Efficacy/safety of entinostat (ENT) and pembrolizumab (PEMBRO) in NSCLC patients previously treated with anti-PD-(L)1 therapy

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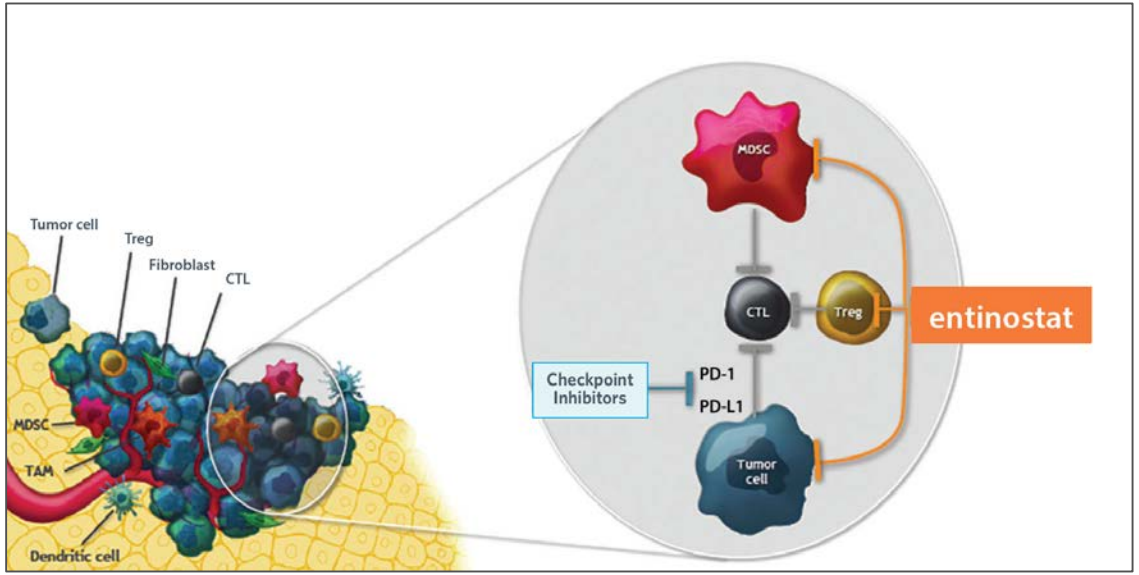
Treatment options are limited for patients with NSCLC whose disease has progressed on anti-PD-(L)1 therapy[1]

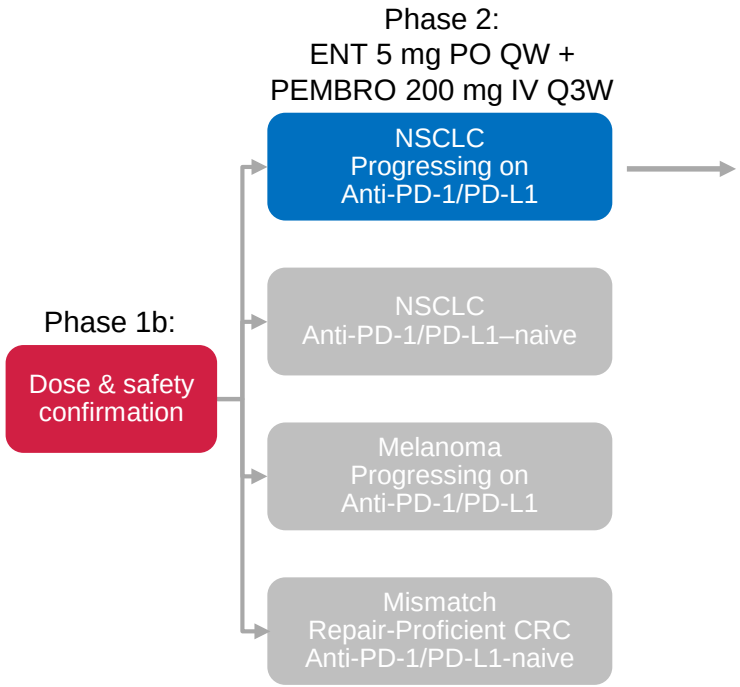
- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor[2]
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment[2]
- Synergy with anti-PD1 inhibition in preclinical models[2]
- Promising activity shown in combination with pembrolizumab in patients with melanoma and lung cancer[3,4]



NSCLC, non-small cell lung cancer.

1. Zimmer L, et al. *Eur J Cancer*. 2017;75:47-55. **2.** Orillion A, et al. *Clin Cancer Res*. 2017;23:5187-5201. **3.** Agarwala SS, et al. Presented at ASCO 2018. Abstract 9530. **4.** Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

ENCORE-601: Open-label study evaluating ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy



Inclusion Criteria:

- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on anti-PD(L1) treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status < 2
- Willingness to baseline and on-Tx biopsy and blood samples

Phase 2 Primary Endpoint

- ORR (irRECIST)

Phase 2 Secondary Endpoints

- PFS, OS, safety & tolerability

76 patients enrolled (72 efficacy evaluable*), last patient enrolled December 2017

- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

*4 patients were non-evaluable due to withdrawal of consent or discontinuations for administrative reasons prior to the first tumor assessment.

ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, entinostat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; QW, once a week; Q3W, every 3 weeks.

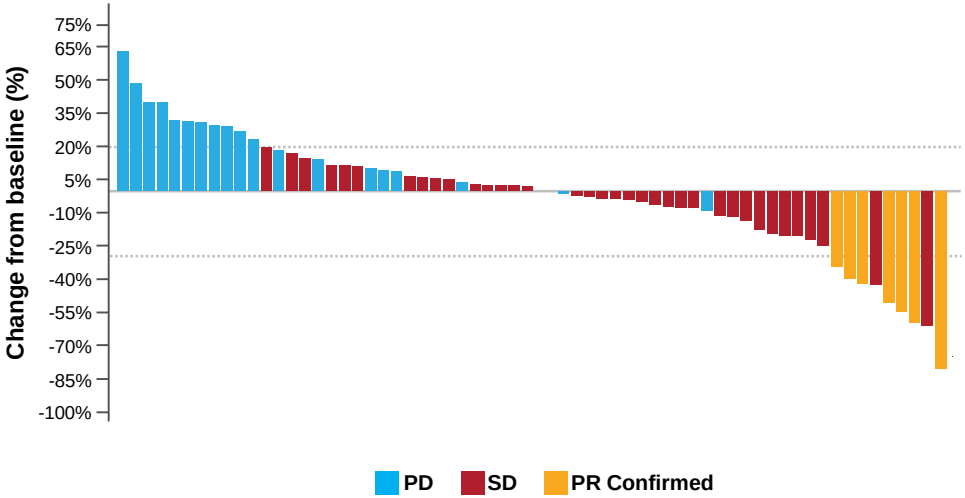
Patient baseline demographics and PD-(L)1 history

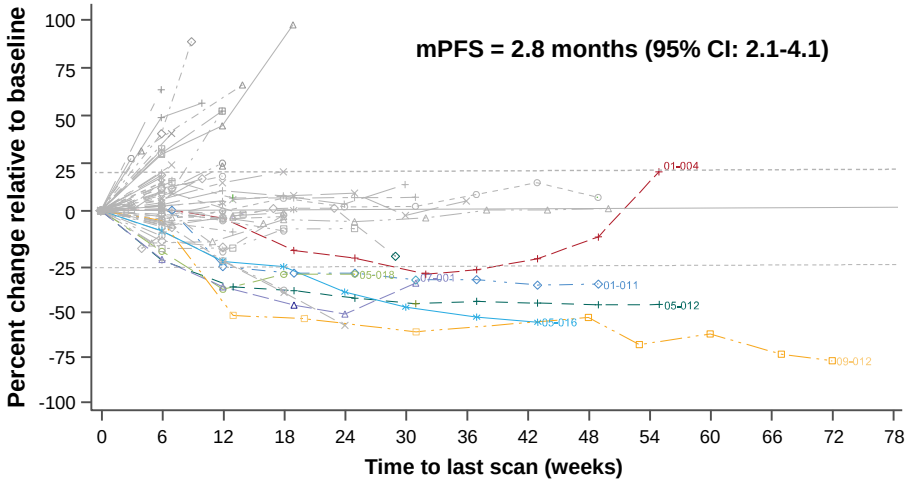
Demographics	N=76
Male, %	53%
Median age (range)	67 yrs (30-85)
ECOG Performance Status, %	
Grade 0 / Grade 1 / Missing	28% / 71% / 1%
Current/Former Smoker	88%
PD-L1 Expression (N=60)	
≥50%	15%
1%-49%	43%
<1%	42%
Data not available for 16 patients	

PD-(L)1 history	N=76
Best Response on Prior Anti-PD-(L)1, %	
Complete Response	1%
Partial Response	7%
Stable Disease	45%
Disease Progression	37%
Unknown	11%
Duration on Prior Anti-PD-(L)1	
Median	5.3 months
Time from Prior Anti-PD-(L)1 to Study Therapy	
Median	2.2 months
PD-(L)1 as immediate prior therapy, n (%)	47 (62%)

ECOG, Eastern Cooperative Oncology Group.

Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy



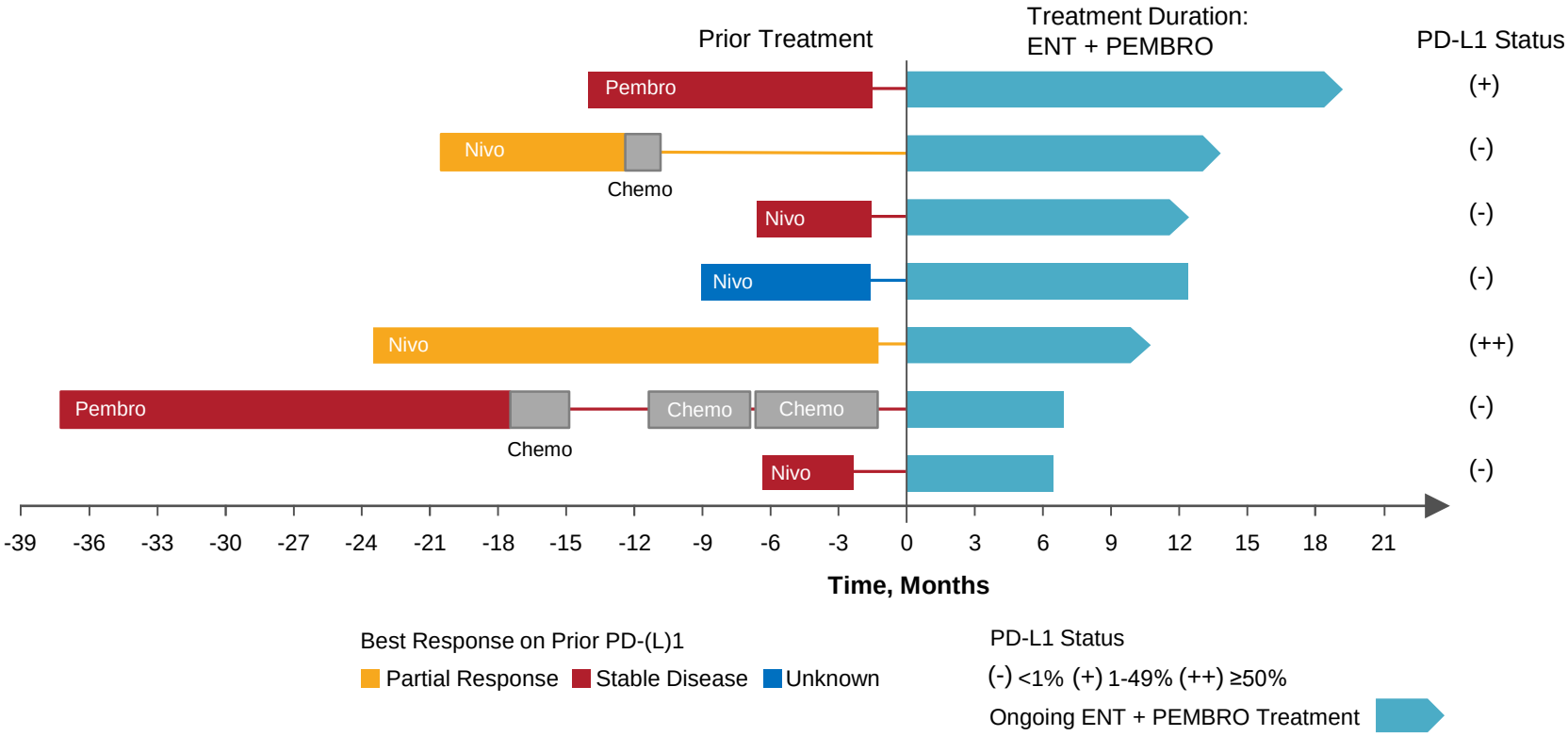


- Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)
  - Prespecified ORR target not reached; median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- Experience similar in PD1-pretreated melanoma (ORR = 18%)[1]

CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

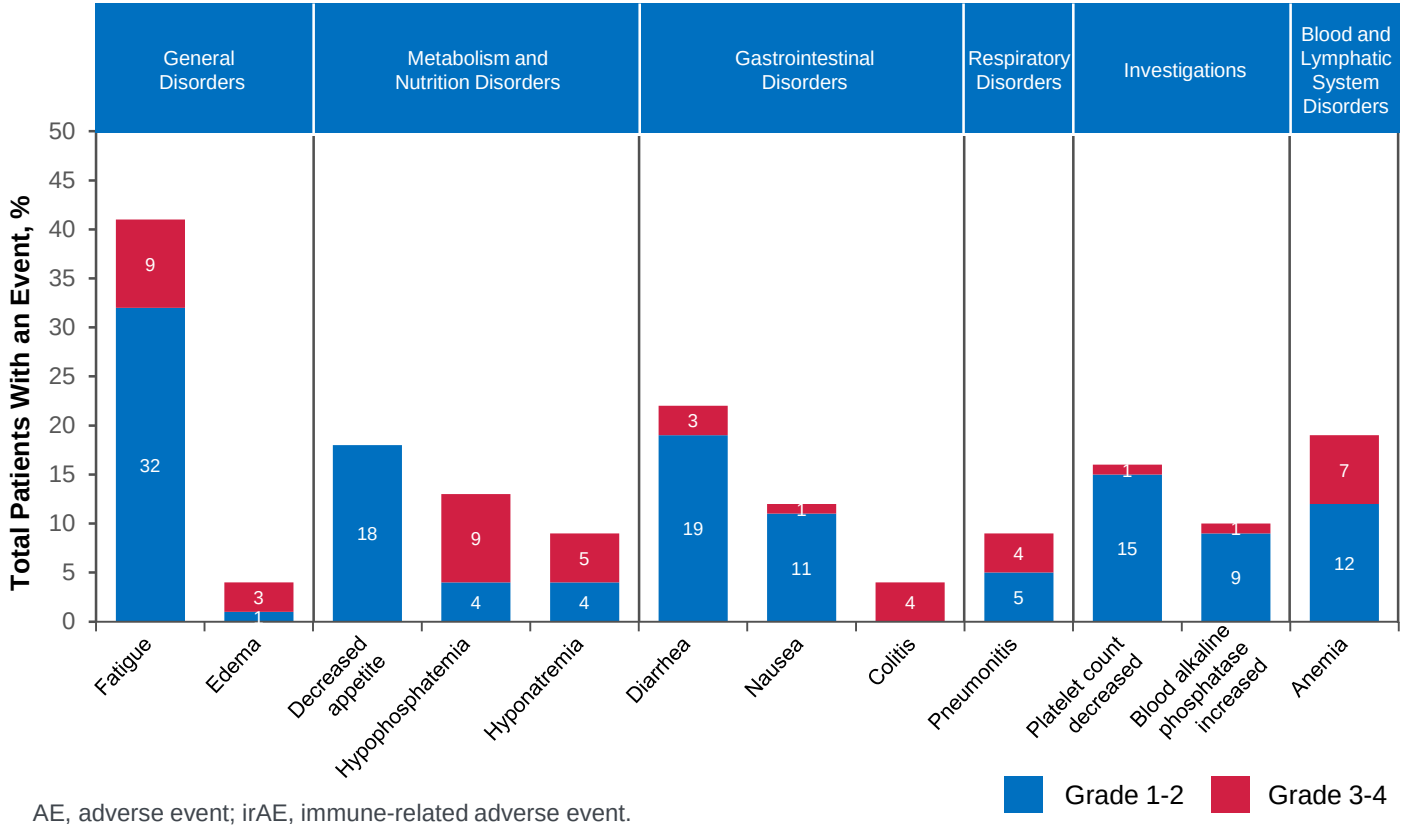
1. Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

Responses observed regardless of prior treatment history or PD-L1 status



Chemo, chemotherapy; ENT, entinostat; Nivo, nivolumab; PEMBRO, pembrolizumab.

Treatment-related adverse events occurring in ≥ 10% of patients for All Grade or ≥ 2 patients for Grade 3/4



- 7 patients (9.2%) experienced Grade 3/4 related irAEs
  - pneumonitis, 3; colitis, 3; hyperthyroidism, 1
- 23 patients (30.3%) experienced other Grade 3/4 related AEs
- 11 patients (14%) discontinued a study drug due to a treatment-related AE
- 13 patients (17%) required a dose reduction of study drug, of which 11 remained on study

AE, adverse event; irAE, immune-related adverse event.

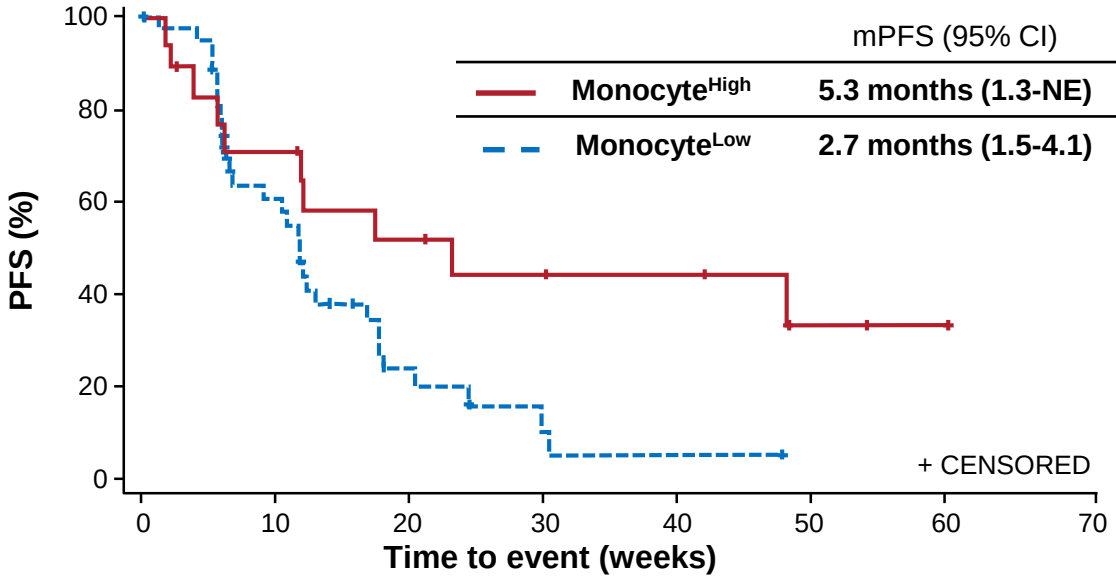
Biomarkers: Identifying factors that may predict response to ENT + PEMBRO

Extensive analysis of baseline demographic features, blood, tissue

- No significant association of response with
  - Smoking status
  - PD-L1 expression
  - Prior PD-(L)1 treatment history
  - Other baseline characteristics*
- Peripheral monocyte frequency as a predictor of anti-tumor immune response has been previously shown[1]
  - An association of monocyte levels with response was observed and further explored

*Age, sex, ECOG and visceral involvement.
ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; PEMBRO, pembrolizumab.
1. Krieg C, et al. *Nat Med*. 2018;24:144-153.

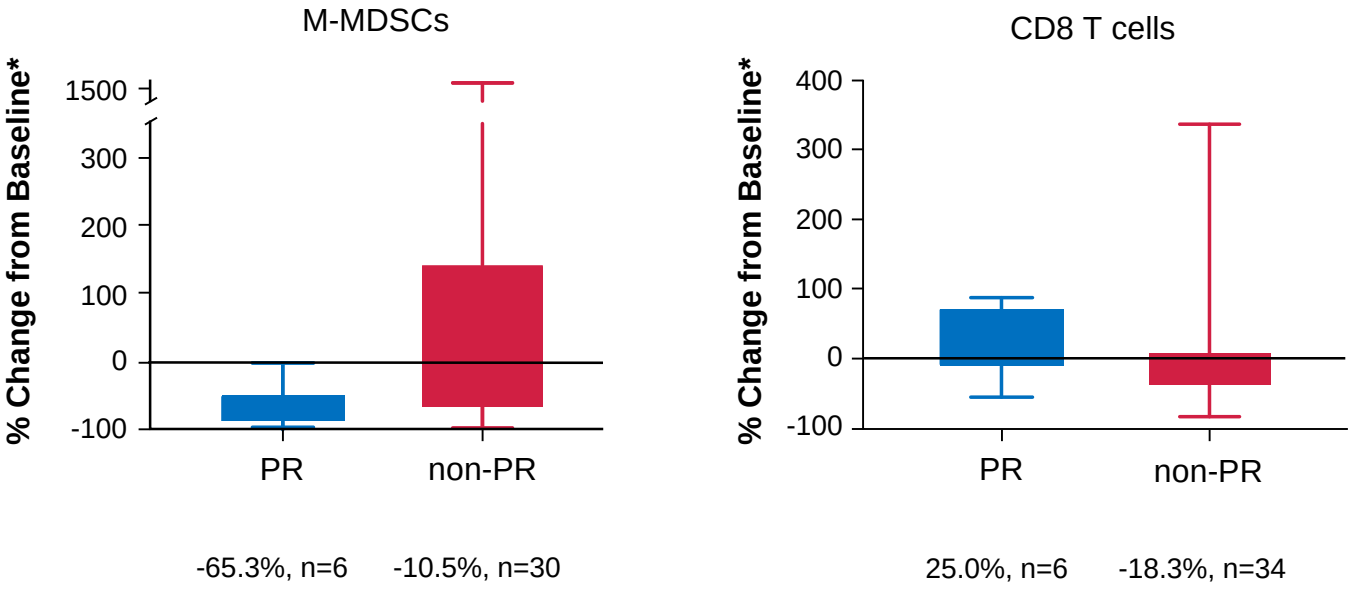
Higher baseline levels of peripheral CD14+CD16-HLA-DR^{HI} classical monocytes are associated with ORR and PFS benefits



- 26% of patients in the monocyte high group (5 of 19) are ongoing and 2% of patients in the monocyte low group (1 of 46) are ongoing.

*High / low defined by midpoint (13.1% of live PBMCs / ml) of range of peripheral monocyte values from available samples.
CI, confidence interval; NE, not estimable; ORR, objective response rate, mPFS, median progression-free survival.

Reduced circulating MDSCs (CD14^{+}HLA-DR$^{neg/low}$) associated with clinical responses



- Circulating MDSC cell reduction consistent with hypothesized entinostat MOA
- Trend in increased CD8+ T cells observed in responding patients

*% change from baseline was measured at C2D15 (5 wks).
MDSCs, myeloid-derived suppressor cells.

Conclusions: ENT + PEMBRO in PD-(L)1 Pre-treated NSCLC

- ENT + PEMBRO demonstrated anti-tumor activity (ORR 10%) in patients with NSCLC who have progressed on prior PD-(L)1 blockade
  - Prespecified ORR target not reached; may represent clinically meaningful activity
  - An additional 50% of patients achieved disease stabilization
- Most patients tolerated the therapy well
- Responses to ENT+ PEMBRO were independent of baseline PD-L1 expression
- Exploratory biomarker analyses identified baseline levels of peripheral classical monocytes as potential predictors of clinical benefit
- Future trial designs prospectively incorporating biomarkers for patient selection are under discussion

ENT, entinostat; ORR, objective response rate; NSCLC, non-small cell lung cancer; PEMBRO, pembrolizumab.

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