Safety, Efficacy, and Immune Correlates of Alternative Doses and Schedules of Entinostat Combined With Pembrolizumab in Patients With Advanced Solid Tumors – Results From SNDX-275-0141 Phase I Trial

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Disclosure Information: AACR Annual Meeting 2018
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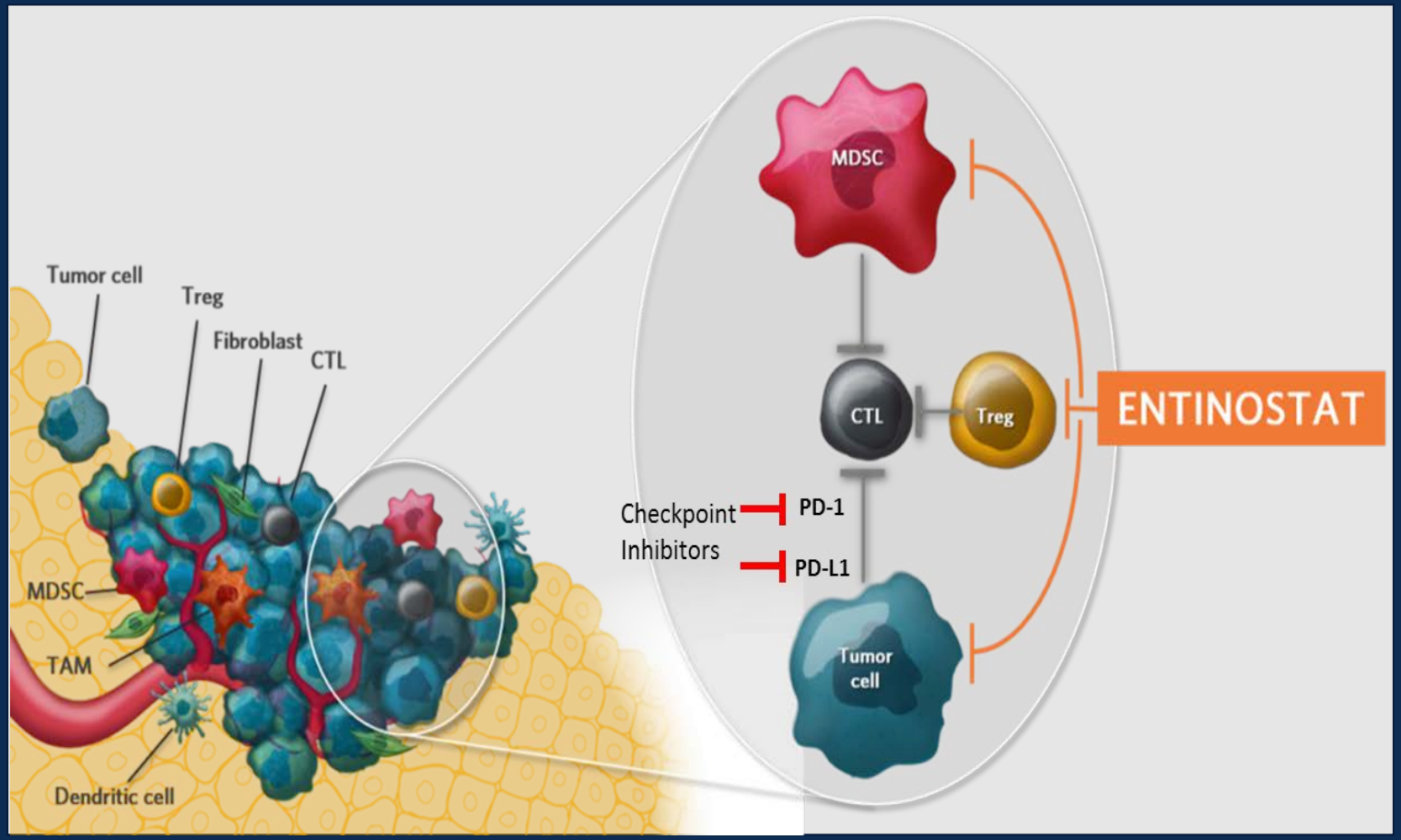
I have the following financial relationships to disclose:

- Grant/Research support from Syndax for the conduct of this study
- Employee of: Past Employment at START, now NEXT Oncology

- I will discuss the following off label use and/or investigational use in my presentation: Combination of entinostat and pembrolizumab

Immune Checkpoint Inhibitors & Entinostat Target Complementary Immunosuppression Mechanisms in the Tumor Microenvironment

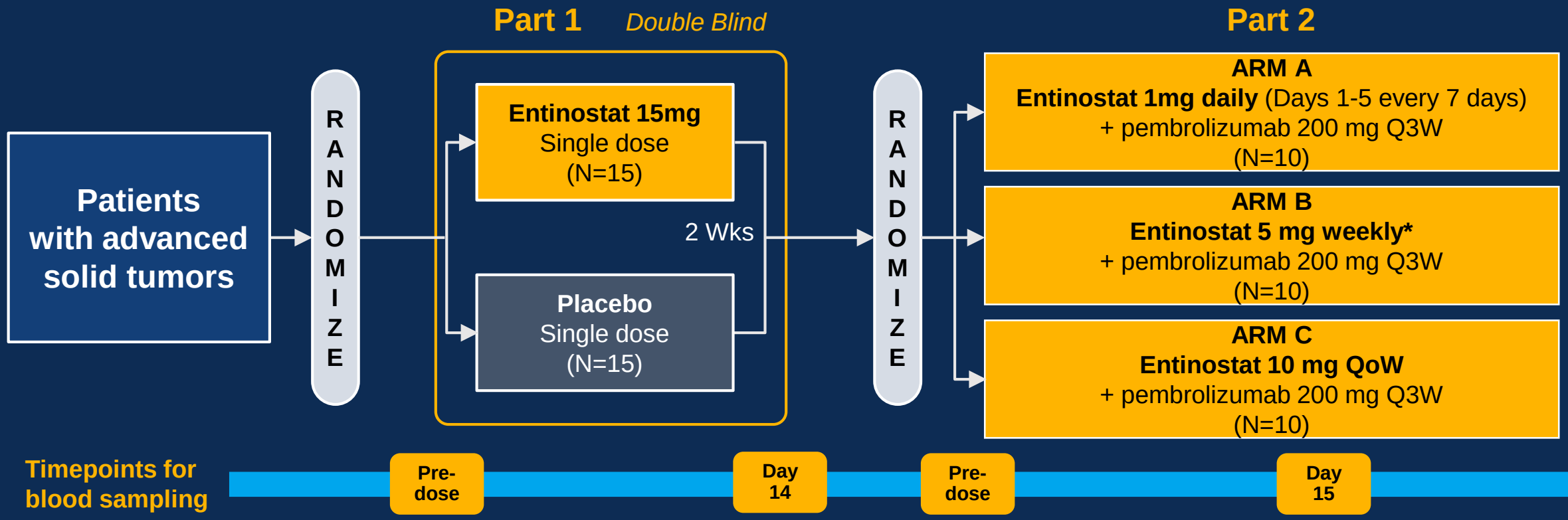
- Entinostat – oral, class I selective histone deacetylase inhibitor
- Has demonstrated potent immunomodulatory activity by inhibition of myeloid-derived suppressor cell (MDSC) function[1]
- Encouraging preliminary data of the combination of entinostat plus pembrolizumab in PD-1 pretreated patients have been reported:
  - Melanoma: 4 of 13 responders (31% ORR)[2]
  - NSCLC: 3 of 31 responders (10% ORR)[3]



1. Orillion A, et al. *Clin Cancer Res*. 2017;23(17):5187-5201. 2. Johnson M, et al. SITC, 2017. 3. Gandhi L, et al. SITC, 2017.

Overview of Study 0141 Design and Schedule of Blood Samples

Alternative doses were hypothesis generating



Objectives

- Cardiac safety, PK, safety/tolerability *(ECG/ 24 hour Holter monitor)*
- **Immune correlatives**

Objectives

- Safety/tolerability, PK, efficacy
- Impact on immune correlatives

* 5 mg weekly is the dose being used in all ongoing Phase 2 PD-1 combination trials as well as E2112.

Baseline Demographics of Treatment Arms Are Similar

	Arm A 1 mg Days 1-5 every 7 (N=8)	Arm B 5 mg weekly (N=9)	Arm C 10 mg QoW (N=9)	Total (N=26)
Age (years), median (range)	59.5 (22 - 68)	56.0 (44 -75)	65.0 (41-70)	60.5 (22-75)
Sex, n (%)				
Male	2 (25.0)	2 (22.2)	3 (33.3)	7 (26.9)
Female	6 (75.0)	7 (77.8)	6 (66.7)	19 (73.1)
ECOG Performance Status, n (%)				
0	2 (25.0)	3 (33.3)	3 (33.3)	8 (30.8)
1	6 (75.0)	6 (66.7)	6 (66.7)	18 (69.2)
Tumor Type, n (%)				
Breast (all HR+)	4 (50.0)	4 (44.4)	3 (33.3)	11 (42.3)
Prostate	0 (0.0)	2 (22.2)	2 (22.2)	4 (15.4)
Ovarian	1 (12.5)	0 (0.0)	1 (11.1)	2 (7.7)
Other	3 (37.5)	3 (33.3)	3 (33.3)	9 (34.6)

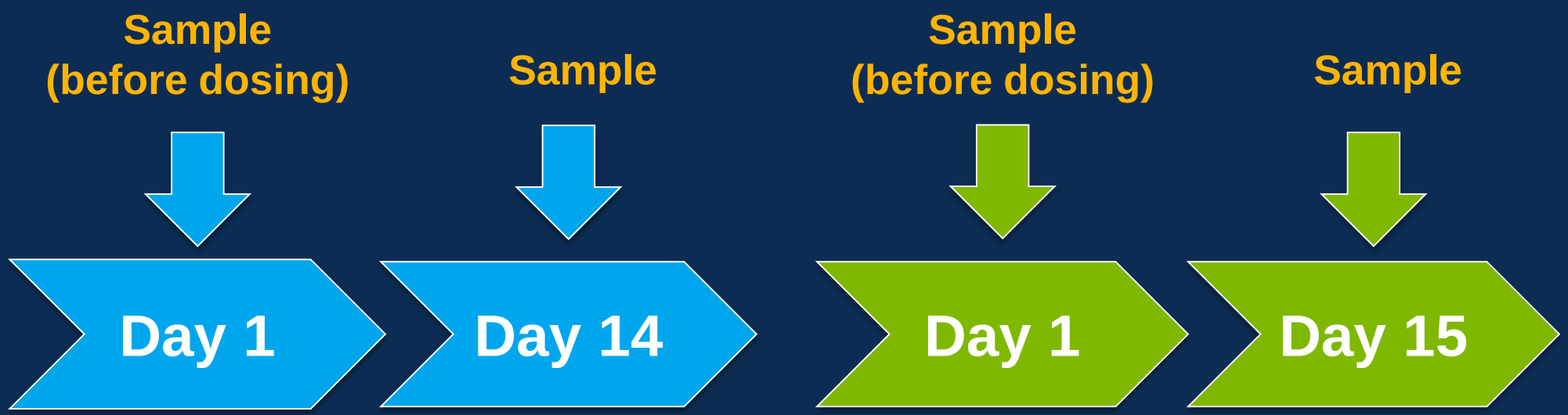
Principal Biomarker Correlates

Hypothesis: Myeloid Derived Suppressor Cells Mediate Resistance to PD1 axis targeting

- Determine the effect on MDSC population in blood after exposure to entinostat or placebo in the lead-in portion of the study

- Determine the effect of MDSC population in blood after exposure to continuous entinostat amongst three administration schedules

Immune (MDSC) Biomarkers Were Analyzed at Four Timepoints



Randomize:

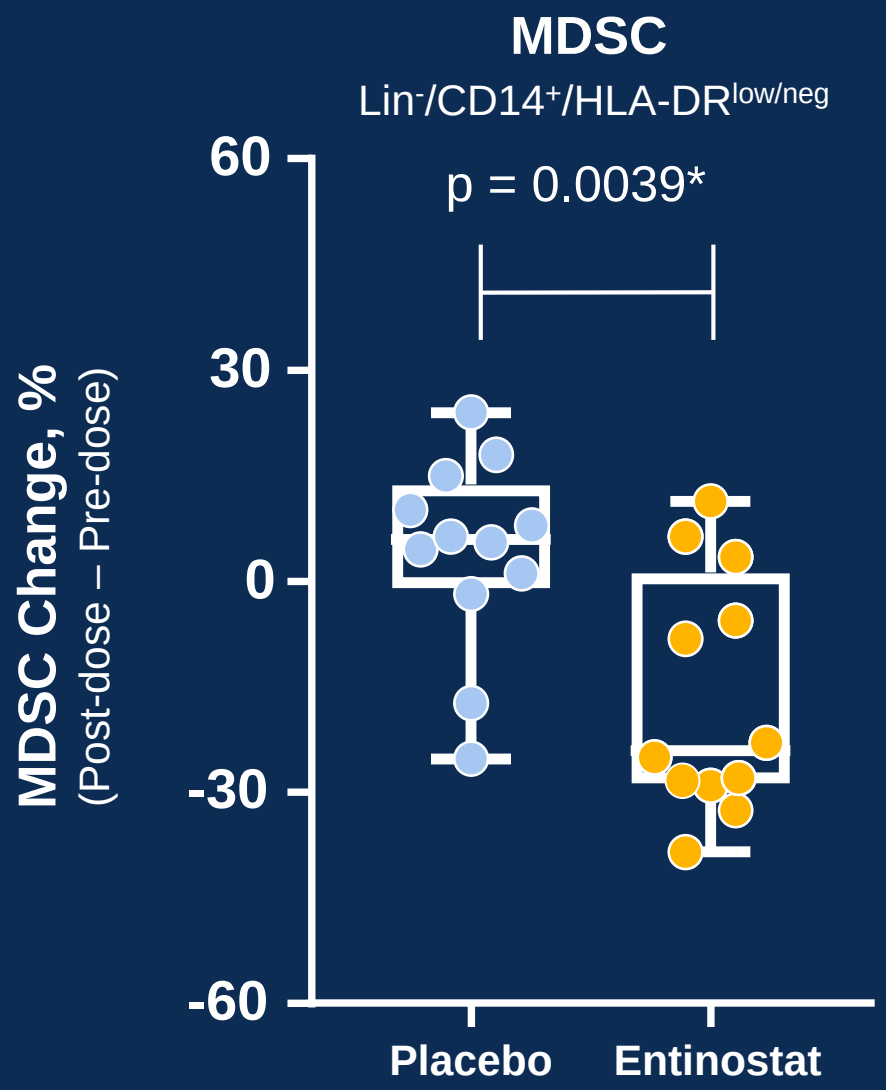
- 15 mg entinostat
- Placebo

Randomize:

- Arm A – 1 mg entinostat, Days 1-5 every 7 days
- Arm B – 5 mg entinostat weekly
- Arm C – 10 mg entinostat every other week

All arms receive pembrolizumab 200 mg Q3W

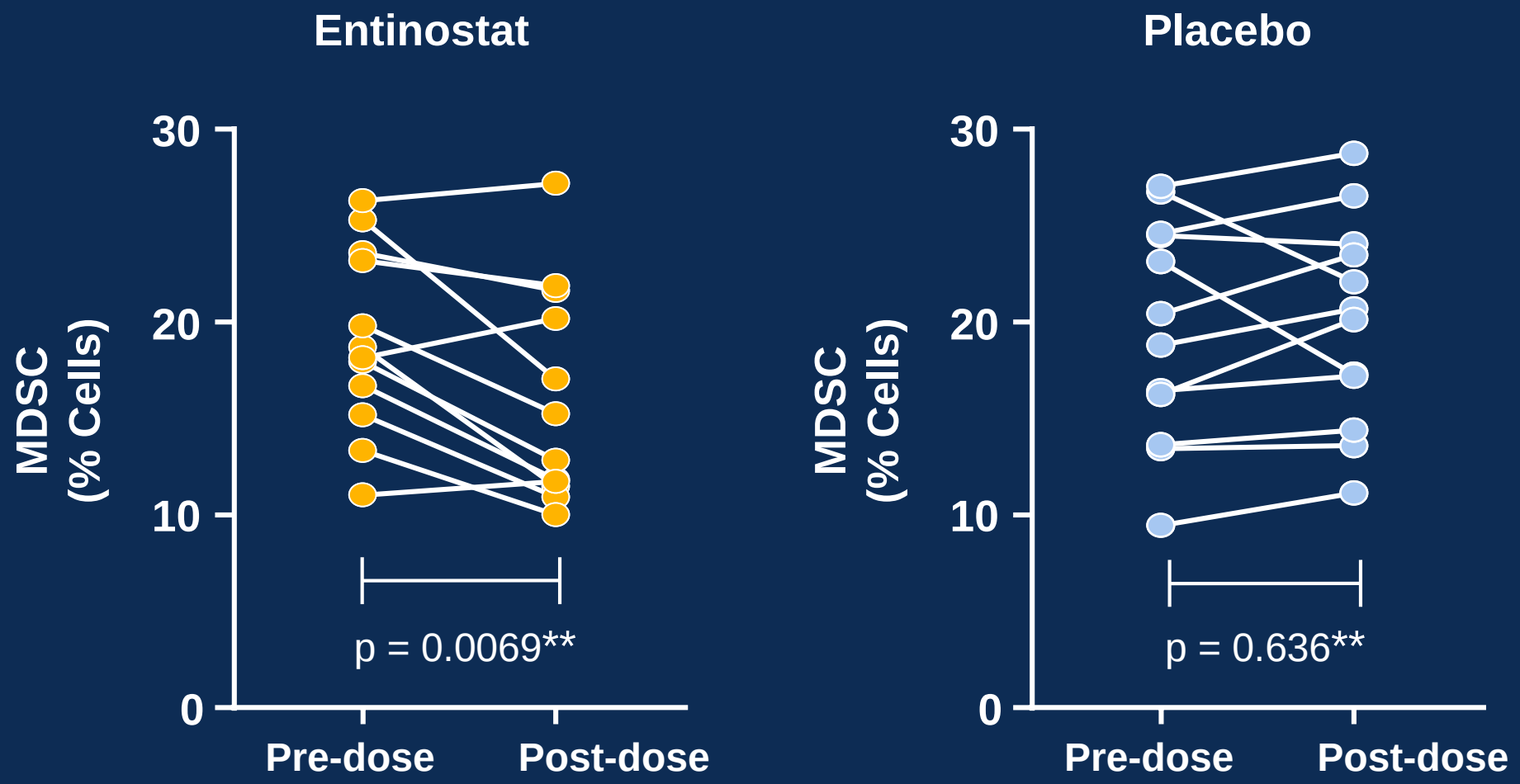
Lead-in Shows MDSCs Are Significantly Lowered by Entinostat Treatment Compared to Placebo



- After a single entinostat dose, MDSC cell frequency was significantly decreased in patients who received entinostat compared to placebo
- No statistical difference was observed in frequency of NK, T cell, or B cell populations in patients receiving entinostat relative to the placebo control

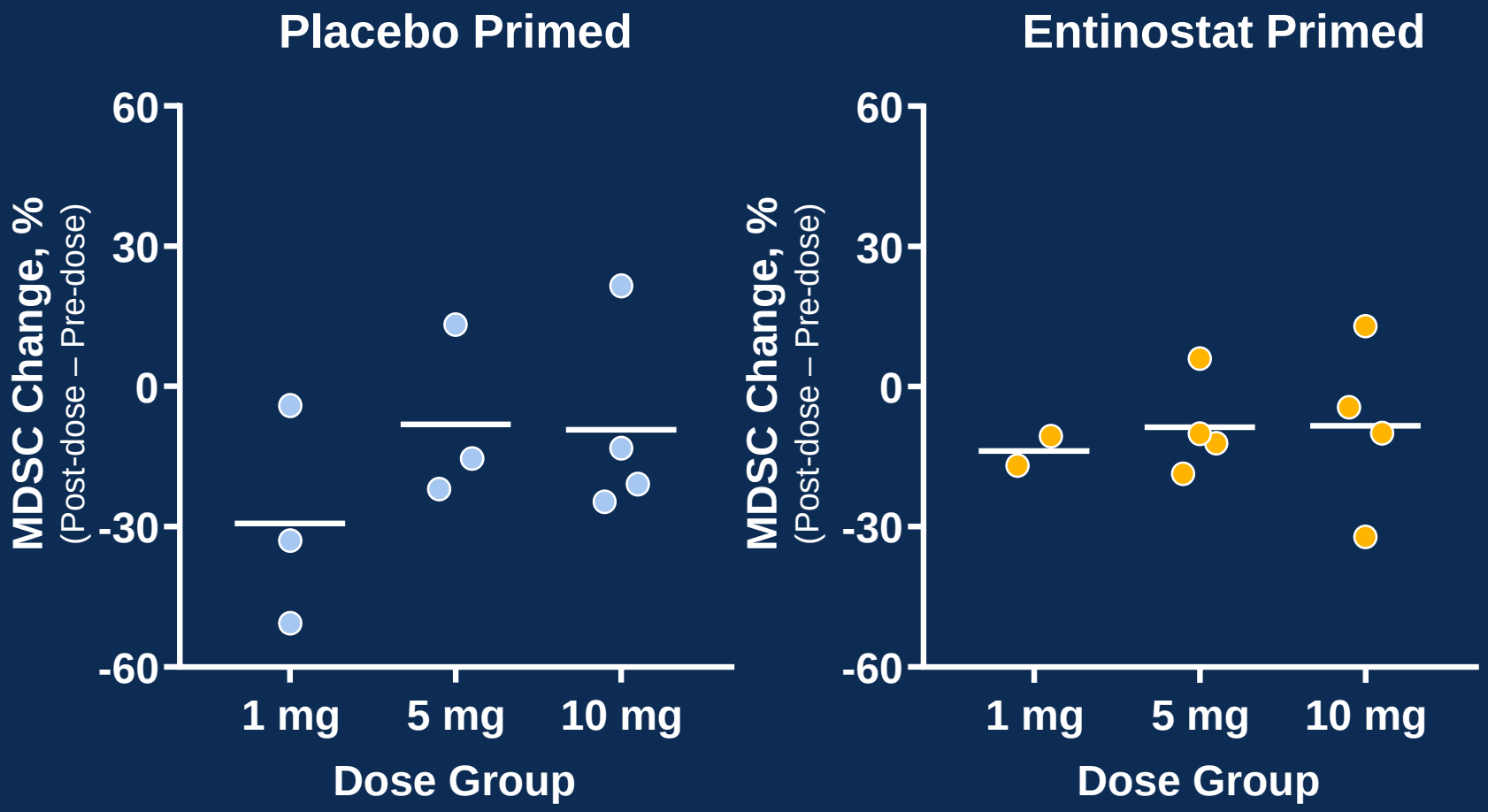
* Unpaired t-test.

Lead-in Shows MDSCs Are Significantly Lowered by Entinostat Treatment Compared to Placebo



** Paired t-test.

In Part 2, Continuous Dosing Maintains Observed Decrease in MDSCs – (141) C1D15

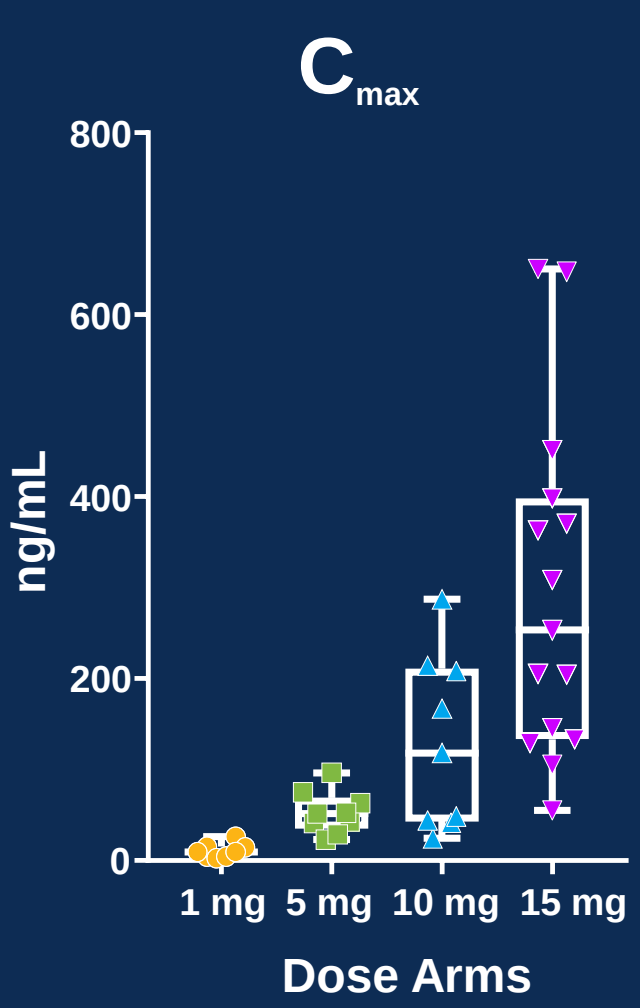


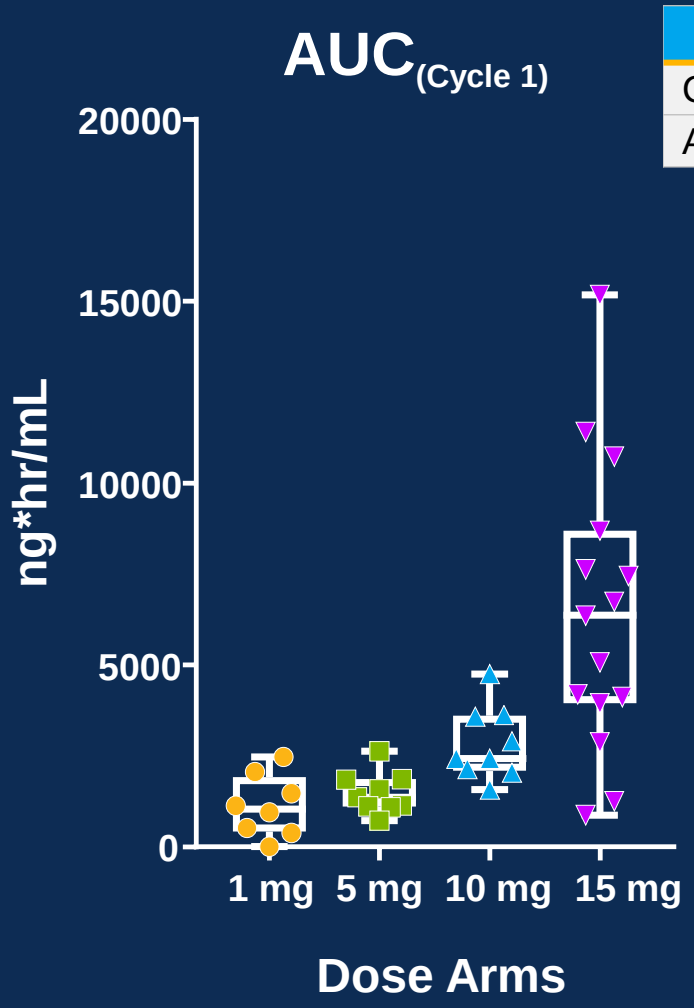
Entinostat Dosing Arms:

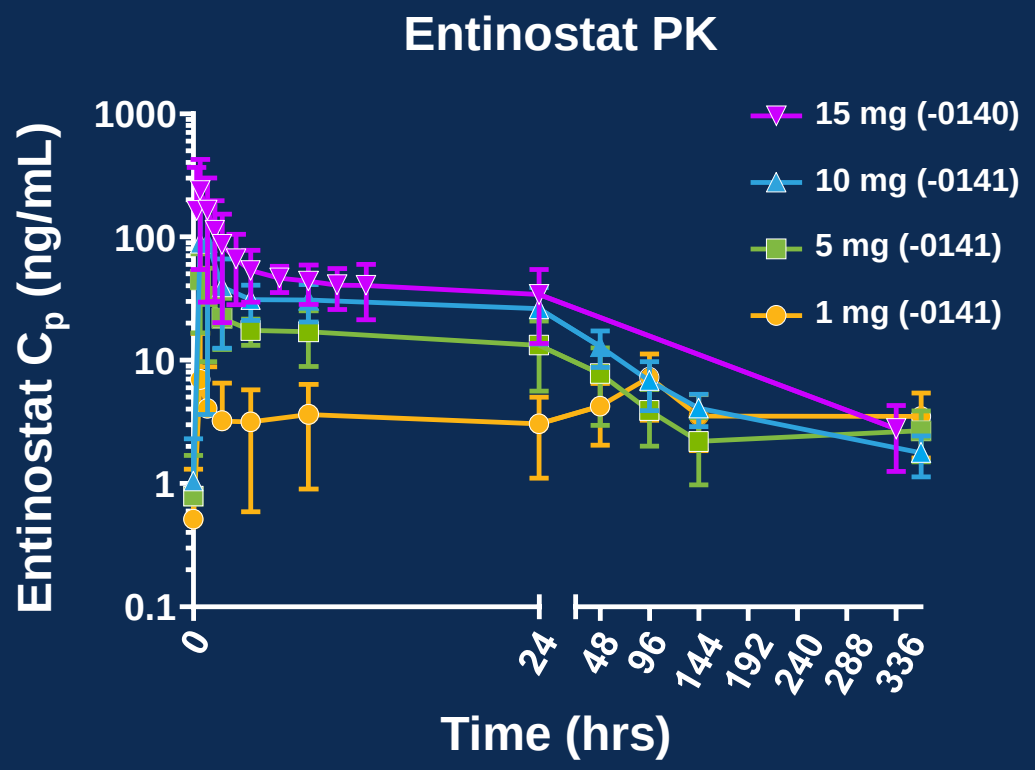
- **Arm A:** 1 mg Days 1-5 every 7 days
- **Arm B:** 5 mg once weekly
- **Arm C:** 10 mg once every other week

Entinostat Pharmacokinetics Contribute to Durable Exposure

	1 mg	5 mg	10 mg	15 mg
C_{max} ng/mL	9	52	118	253
$AUC_{(cycle1)}$ ng*hr/mL	1040	1366	2432	6359







- Entinostat exposure during the first cycle of treatment increases in a dose dependent manner over the first cycle of treatment by both C_{max} and AUC
- Peak exposure generally occurs within 1 hour of dosing, with a residual exposure tail persisting up to 15 days.

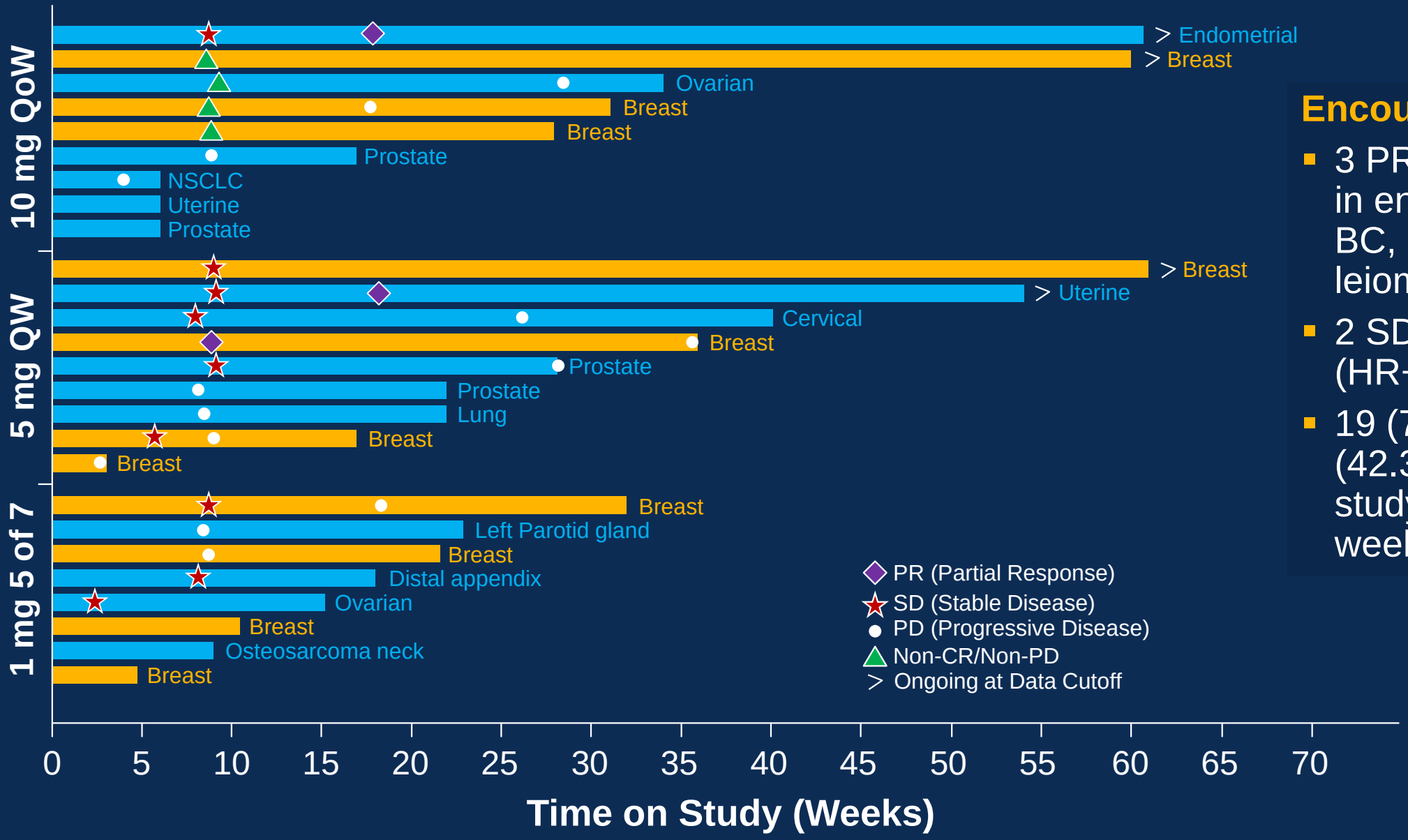
A Similar Safety Profile Is Observed As Previously Reported[1,2] – Grade 3/4 Related Adverse Events

	Total (N=26)
Subjects With At Least One Grade >= 3 Related Treatment-Emergent Adverse Event	10 (38.5)
Neutrophil count decreased	5 (19.2)
White blood cell count decreased	3 (11.5)
Lymphocyte count decreased	2 (7.7)
Anemia	1 (3.8)
Arthralgia	1 (3.8)
Colitis	1 (3.8)
Hyperglycemia	1 (3.8)
Neutropenia	1 (3.8)
Vomiting	1 (3.8)

- No notable differences in the safety profile were observed among the 3 arms
- The overall safety profile observed in this study was consistent with previously reported experience of entinostat combined with pembrolizumab[1,2]

[1]Johnson M, et al. SITC, 2017. [2]Gandhi L, et al. SITC, 2017.

Entinostat + Pembrolizumab Shows Promising Activity In Patients with Heavily Pretreated Cancers



Encouraging activity:

- 3 PRs (ORR = 11.5%) in endometrial, HR+ BC, uterine leiomyosarcoma
- 2 SDs > 6 months (HR+ BC)
- 19 (73.1%) and 11 (42.3%) patients on study for 12 and 24 weeks respectively

Conclusions

- Consistent with previous reports, entinostat treatment results in reductions in circulating MDSCs
- No notable differences in the safety profile were observed among the 3 arms, and the overall safety profile was consistent with previously reported experience of entinostat combined with pembrolizumab
- The combination of entinostat and pembrolizumab continues to show promising activity in patients with heavily pretreated cancers
- This trial supports continued study of entinostat 5 mg weekly, the schedule being used in other entinostat/pembrolizumab studies and in the ongoing Phase III E2112 entinostat/exemestane study

Acknowledgements

- We thank the patients and their families/caregivers
- START study staff

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