-limiting toxicities were reported in any of the dosing cohorts
- The AEs of the combination are no more frequent or severe than those reported in either single-agent trial

All treatment-related Grade 3/4 AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>Patients (N = 83)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Increased lipase</td>
<td>3 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>2 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Increased amylase</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Partial seizures</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Maculo-papular rash</td>
<td>1 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.


Data cut-off: April 5, 2019
Pharmacokinetics: Cohorts 50 to 800 µg

- Fast absorption of MIW815 (ADU-S100) to plasma was observed
  - Maximum concentration reached at the end of intratumoral injection
- MIW815 (ADU-S100) was eliminated quickly with short plasma half-life ranging from 8 to 28 min
- No accumulation was observed after multiple dosing at C1D15 and C3D1
- Plasma exposure increases dose-proportionally from 50 to 800 µg

Data cut-off: April 5, 2019

C, cycle; D, day.
Systemic IFN-β concentrations as PD biomarker

**Change in IFN-β at 6 hours post-treatment versus pre-dose**

- MIW815 + spartalizumab (3-weeks-on/1-week-off)
- Cycle 1 Day 1
- Cycle 1 Day 8
- Cycle 1 Day 15
- Cycle 3 Day 1

**PK/PD analysis of IFN-β concentration change from pre-dose by AUC<sub>last</sub>**

- MIW815 + spartalizumab (3-weeks-on/1-week-off)
- Cycle 1 Day 1
- Cycle 1 Day 8
- Cycle 1 Day 15
- Cycle 3 Day 1

- Systemic IFN-β levels appear to increase in a dose-dependent manner
- Trend observed between IFN-β levels and systemic exposure
- Other cytokines detected (IP-10, MCP-1, and IL-6) did not demonstrate significant dose dependency and/or PK/PD relationships

IFN-β conc change (pg/mL)

<table>
<thead>
<tr>
<th>MIW815 dose (+ spartalizumab)</th>
<th>50 ug</th>
<th>100 ug</th>
<th>200 ug</th>
<th>400 ug</th>
<th>800 ug</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIW815 + spartalizumab</td>
<td>0.1</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

AUC<sub>last</sub> (ng/mL*hr)

- Cycle 1 Day 1
- Cycle 1 Day 8
- Cycle 1 Day 15
- Cycle 3 Day 1

Data cut-off: April 25, 2019

AUC<sub>last</sub>, area under the concentration–time curve from time zero to time of last measurable concentration; IL-6, interleukin-6; IP-10, interferon gamma-induced protein 10; MCP-1, monocyte chemoattractant protein 1.
**Preliminary anti-tumor activity**

<table>
<thead>
<tr>
<th>MIW815 (ADU-S100)</th>
<th>Confirmed responses were achieved in five patients, one of which was a CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-weeks-on/1-week-off</td>
<td>• Three of these responses (including the CR) were observed in patients with IO-naive TNBC; these patients are continuing to receive treatment at time of data cut</td>
</tr>
<tr>
<td></td>
<td>• Two of these patients with TNBC expressed PD-L1 levels of &gt;1% at baseline (data from the third patient are not available)</td>
</tr>
<tr>
<td></td>
<td>• The two remaining responders had previously IO-treated melanoma (of 35 melanoma patients enrolled across the whole study, 7 not yet reimaged)</td>
</tr>
<tr>
<td></td>
<td>• An additional 12 patients achieved SD</td>
</tr>
<tr>
<td></td>
<td>• Tumor types: Sarcoma, melanoma, SCC skin, breast, lymphoma, and head and neck</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIW815 (ADU-S100)</th>
<th>No patients achieved a response; however, six patients achieved a SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>monthly</td>
<td>• Tumor types: Ovarian, breast, uveal melanoma, head and neck, and cutaneous melanoma</td>
</tr>
<tr>
<td></td>
<td>• Four of whom maintained SD for ≥6 months</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; SCC, squamous cell carcinoma.

Data cut-off: April 5, 2019
Response and duration of exposure
MIW815 weekly (3-weeks-on/1-week-off) + spartalizumab monthly

- The patient population was enriched for TNBC and melanoma indications by allowing backfill of lower-dose cohorts.

Data cut-off: April 5, 2019
CR, complete response; IO, immuno-oncology.
Response and duration of exposure
MIW815 monthly + spartalizumab monthly

Data cut-off: April 5, 2019

- **Response**
  - PR
  - SD
  - PD

- **Duration of exposure (months)**

- **Dose of MIW815 (+ spartalizumab)**
  - 50 μg
  - 100 μg
  - 200 μg
  - 400 μg
  - 800 μg
  - 1600 μg

- **Cancers**
  - Ovarian cancer
  - Head and neck cancer
  - Cutaneous melanoma
  - Melanoma
  - Other
  - Squamous cell carcinoma of skin
  - Uveal melanoma
  - Esophageal cancer
  - Breast cancer
  - Prostate cancer
  - Lymphoma
  - - Non-Hodgkin’s disease
  - - Hodgkin’s disease
  - Colorectal cancer
  - Head and neck cancer
  - Merkel cell carcinoma
  - Other

- **Dose of MIW815 (+ spartalizumab)**
  - 50 μg
  - 100 μg
  - 200 μg
  - 400 μg
  - 800 μg
  - 1600 μg

- **Response**
  - PR
  - SD
  - PD

- **Ongoing**
  - Y

- **Prior IO**
  - ★
Percentage change from baseline
Sum of target lesion diameters (evaluable patients)

MIW815 weekly (3-weeks-on/1-week-off) + spartalizumab

- Ongoing
- Response:
  - CR
  - PR
  - SD
  - PD

MIW815 Dose Level (μg):
- 50
- 100
- 200
- 400
- 800
- 1600

MIW815 monthly + spartalizumab

Data cut-off: April 5, 2019
CD8 IHC increased in responding patients with high PD-L1 at baseline

- Two patients demonstrating best response (PR) had high levels of PD-L1* staining in their injected lesions at screening

*Tumor samples were stained using the PD-L1 IHC 22C3 pharmDx assay on the Dako autostainer and given a tumor positivity score by a pathologist.

IHC, immunohistochemistry; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; UNK, unknown.

Data cut-off: April 25, 2019
Response and duration of exposure in patients with TNBC

- Three patients had durable PR/CR, five patients had radiographic or clinical PD, one patient had pneumonitis, and the two remaining patients are too early for assessment

*Tumor samples were stained using the PD-L1 IHC 22C3 pharmDx assay on the Dako autostainer and given a tumor positivity score by a pathologist; †3-weeks-on/1-week-off. NA, data not available.

Data cut-off: April 5, 2019
Patient vignette

• 64-year-old post-menopausal female diagnosed with stage I TNBC, now with metastases to the brain, axilla, lung, skin, and thigh

• Prior therapy:
  • S/P surgical resection and adjuvant cyclophosphamide, doxorubicin, 5-fluorouracil and paclitaxel, radiotherapy
  • S/P eribulin for metastatic disease
  • S/P radiotherapy to brain

• Remains on study 18+ months

• Developed hyperthyroidism on study

S/P, status post.
IHC of injected lesion, Sub-Q tissue - PR

Screening: Large numbers of macrophages throughout tumor nest
Both macrophages and tumor cells appear positive for PD-L1
On treatment: Tumor cells limited to areas of non-viable tissue and debris

* % biomarker area (image analysis).
** % tumor-positive score (pathologist scored).
Imaging

Baseline

4.4 x 4.3 cm

Cycle 4
Day 22

3.6 x 2.6 cm

1.8 x 1.8 cm

0.0 cm

0.0 cm

0.5 x 0.3 cm

Baseline

4.4 x 4.3 cm

Cycle 4
Day 22

3.6 x 2.6 cm

1.8 x 1.8 cm

0.0 cm

0.0 cm

0.5 x 0.3 cm
Conclusions

• MIW815 (ADU-S100) + spartalizumab was generally well tolerated in patients with solid tumors or lymphomas, with no dose-limiting toxicities reported as of the data cut-off

• The MTD has not been reached and dose-escalation is ongoing

• MIW815 plasma exposure increases dose-proportionally

• IFN-β concentrations appeared to increase with increasing exposure to MIW815 (ADU-S100)

• The combination has demonstrated anti-tumor activity in PD-1–naive TNBC and PD-1–relapsed/refractory melanoma
Acknowledgments

Study sites
- MD Anderson Cancer Center
- Peter MacCallum Cancer Centre
- Angeles Clinic and Research Institute
- Princess Margaret Cancer Centre
- University of Chicago Cancer Center
- National Cancer Center Hospital Japan
- Hospital Kliniken Essen-Mitte
- Netherlands Cancer Institute
- Melanoma Institute of Australia
- Comprehensive Cancer Center Zürich
- Institut Català d’Oncologia

Aduro
- Andrea van Elsa
- Sarah McWhirter
- Thomas Mueller
- Anthony Desbien
- Leticia Corrales

Novartis
- Jose Carlos Torres
- Saero Park
- Xinhui Heller Chen
- Marc Pelletier
- Helen Oakman
- Fang Xiang
- Jincheng Wu

- The authors would like to thank the patients who participated in the trial, and their families/caregivers
- This study was funded by Novartis Pharmaceuticals Corporation and Aduro Biotech
- Editorial assistance was provided by Zoe Crossman, PhD of ArticulateScience Ltd. and was funded by Novartis Pharmaceuticals Corporation and Aduro Biotech