ENCORE 603: A Phase II Randomized Study of Avelumab Plus Entinostat vs Avelumab Plus Placebo in Patients With Advanced and Recurrent Epithelial Ovarian Cancer

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PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

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PRESENTED BY: Karen Cadoo, MD

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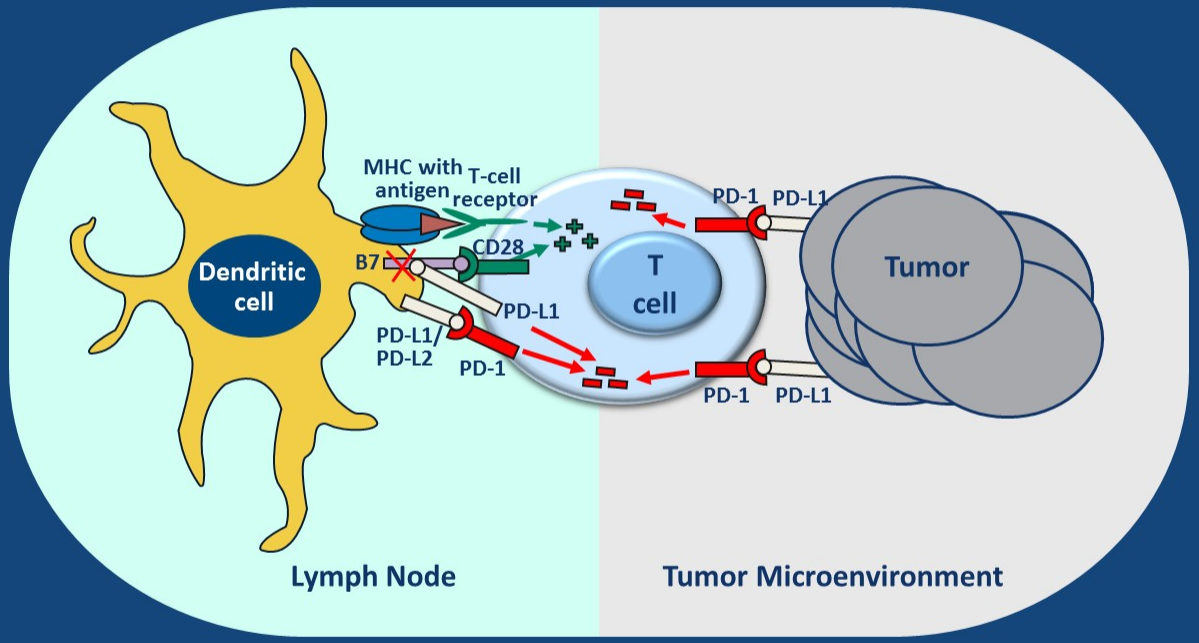
Background

- Avelumab is a humanized anti-PD-L1 IgG1 monoclonal antibody
- FDA approved in metastatic merkle cell carcinoma, advanced urothelial carcinoma and renal cancer



CD28, cluster of differentiation 28; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.
Adapted from: Postow MA, et al. *J Clin Oncol*. 2015;33(17):1974-1982.

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Single-Agent Immune Checkpoint Inhibition Has Shown Limited Efficacy in Pretreated Ovarian Cancer

	KEYNOTE-028[1]	JAVELIN Solid Tumor[2]	KEYNOTE-100[3]
Phase	1b	1b	2
Patients, N	26	125	376
Population	PD-L1–positive advanced	Recurrent/refractory	Advanced recurrent
Prior lines of therapy, %	73% had ≥ 3 prior lines of therapy	65% had ≥ 3 prior lines of therapy	45% had ≥ 3 prior lines of therapy
Treatment(s)	Pembrolizumab	Avelumab	Pembrolizumab
ORR, %	11.5	9.6	8.0
CR, %	3.8	0.8	1.9
PR, %	7.7	8.8	6.1
SD, %	26.9	42.4	29.3
mPFS (95% CI), mo	1.9 (1.8–3.5)	2.6 (1.4–2.8)	2.1
mOS (95% CI), mo	13.8 (6.7–18.8)	11.2 (8.7–15.4)	Cohort A†: NR (16.8–NR); Cohort B†: 17.6 (13.3–NR)
Timing of scans	Baseline and every 8 weeks*	Baseline and every 6 weeks	Every 9 weeks‡

*After 6 months, scans were taken every 12 weeks. † Cohort A had 1-3 prior lines of therapy and Cohort B had 4-6 prior lines of therapy. ‡Scans were taken every 12 weeks after week 54.
CI, confidence interval; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease.
1. Varga A, et al. *Gynecol Oncol*. 2019;152(2):243-250. 2. Disis ML, et al. *JAMA Oncol*. 2019;5(3):393-401. 3. Matulonis UA, et al. *Ann Oncol*. 2019 May 2. doi: 10.1093/annonc/mdz135. [Epub ahead of print].

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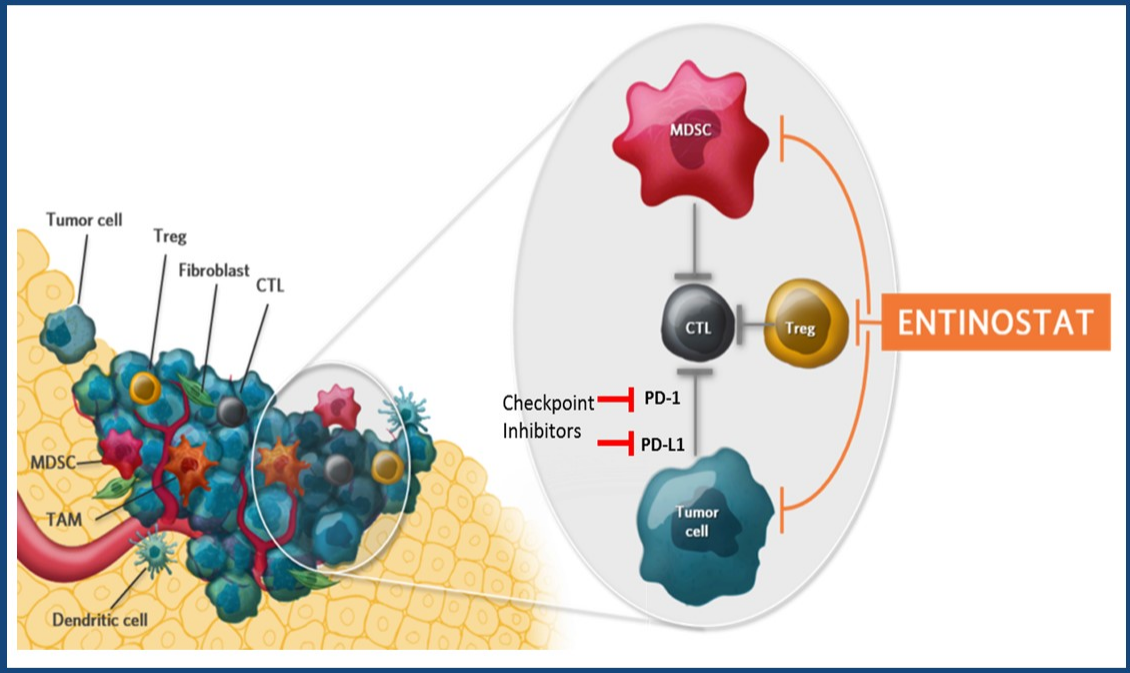
Potential for Immune Modulation with the Histone Deacetylase (HDAC) Inhibitor Entinostat

- Entinostat is an oral class I-selective histone deacetylase inhibitor
- Entinostat regulates the tumor microenvironment, immune inhibitory cells, induces a pro-inflammatory cascade, enhances antigen presentation
- Entinostat leads to additional beneficial effects on T_{eff} and NK cells



CTL, cytotoxic T lymphocytes; MDSC, myeloid-derived suppressor cells; NK, natural killer; TAM, tumor-associated macrophages; Teff, effector T cell; Treg, regulatory T cell.
Orillion A, et al. *Clin Cancer Res*. 2017;23(17):5187-5201.

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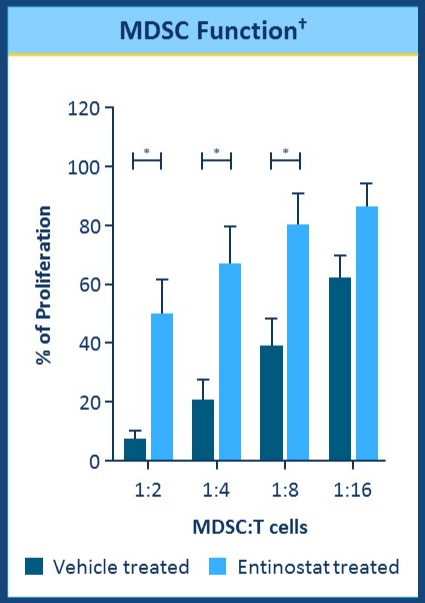
Preclinical Data has Demonstrated Synergy with Entinostat and anti PD-1 inhibition

- Entinostat leads to downregulation of immunosuppressive cell types (MDSC) in the tumor microenvironment



*P<0.05. **P<0.001. † *In vivo* and *in vitro* studies were performed using Lewis Lung Carcinoma (LLC) cells.
Ab, antibody; Arg1, arginase 1; COX2, cytochrome oxidase subunit 2; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells.
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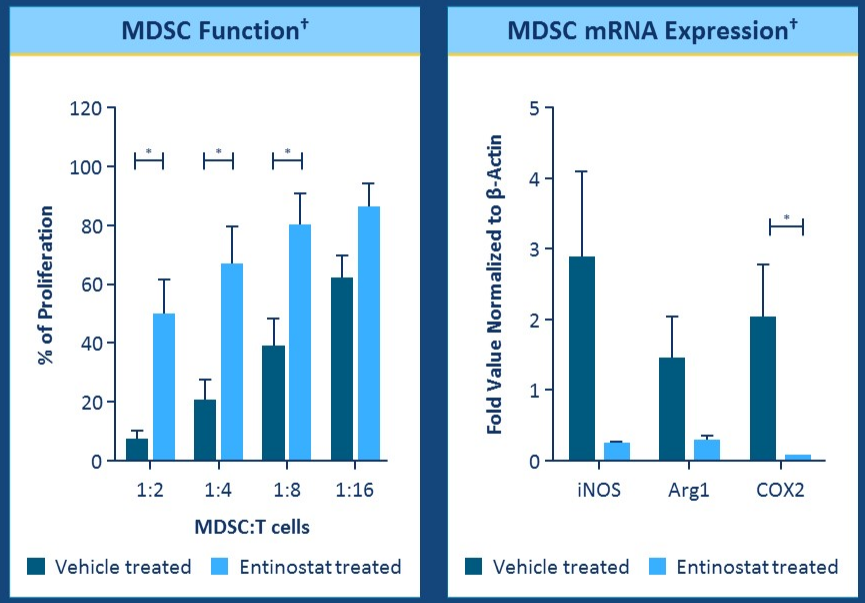

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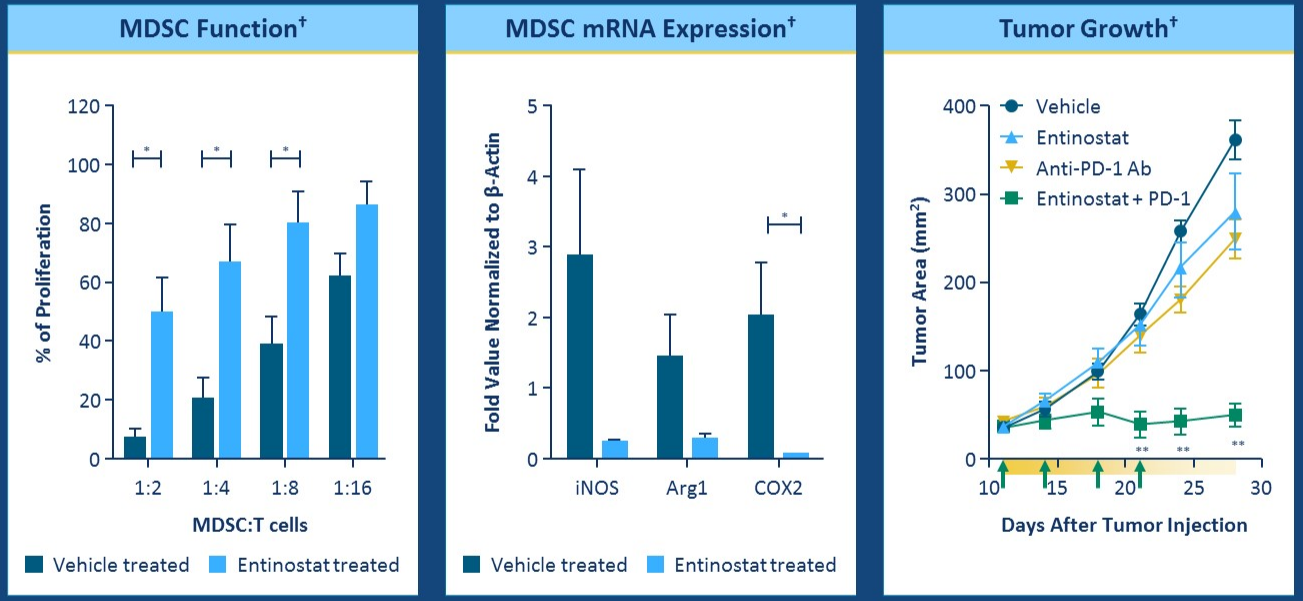
Preclinical Data has Demonstrated Synergy with Entinostat and anti PD-1 inhibition

- Entinostat leads to downregulation of immunosuppressive cell types (MDSC) in the tumor microenvironment
- Entinostat showed synergy with anti-PD-1 inhibition in preclinical models



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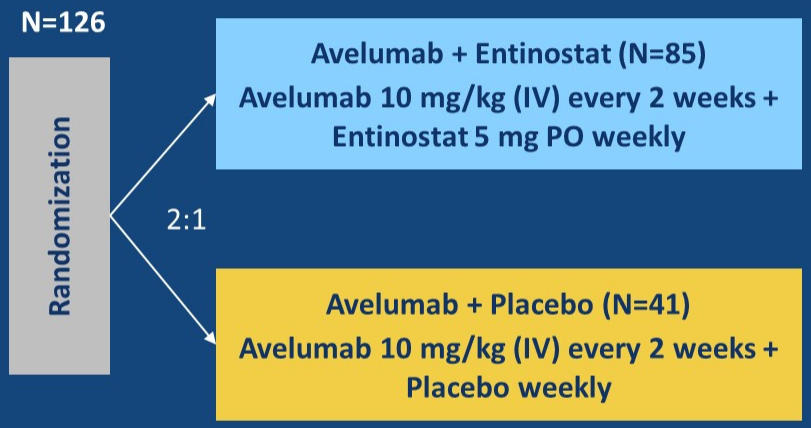
ENCORE-603: Phase 2, Randomized, Double-Blind Study of Avelumab With or Without Entinostat in Patients With Advanced Epithelial Ovarian Cancer



Radiological disease assessments performed at baseline and every 6 weeks through week 36, thereafter every 8 weeks

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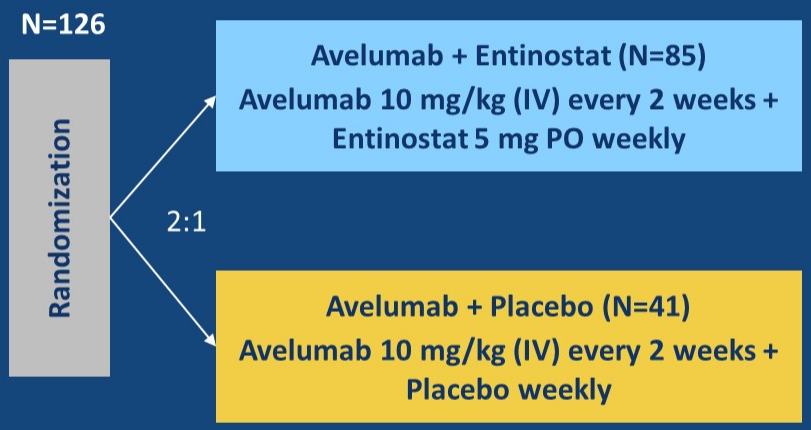

Key eligibility:

- Patients must have progressive or recurrent ovarian cancer and 3-6 prior therapies
- Patients were agnostic to platinum sensitivity status
- No prior immunotherapy was allowed

Radiological disease assessments performed at baseline and every 6 weeks through week 36, thereafter every 8 weeks

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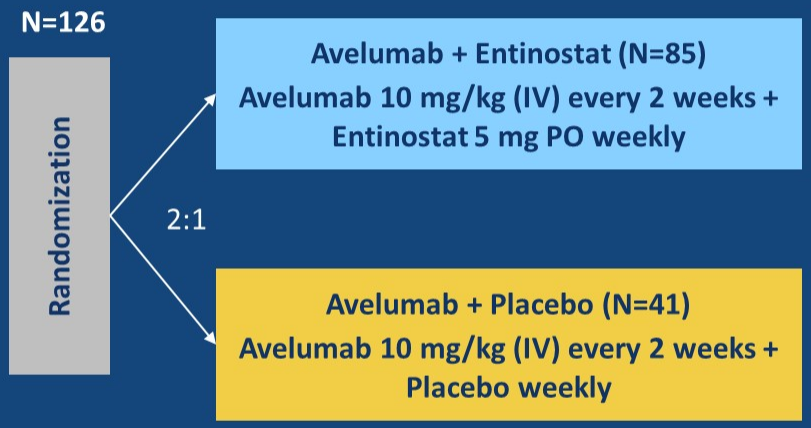

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Stratification:

- Presence of bulky disease (tumor ≥ 50mm) vs not
- History of progression during primary platinum treatment (or within 1 month completion) vs not

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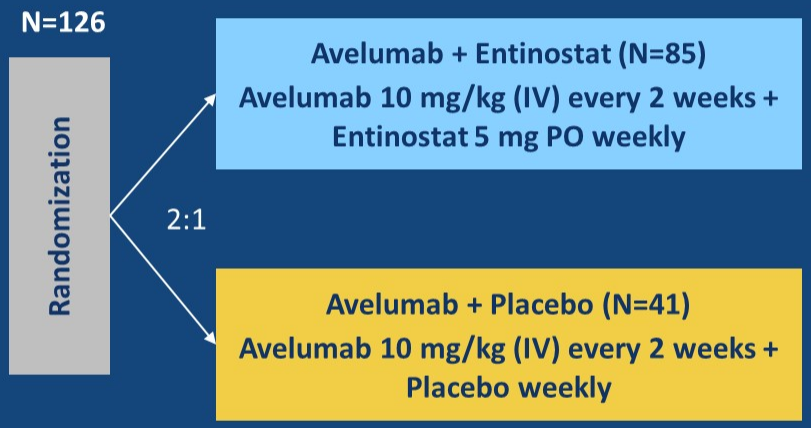

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Date of first patient in: July 11, 2017

Date of last patient in: April 17, 2018

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Endpoints and Statistics

- Primary endpoint: Progression-Free Survival (PFS) based on RECIST 1.1
- Hypothesis: Avelumab + Entinostat would reduce the hazard of progression of disease or death by 43%, representing a 75% improvement in median PFS. 97 events (from 120 pts) provided 90% power with 1-sided significance level of 0.10
- Data cutoff date for final analysis of PFS: September 27, 2018
- Secondary endpoints: ORR by RECIST 1.1 and irRECIST, PFS by irRECIST, OS, CBR by RECIST 1.1 and irRECIST, AE, SAEs

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Patient Demographics and Baseline Characteristics

	Avelumab + Placebo (N=41)	Avelumab + Entinostat (N=85)
	N (%)	N (%)
Median Age (range)	64 (45–79)	63 (43–82)
Race		
White	37 (90.2)	79 (92.9)
Other	4 (9.8)	6 (7.1)
ECOG Performance Status		
0	21 (51.2)	46 (54.1)
1	20 (48.8)	38 (44.7)
Body Mass Index		
< 30 kg/m^2	27 (65.9)	55 (64.7)
≥ 30 kg/m^2	12 (29.3)	24 (28.2)
Disease Stage at Initial Diagnosis		
II	4 (9.8)	10 (11.8)
III	25 (61.0)	45 (52.9)
IV	6 (14.6)	17 (20.0)

N (%)	Avelumab + Placebo (N=41)	Avelumab + Entinostat (N=85)
	N (%)	N (%)
Median Prior Therapies	4	4
Duration of Immediate Prior Therapy, Months		
Mean (SD)	3.5 (2.9)	4.1 (3.6)
Median (range)	2.8 (0.1–13.9)	3.5 (0.0–18.6)
Presence of Bulky Disease (>50mm)		
Yes	11 (26.8)	25 (29.4)
No	30 (73.2)	60 (70.6)
Histologies		
Serous	36 (87.8)	69 (81.2)
Endometroid	1 (2.4)	4 (4.7)
Clear cell	1 (2.4)	3 (3.5)
Other	0 (0.0)	5 (5.9)

ECOG, Eastern Cooperative Oncology Group.

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Patients Randomized	41 (100)	85 (100)
Safety Population	40 (97.6)	85 (100)
Treatment Status		
On study treatment	4 (10.0)	9 (10.6)
Discontinued study therapy	36 (90.0)	76 (89.4)
Progressive disease (RECIST 1.1)	21 (52.5)	46 (54.1)
Progressive disease (irRECIST)	2 (5.0)	4 (4.7)
Clinical progression	1 (2.5)	5 (5.9)
Adverse event	7 (17.5)	17 (20.0)
Withdrawal of consent	3 (7.5)	1 (1.2)
Other	2 (5.0)	3 (3.5)
Stayed on treatment after RECIST 1.1 PD	10 (24.4)	18 (21.2)

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Stayed on treatment after RECIST 1.1 PD	10 (24.4)	18 (21.2)

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Patient Status

N (%)	Avelumab + Placebo (N=41)	Avelumab + Entinostat (N=85)
Patients Randomized	41 (100)	85 (100)
Safety Population	40 (97.6)	85 (100)
Treatment Status		
On study treatment	4 (10.0)	9 (10.6)
Discontinued study therapy	36 (90.0)	76 (89.4)
Progressive disease (RECIST 1.1)	21 (52.5)	46 (54.1)
Progressive disease (irRECIST)	2 (5.0)	4 (4.7)
Clinical progression	1 (2.5)	5 (5.9)
Adverse event	7 (17.5)	17 (20.0)
Withdrawal of consent	3 (7.5)	1 (1.2)
Other	2 (5.0)	3 (3.5)
Stayed on treatment after RECIST 1.1 PD	10 (24.4)	18 (21.2)

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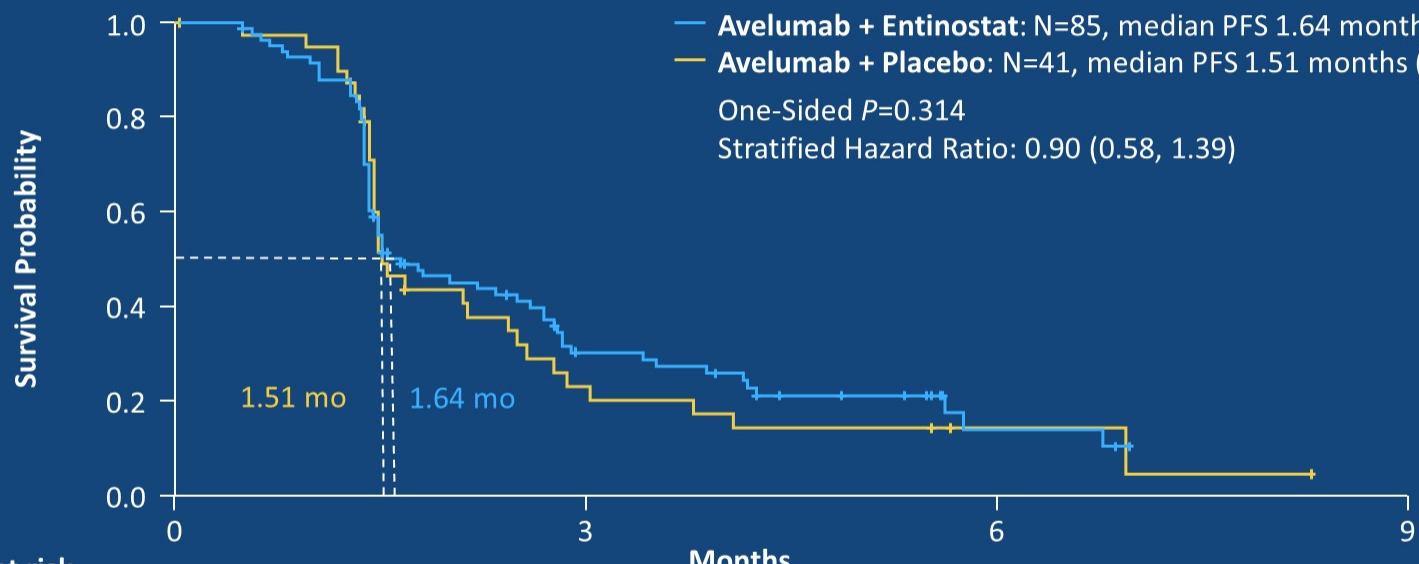
Primary Endpoint Progression-Free Survival RECIST 1.1



No. event / No. at risk			
Avelumab + Entinostat	56 / 85	8 / 21	1 / 4
Avelumab + Placebo	28 / 41	3 / 8	2 / 3

Radiological disease assessments performed at baseline and every 6 weeks through week 36, and after week 36 every 8 weeks

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Subgroup Analysis

Subgroup	N (%)	Median PFS (mo) Entinostat / Placebo	Hazard Ratio Plot	Hazard Ratio (95% CI)
Overall	126 (100%)	1.64 / 1.51		0.895 (0.587, 1.365)
Presence of bulky disease				
No	90 (71.4%)	2.50 / 1.48		0.621 (0.380, 1.015)
Yes	36 (28.6%)	1.46 / 2.56		2.441 (0.960, 6.211)
Progression while on primary platinum treatment or within one month from completion of the regimen				
No	122 (96.8%)	1.54 / 1.51		0.915 (0.596, 1.403)
Number of prior platinum-based therapies				
< 2	18 (14.3%)	1.81 / 2.02		0.831 (0.261, 2.644)
≥ 2	106 (84.1%)	1.51 / 1.51		0.891 (0.564, 1.407)
Disease stage at initial diagnosis				
Stage II	14 (11.1%)	2.89 / 1.91		0.611 (0.150, 2.489)
Stage III	70 (55.6%)	1.51 / 1.48		0.802 (0.467, 1.377)
Stage IV	23 (18.3%)	1.41 / 2.76		0.880 (0.278, 2.783)
CA-125 results				
≤ 35 μ/mL	19 (15.1%)	5.62 / 2.30		0.475 (0.148, 1.525)
> 35 μ/mL	104 (82.5%)	1.51 / 1.48		1.010 (0.621, 1.641)

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Secondary Endpoints: Objective Response Rate and Clinical Benefit Rate

Endpoint	Avelumab + Placebo (N=41)	Avelumab + Entinostat (N=85)
	N (%)	N (%)
Objective Response Rate (RECIST 1.1)	2 (4.9)	5 (5.9)
Exact 95% confidence interval	(0.6, 16.5)	(1.9, 13.2)
Clinical Benefit Rate (CR+PR+SD ≥ 6 months)	4 (9.8)	10 (11.8)
Exact 95% confidence interval	(2.7, 23.1)	(5.8, 20.6)
Stable Disease ≥ 4 months	3 (7.3)	15 (17.6)
Exact 95% confidence interval	(1.5, 19.9)	(10.2, 27.4)

*Per protocol, clinical benefit rate was defined as complete response + partial response + stable disease ≥ 6 months.

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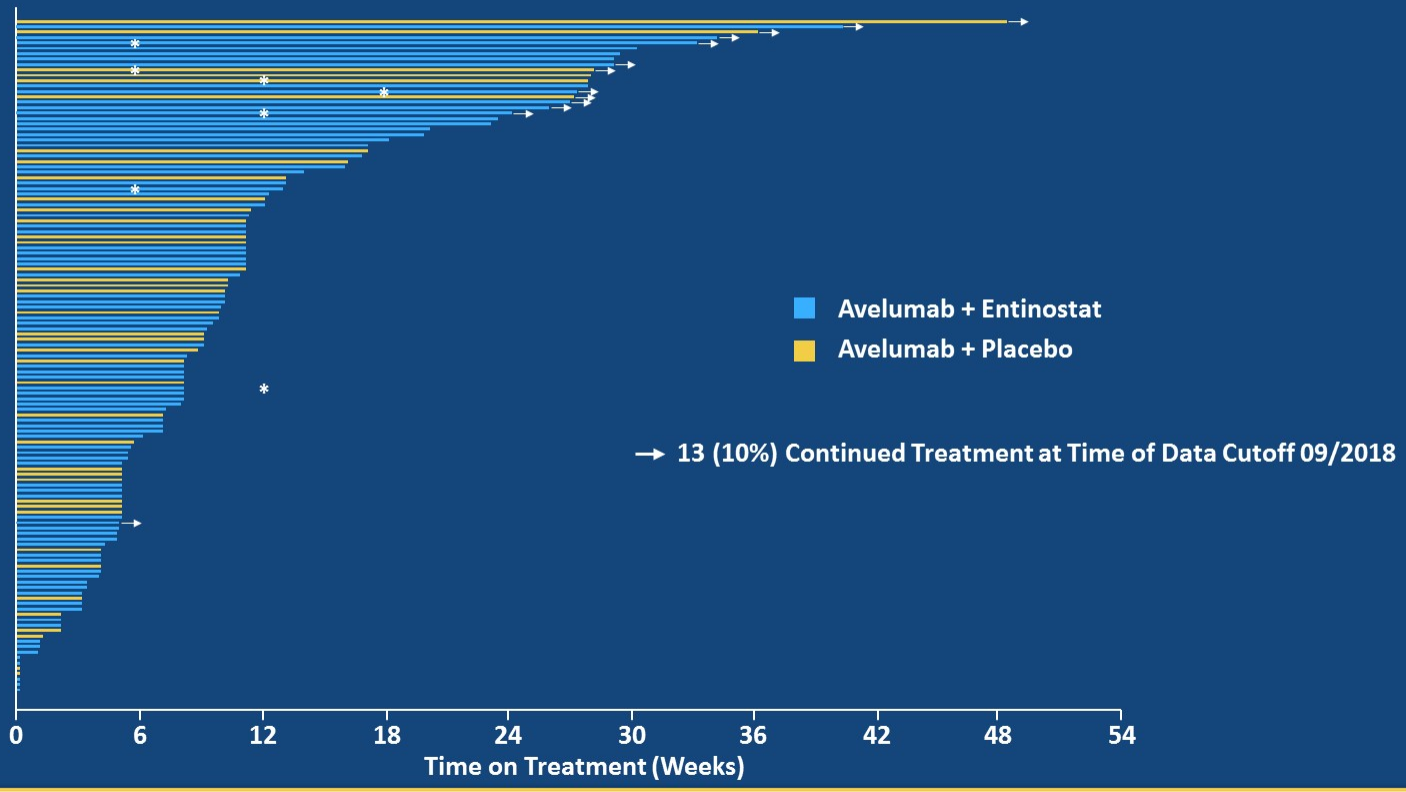
Select Patients With Durable Benefit



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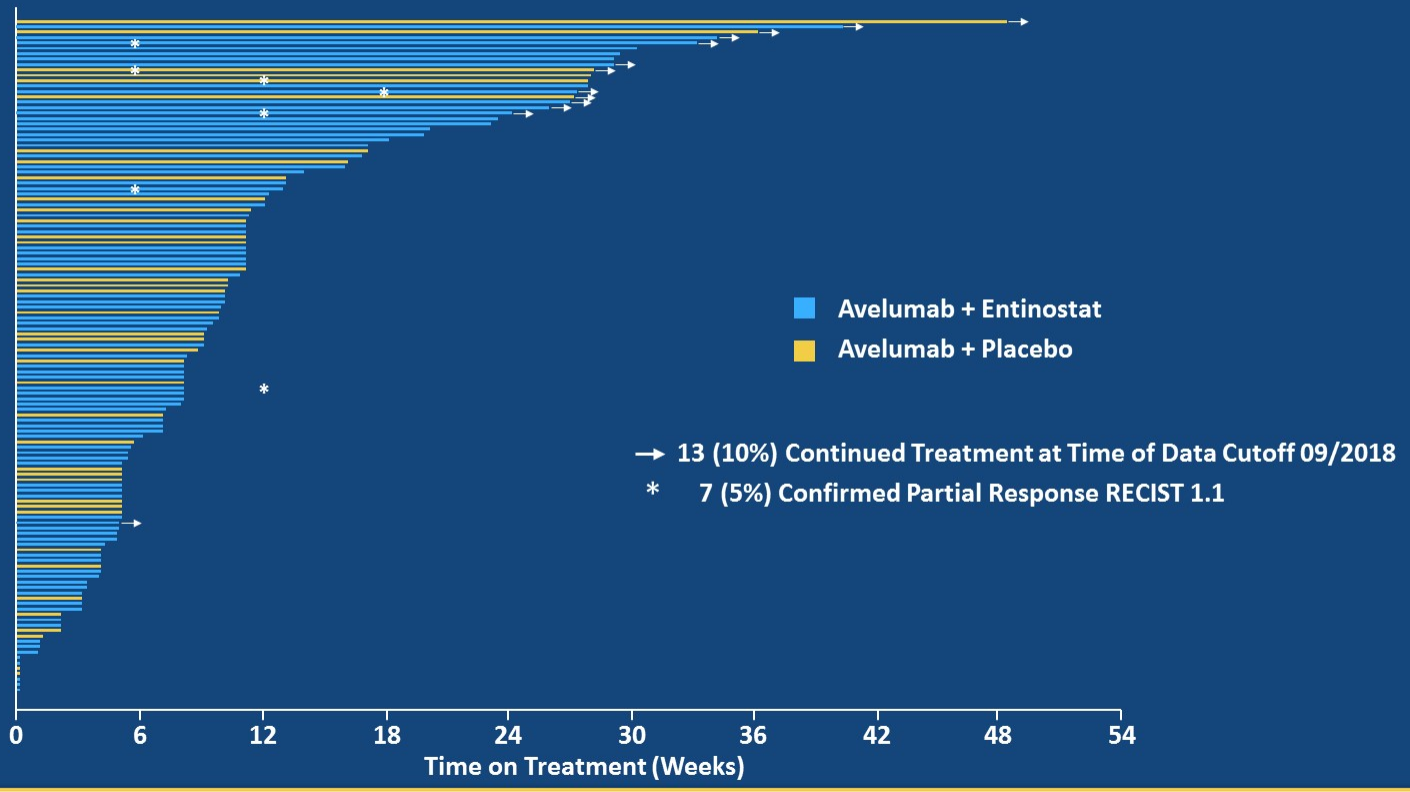
Select Patients With Durable Benefit



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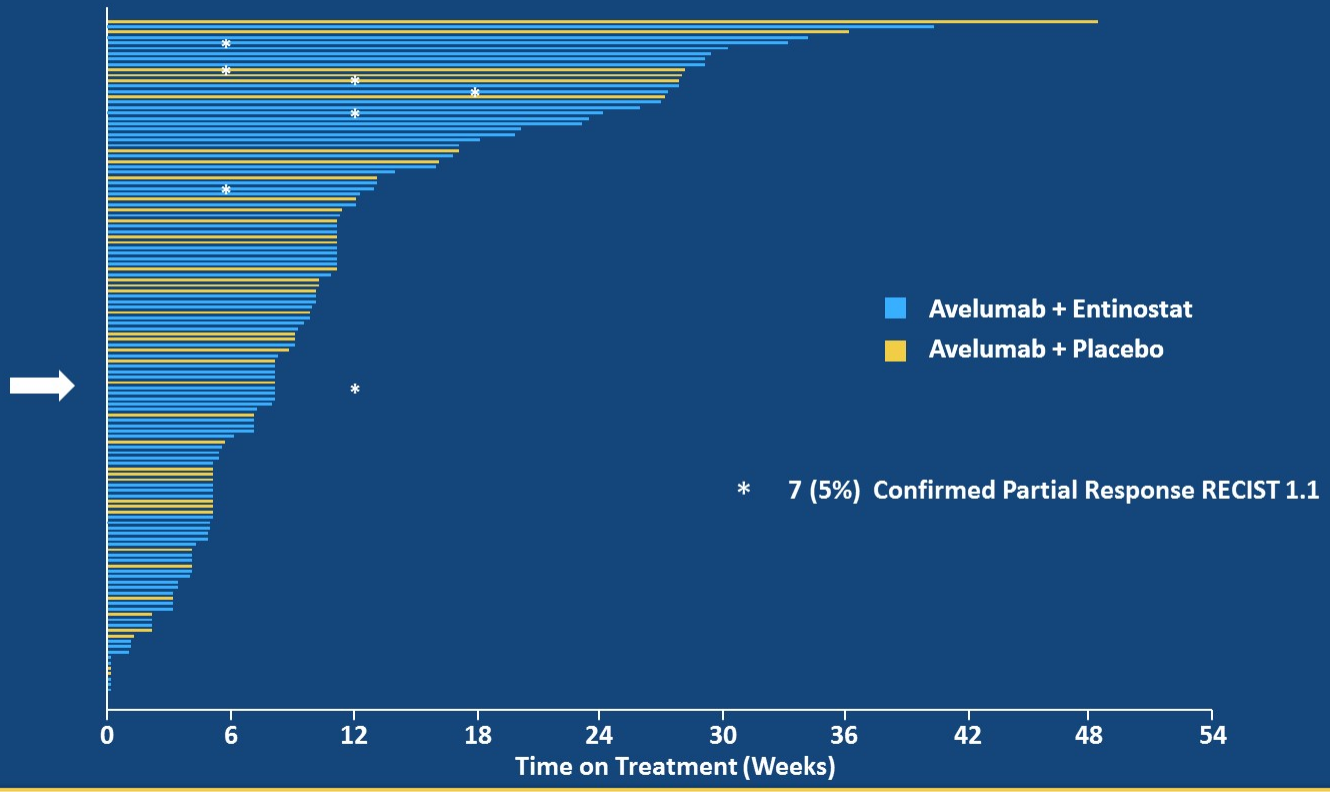

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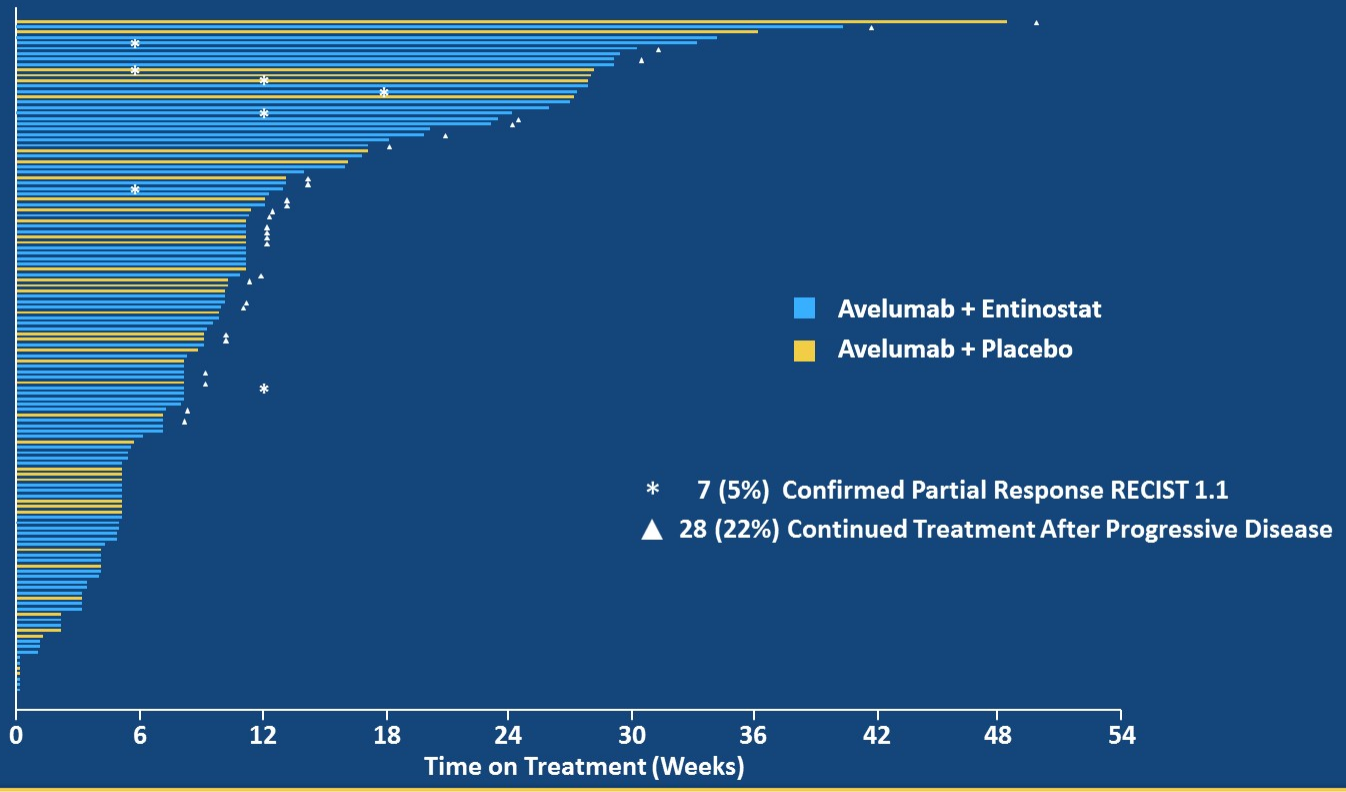

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Safety Summary

Patients with:	Avelumab + Placebo (N=40)	Avelumab + Entinostat (N=85)
	N (%)	N (%)
Any related TEAE	31 (77.5)	79 (92.9)
Related grade 3/4 TEAE	4 (10.0)	35 (41.2)
TEAE that led to any study drug being permanently discontinued	7 (17.5)	18 (21.2)
TEAE that led to any study treatment being dose modified	11 (27.5)	50 (58.8)
Deaths on study, all unrelated	4 (10.0)	6 (7.0)

TEAE- treatment emergent adverse event

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Safety Summary

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TEAE- treatment emergent adverse event

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Grade 3/4 Adverse Events

Grade 3/4 Related Adverse Events in > 1 Patients in Either Treatment Arm	Avelumab + Placebo (N=40)	Avelumab + Entinostat (N=85)
	N (%)	N (%)
Patients With At Least One Treatment Emergent Adverse Event	4 (10.0)	35 (41.2)
Neutropenia	0	11 (12.9)
Fatigue	1 (2.5)	8 (9.4)
Anemia	0	4 (4.7)
Hyponatremia	0	4 (4.7)
Nausea	1 (2.5)	2 (2.4)
Hypocalcemia	0	2 (2.4)
Thrombocytopenia	0	2 (2.4)
Dehydration	1 (2.5)	1 (1.2)
Infusion related reaction	1 (2.5)	1 (1.2)
Vomiting	1 (2.5)	1 (1.2)

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Immune-Related Adverse Events

Immune Related Adverse Events > 1 Patient All Grade	Avelumab + Placebo (N=40)		Avelumab + Entinostat (N=85)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
	N (%)	N (%)	N (%)	N (%)
Hypothyroidism	3 (7.5)	0	3 (3.5)	0
Pruritus	1 (2.5)	0	3 (3.5)	0
Colitis	0	0	3 (3.5)	1 (1.2)
Pneumonitis	0	0	3 (3.5)	0
Rash	1 (2.5)	0	2 (2.4)	0
Rash-maculo-papular	0	0	2 (2.4)	0

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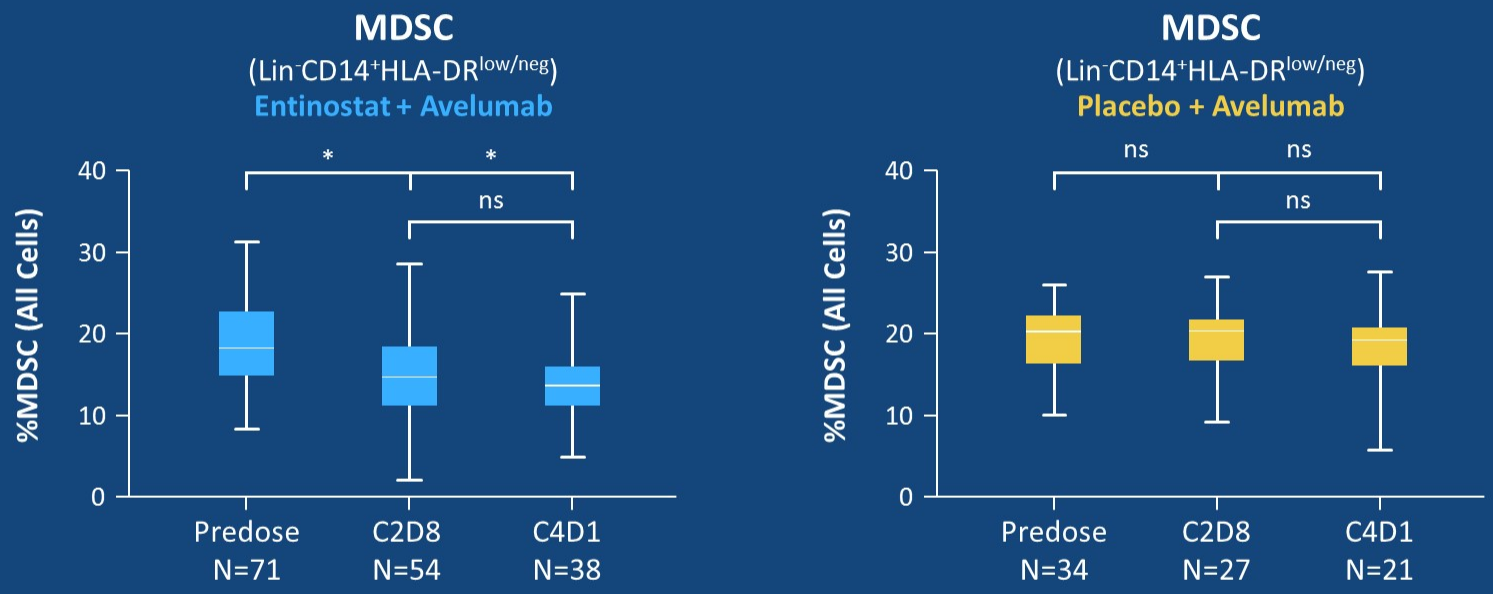
Entinostat Plus Avelumab Reduced Circulating MDSC



- Entinostat plus Avelumab resulted in a statistically significant decrease in MDSC at C2D8 and C4D1 relative to C1D1-Predose, p <0.01
- No significant changes of MDSC levels in Avelumab monotherapy treatment arm

MDSC, myeloid-derived suppressor cells; ns, not significant.

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Conclusions

- Despite good rationale and demonstrating suppression of myeloid derived suppressor cells, the addition of Entinostat did not improve outcomes over Avelumab alone for patients with heavily pretreated advanced ovarian cancer
- As with other immunotherapy studies in ovarian cancer, there are clearly patients who benefit
- Overall survival data remains immature and correlative studies are ongoing, we are eagerly awaiting further data which may help us to understand which patients with ovarian cancer benefit from immunotherapy

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Conclusions

- There was no new safety signal and the addition of Entinostat did not lead to an excess of immune-related adverse events
- Only approximately 20% of patients remained on therapy beyond RECIST 1.1 progression of disease
- This remains an area of huge unmet need, we enrolled 126 advanced ovarian cancer patients in 9 months

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Acknowledgments

- We thank the patients and their families
- Co-Investigators and study staff

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