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

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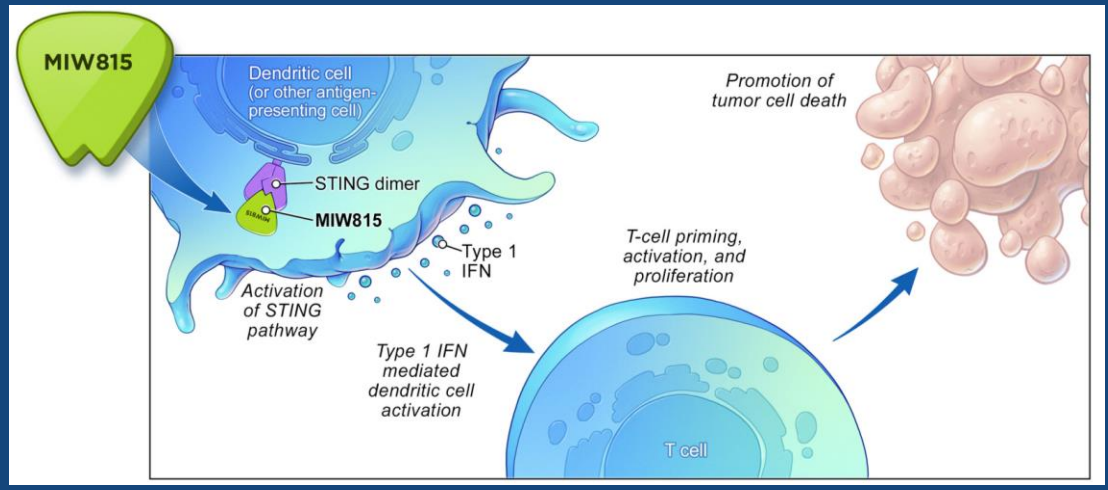
Stimulator of Interferon Genes (STING) pathway

- 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]

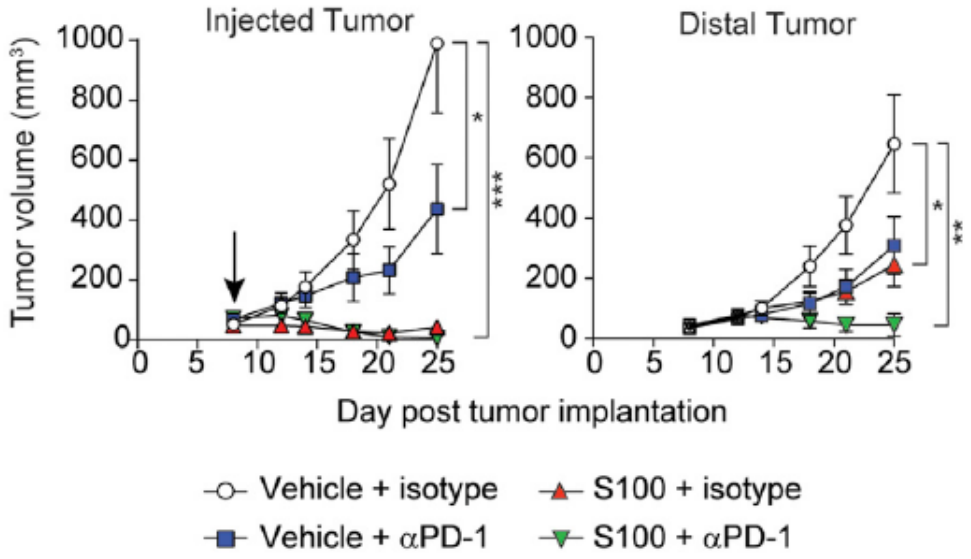


APC, antigen-presenting cell; IFN, interferon.

1. Ishikawa H, Barber GN. *Nature* 2008;55:674–678; 2. Woo SR, et al. *Immunity* 2014;41:830–842; 3. Glickman LH, et al. *Cancer Res* 2016;76(14 Suppl):abst 1445;
4. Corrales L, et al. *Cell Rep* 2015;11:1018–1030.

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 proliferation[1,2]
- Combining the modulation of the tumor microenvironment provided by STING activation with the increase in T-cell activity provided by PD-1 blockade[1–3] may further improve anti-tumor immunity
- Spartalizumab (PDR001) is an investigational monoclonal antibody that blocks the interaction between PD-1 and PD-L1/2[5]



- Combining MIW815 (ADU-S100) with systemic anti-PD-1 elicited near complete clearance of injected and non-injected tumors in mice[3,4]

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

*p < 0.05, **p < 0.01, ***p < 0.001.

1. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264; 2. Keir ME, et al. *Annu Rev Immunol* 2008;26:677–704; 3. Sivick KE, et al. *Cell Rep* 2018;25:3074–3085;
4. Sivick KE, et al. SITC 2018. Poster presentation:abstract P351; 5. Wirth L, et al. ASCO 2018. Poster presentation; abstract 6024.

Ph Ib MIW815 (ADU-S100) + spartalizumab in patients with advanced solid tumors or lymphomas

Dose Escalation
Solid tumors and lymphomas
Parallel non-randomized assignment

MIW815 (ADU-S100)
(intratumoral injection)
Weekly (3-weeks-on/1-week-off)
+ spartalizumab (400 mg IV) monthly

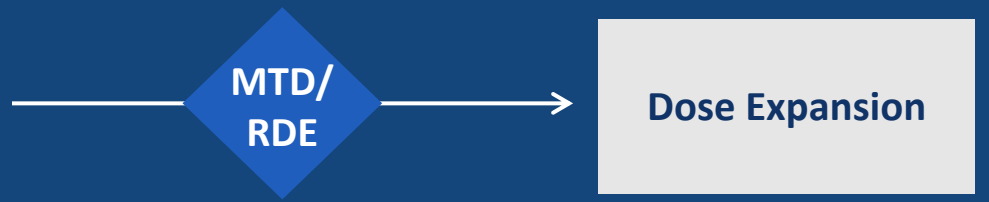
MIW815 (ADU-S100)
(intratumoral injection) Monthly
+ spartalizumab (400 mg IV) monthly

MIW815 (ADU-S100) dose

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

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

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

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

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

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

Patient disposition

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

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

AE	Patients (N = 83)
	Any grade, n (%)
Total	48 (57.8)
Injection site pain	11 (13.3)
Pyrexia	10 (12.0)
Diarrhea	8 (9.6)
Rash	5 (6.0)

- 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[1,2]

All treatment-related Grade 3/4 AEs

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

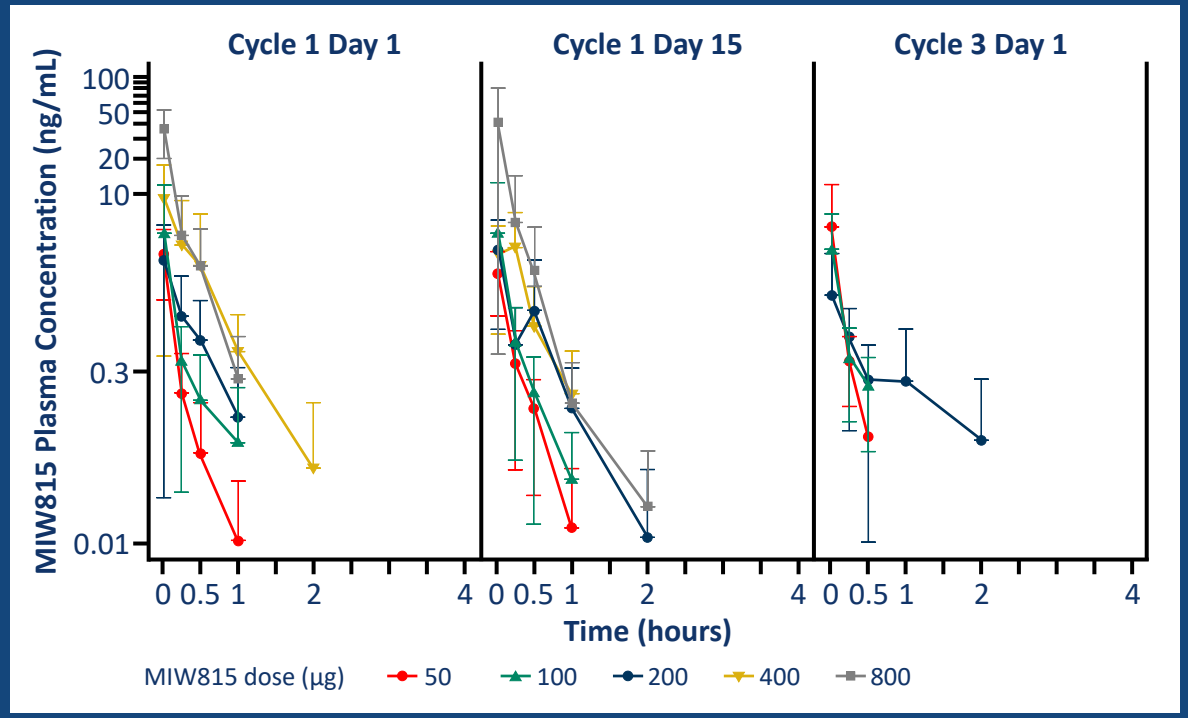
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

1. Meric-Bernstam F, et al. SITC 2018 poster presentation: abstract P309; 2. Naing A, et al. ASCO 2016 poster presentation: abstract 3060.

Data cut-off: April 5, 2019

Pharmacokinetics: Cohorts 50 to 800 µg

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



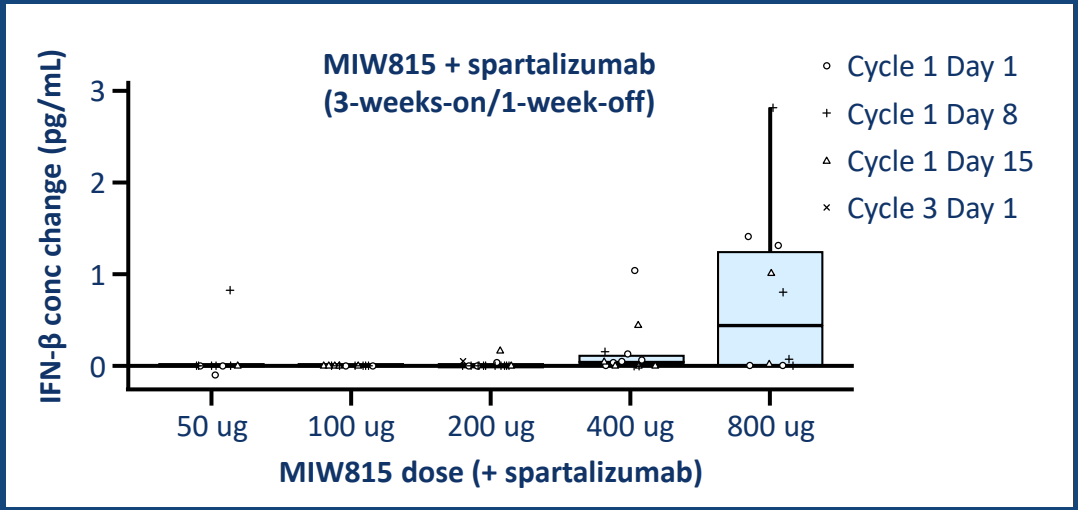
Data cut-off: April 5, 2019

C, cycle; D, day.

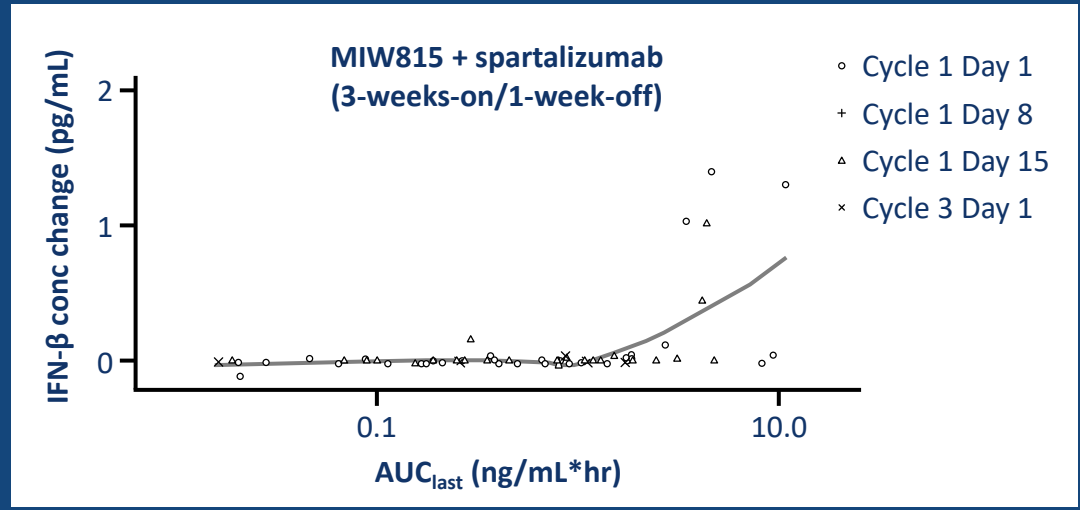
- Fast absorption of MIW815 (ADU-S100) to plasma was observed
  - Maximum concentration reached at the end of intratumoral injection
- MIW815 (ADU-S100) was eliminated quickly with short plasma half-life ranging from 8 to 28 min
- No accumulation was observed after multiple dosing at C1D15 and C3D1
-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

Systemic IFN-β concentrations as PD biomarker

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



PK/PD analysis of IFN-β concentration change from pre-dose by AUC_{last}



- 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

Data cut-off: April 25, 2019

AUClast, 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

MIW815 (ADU-S100) 3-weeks-on/1-week-off

Confirmed responses were achieved in five patients, one of which was a CR

- 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
  - Two of these patients with TNBC expressed PD-L1 levels of >1% at baseline (data from the third patient are not available)
- The two remaining responders had previously IO-treated melanoma (of 35 melanoma patients enrolled across the whole study, 7 not yet reimaged)
- An additional 12 patients achieved SD
  - Tumor types: Sarcoma, melanoma, SCC skin, breast, lymphoma, and head and neck

MIW815 (ADU-S100) monthly

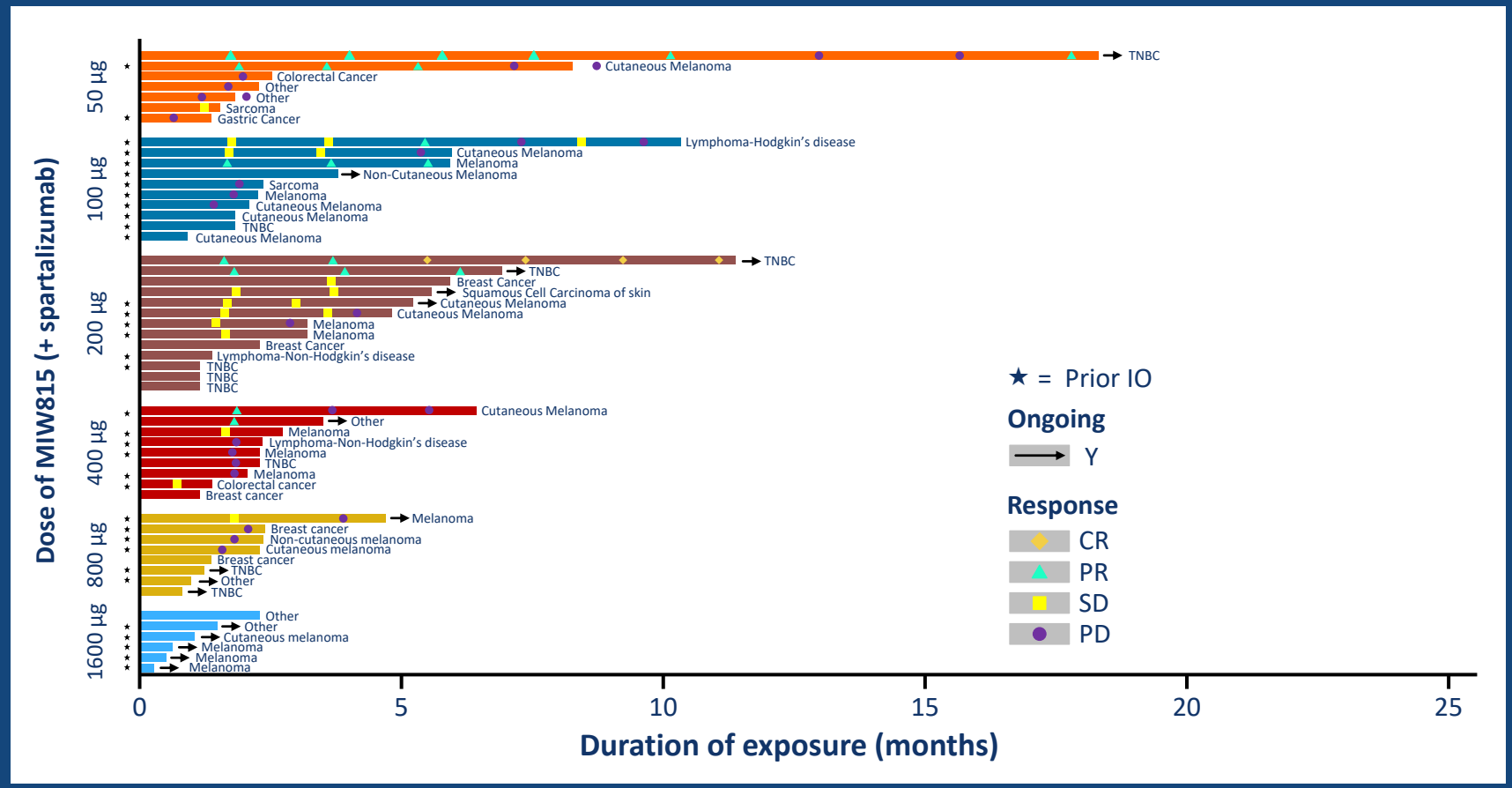
No patients achieved a response; however, six patients achieved a SD

- Tumor types: Ovarian, breast, uveal melanoma, head and neck, and cutaneous melanoma
- Four of whom maintained SD for ≥6 months

CRC, colorectal cancer; SCC, squamous cell carcinoma.

Data cut-off: April 5, 2019

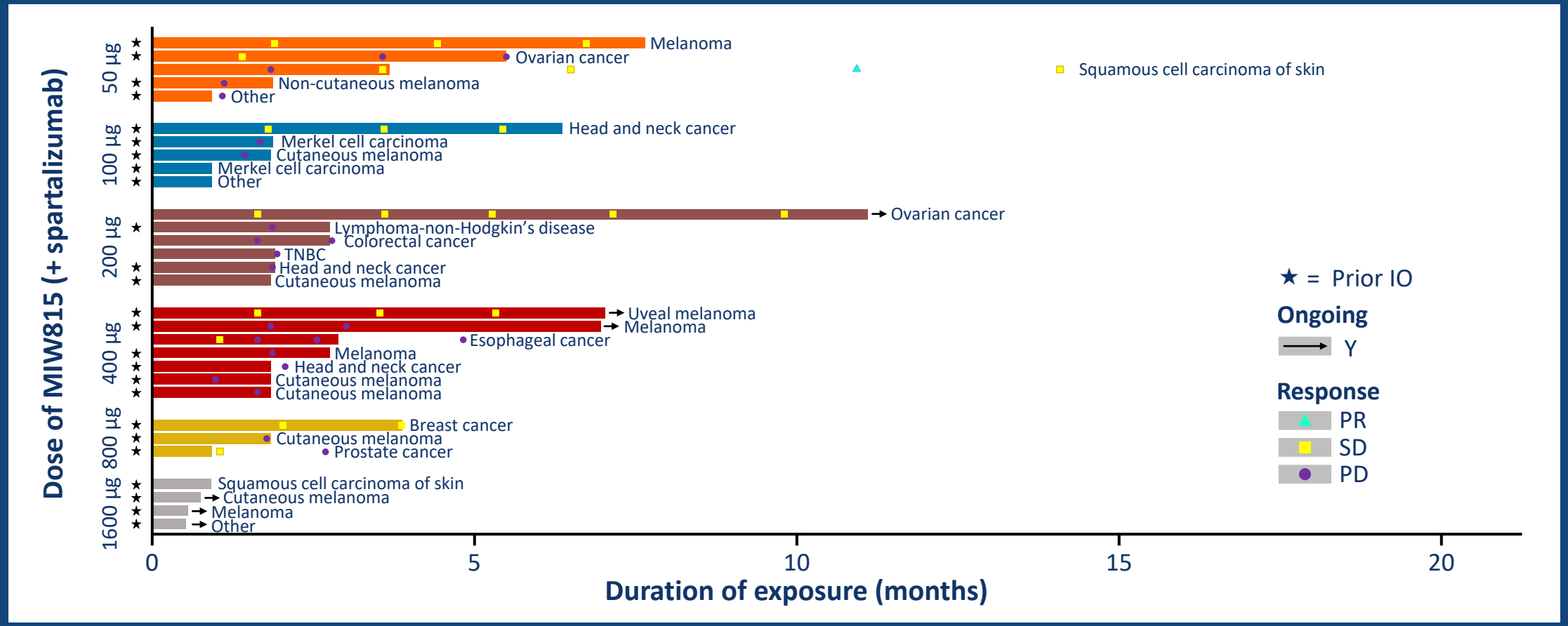
Response and duration of exposure MIW815 weekly (3-weeks-on/1-week-off) + spartalizumab monthly



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

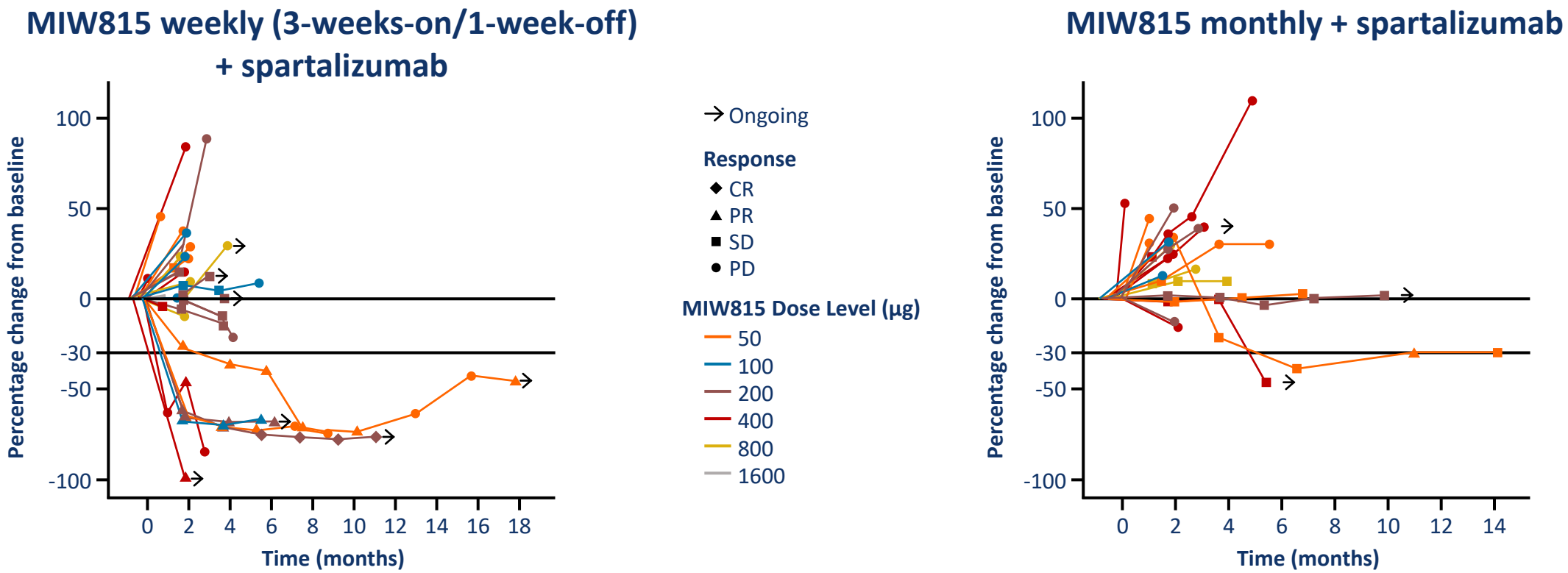
Data cut-off: April 5, 2019
CR, complete response; IO, immuno-oncology.

Response and duration of exposure
MIW815 monthly + spartalizumab monthly



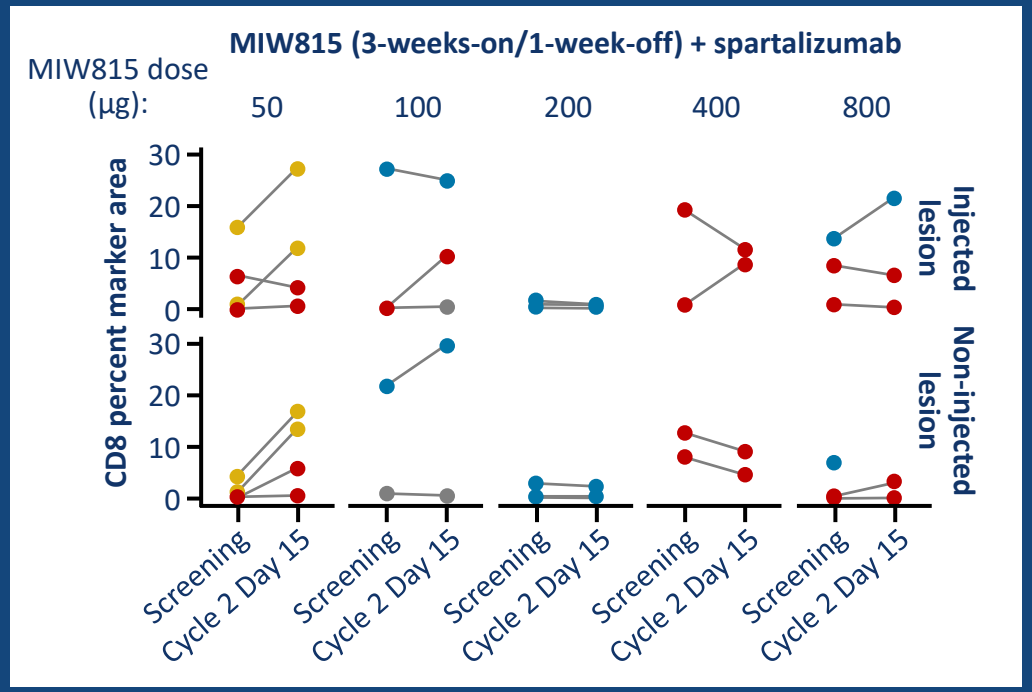
Data cut-off: April 5, 2019

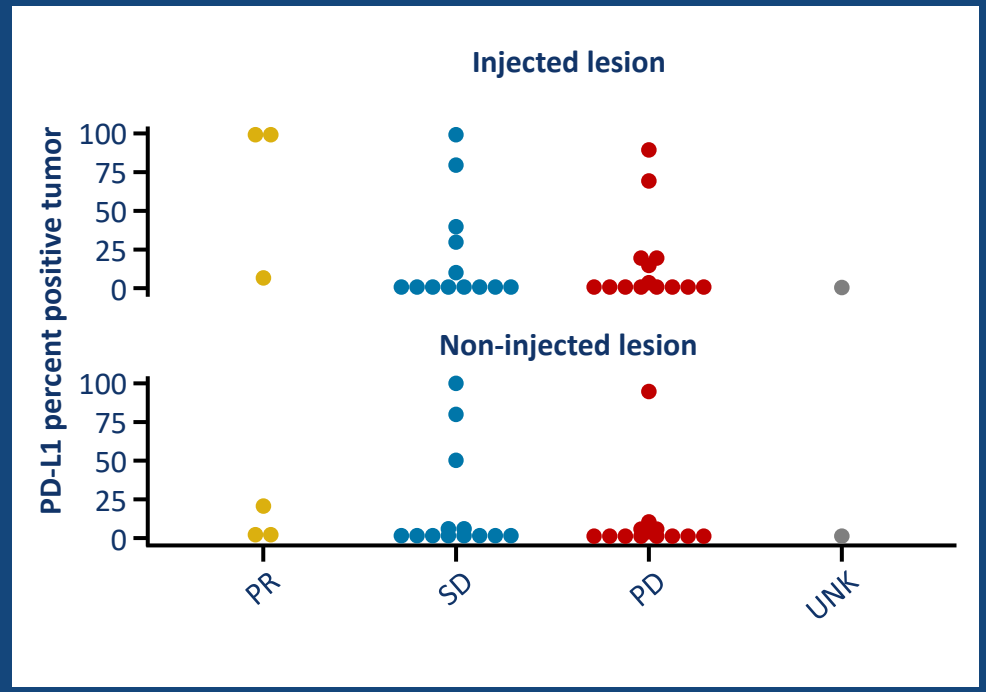
Percentage change from baseline
Sum of target lesion diameters (evaluable patients)



Data cut-off: April 5, 2019

CD8 IHC increased in responding patients with high PD-L1 at baseline





Best overall response per RECIST v1.1 or Cheson 2014 for Lymphoma (with confirmation)

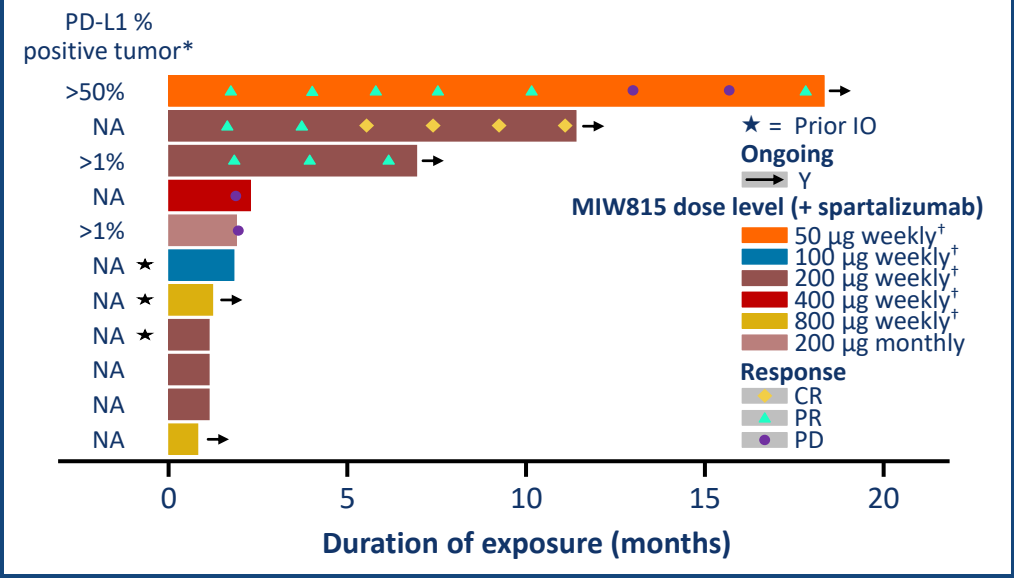
- PR
- SD
- PD
- UNK

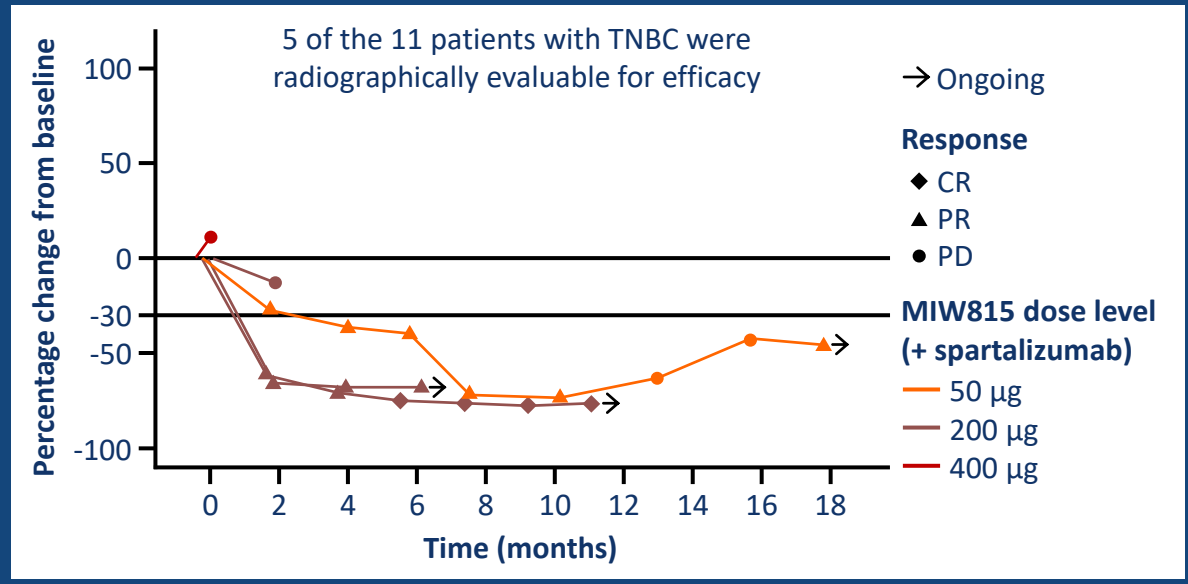
- Two patients demonstrating best response (PR) had high levels of PD-L1* staining in their injected lesions at screening

*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.

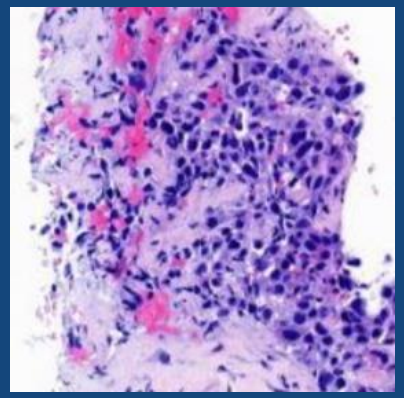
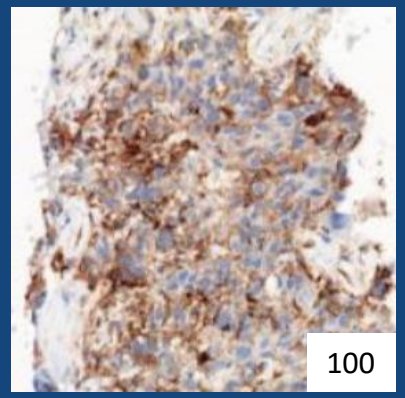
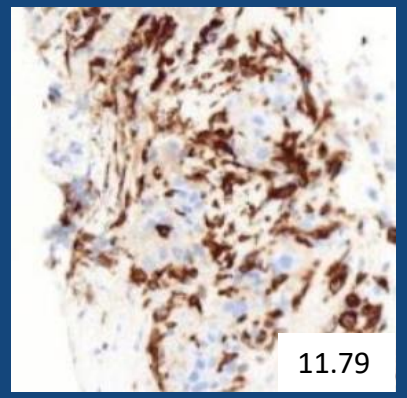
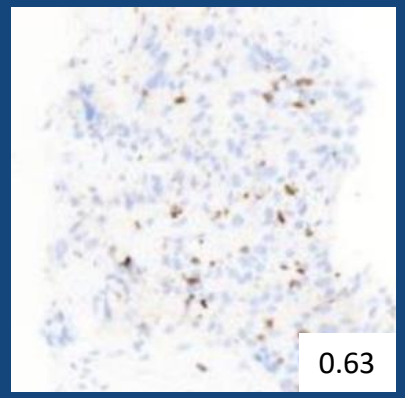
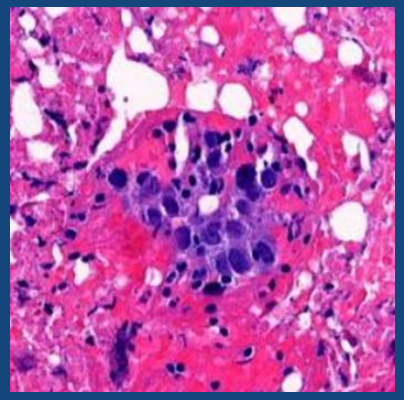
Data cut-off: April 5, 2019

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

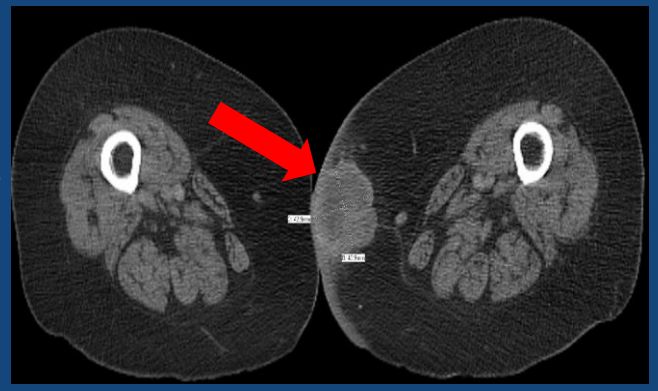
	H&E	PD-L1** (22C3)	CD163*	CD8*
Screening		 100	 11.79	 0.63
C2D18				

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

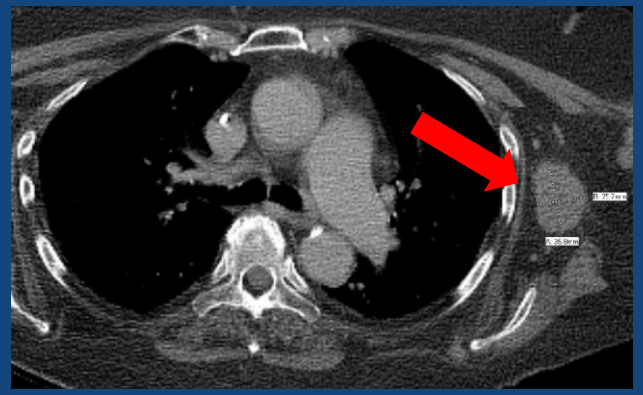
* % biomarker area (image analysis).
** % tumor-positive score (pathologist scored).

Imaging

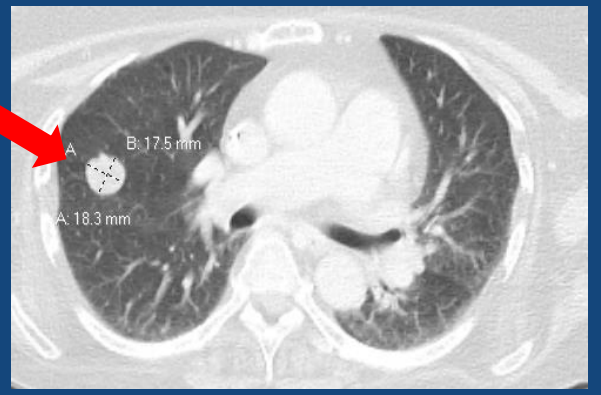
Baseline



4.4 x 4.3 cm

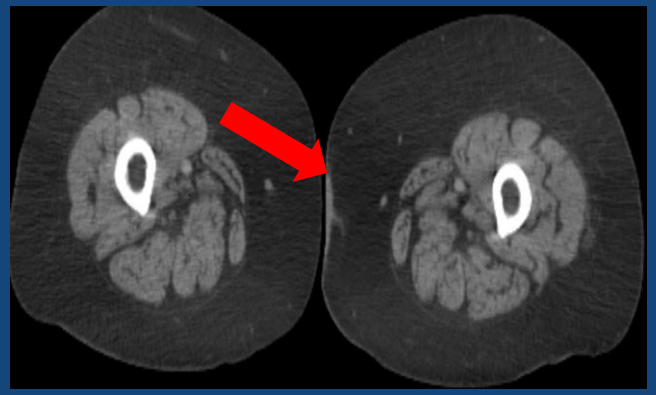


3.6 x 2.6 cm

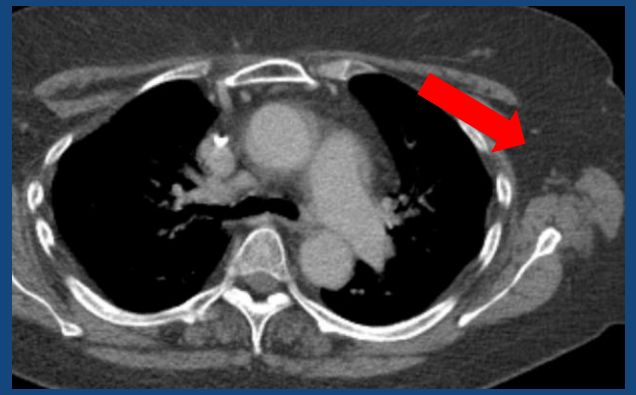


1.8 x 1.8 cm

Cycle 4 Day 22



0.0 cm



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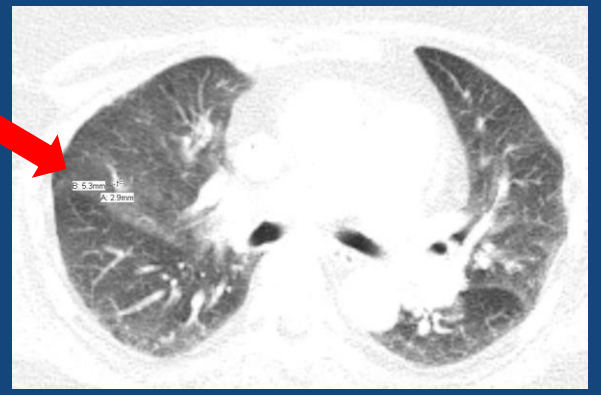

0.5 x 0.3 cm

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

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- Hospital Kliniken Essen-Mitte
- Netherlands Cancer Institute
- Melanoma Institute of Australia
- Comprehensive Cancer Center Zürich
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