Identification of Gene Signatures Associated With Response in a Phase 2 Trial of Entinostat (ENT) Plus Pembrolizumab (PEMBRO) in Non-Small Cell Lung Cancer (NSCLC) Patients Whose Disease Has Progressed on or After Anti-PD-(L)1 Therapy

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Disclosures

Dr. Ramalingam has served on scientific advisory board meetings for AbbVie, Amgen, Astra Zeneca, Bristol-Myers Squibb, Genentech/Roche, Loxo, Merck, Nektar, and Takeda

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Immune Checkpoint Inhibition in NSCLC

PD-1/PD-L1 inhibitors are approved for patients with metastatic NSCLC

- First-line therapy (monotherapy)
- First-line therapy (combination with chemotherapy)
- Second-line therapy (monotherapy)

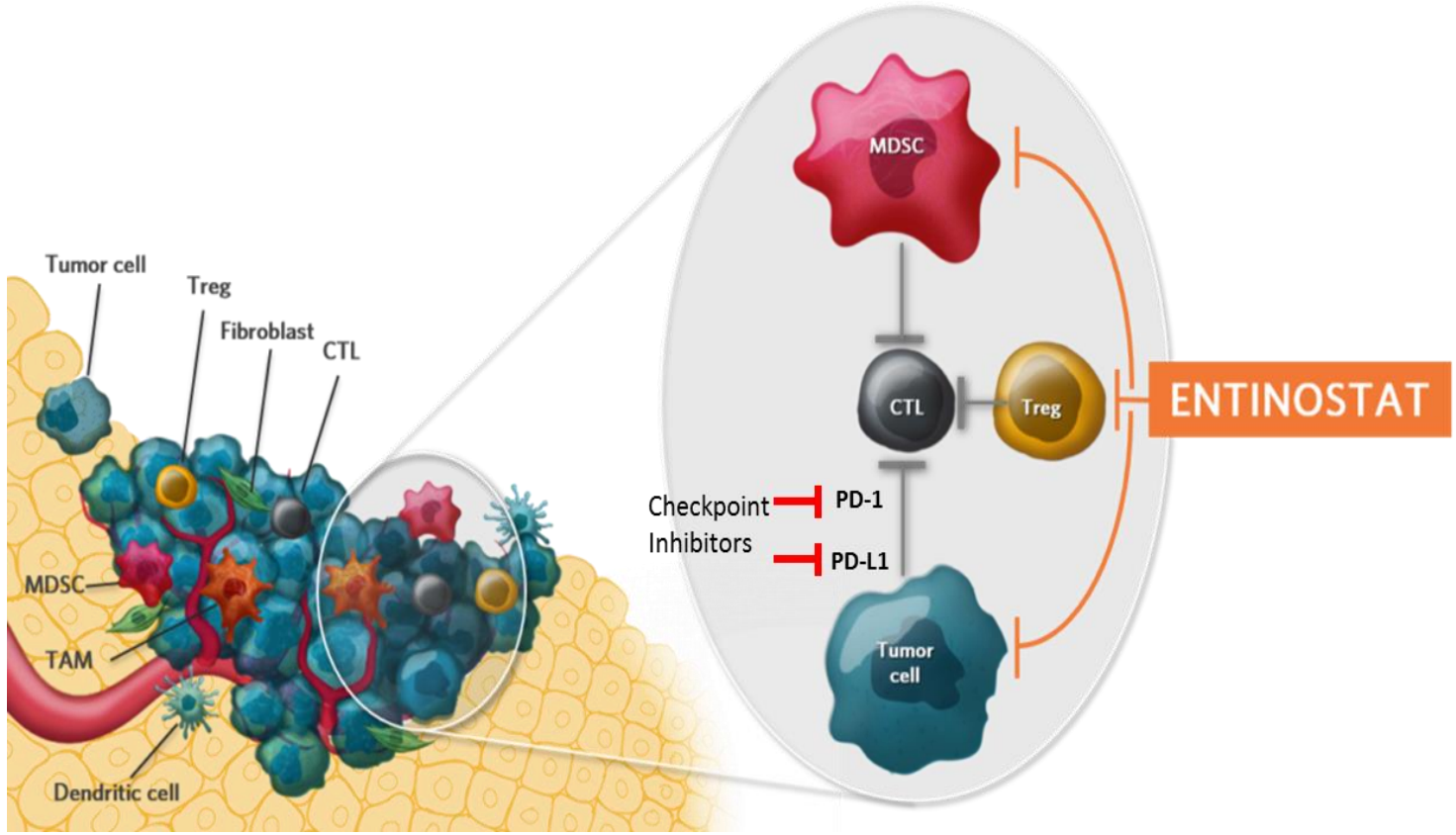
There is an unmet need for novel options for patients who have disease progression after checkpoint inhibition

Rational combination approaches are under extensive evaluation

NSCLC, non-small cell lung cancer.

Proposed Mechanism(s) of Action of Entinostat to Enhance IO Approaches

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT reduces MDSC and Treg number & function
- ENT induces pro-inflammatory cascade in TME
- ENT enhances antigen presentation
- Additional beneficial effects on Teff & NK cells
- Synergy with anti-PD1 inhibition in preclinical models



CTL, cytotoxic T lymphocytes; IO, immunotherapy; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; Teff, effector T-cell; TME, tumor microenvironment; Treg, regulatory T-cell; NK cells, natural killer cells.

Orillion A, et al. *Clin Cancer Res*. 2017;23(17):5187-5201.

ENCORE-601 / KEYNOTE 142 Study Overview

Phase 2 open label study assessing ENT 5 mg PO QW + PEMBRO 200 mg IV Q3W in patients with NSCLC who had progressed on/after anti-PD-1/PD-L1 therapy

Inclusion Criteria

- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on/after anti-PD-(L)1 treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status <2

Primary Endpoint

- ORR (irRECIST) by investigator assessment

Secondary Endpoints

- CBR, 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.

Patient Baseline Demographics and PD-(L)1 History

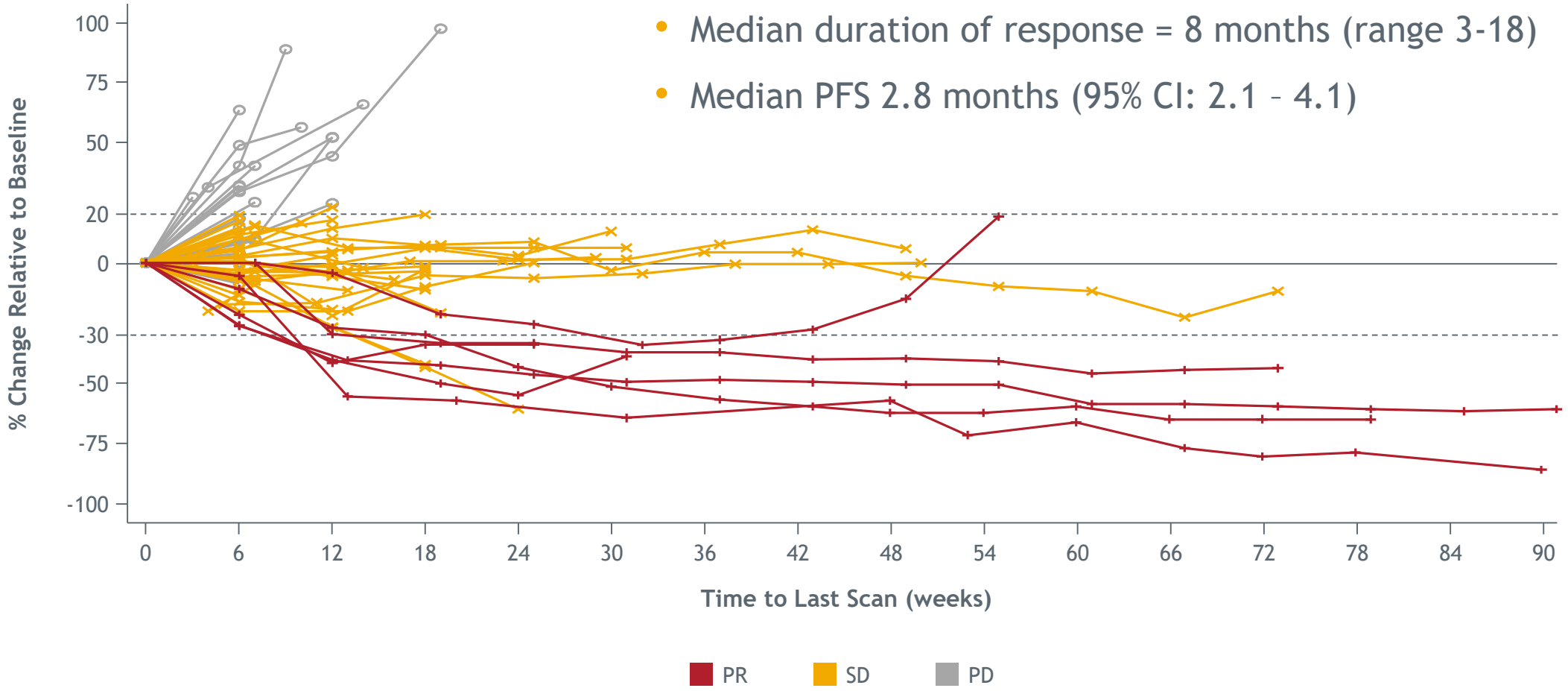
Demographics	N=72
Male, n (%)	38 (53%)
Median age (range)	66 yrs (30-85)
ECOG PS, n (%)	
0 / 1 / Missing	19 (26%) / 52 (72%) / 1 (1%)
Current/fmr smoker, n (%)	64 (89%)
PD-L1 expression, n (%)	
≥50%	9 (13%)
1%-49%	28 (39%)
<1%	24 (33%)
Not available	11 (15%)

PD-(L)1 history	N=72
Best response on prior anti-PD-(L)1, n (%)	
Complete Response	1 (1%)
Partial Response	5 (7%)
Stable Disease	41 (57%)
Disease Progression	21 (29%)
Unknown	4 (6%)
Duration on latest anti-PD-(L)1	
Median	5.6 months
Time from prior anti-PD-(L)1 to study therapy	
Median	2.3 months
PD-(L)1 as immediate prior therapy, n (%)	46 (64%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Durable Responses Were Observed in Patients Who Experienced Progression on Prior Anti-PD(L)1 Therapy

- Overall Response Rate* = 10% (95% CI: 4% - 19%)
  - 50% SD
- Median duration of response = 8 months (range 3-18)
- Median PFS 2.8 months (95% CI: 2.1 – 4.1)



* irRECIST by investigator assessment.

Tissue/Blood Sampling Overview

	Cycle 1, Day 1	Cycle 2, Day 1	Cycle 2, Day 15
Tumor Biopsy	X		
Blood Sample	X	X	X

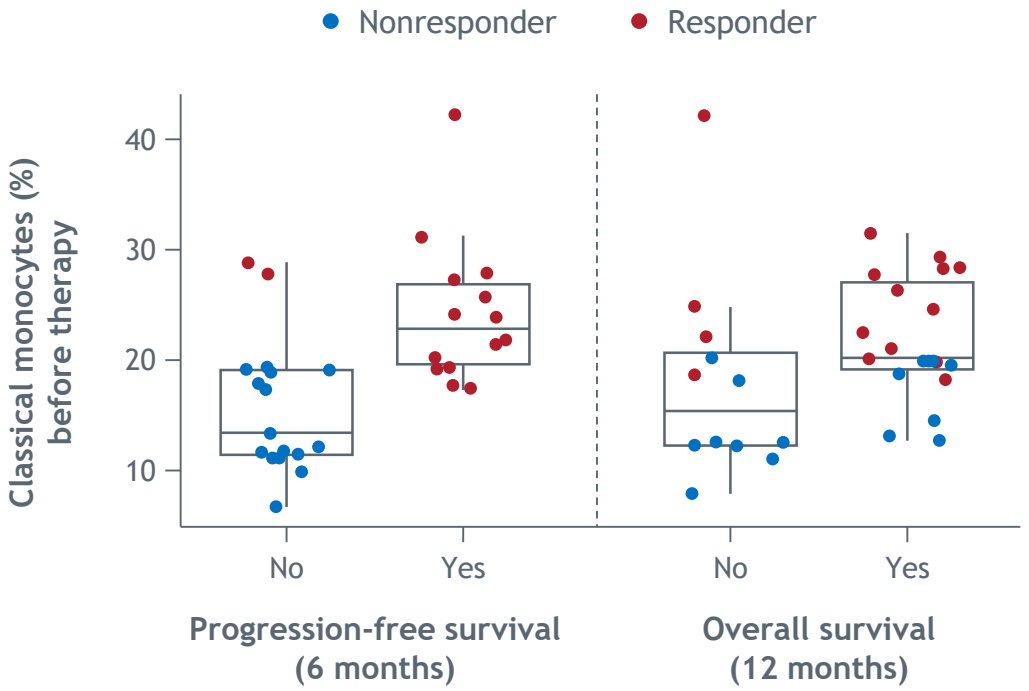
- Cycle 1, Day 1 (pretreatment) monocyte data available for 65/72 (90%) of patients
- Cycle 1, Day 1 (pretreatment) gene expression available for 43/72 (60%) of patients

Cycle = 3 weeks

Biomarkers: Identifying Factors That May Predict Response to ENT + PEMBRO

- 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
  - An association of monocyte levels with response was observed and further explored

High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy

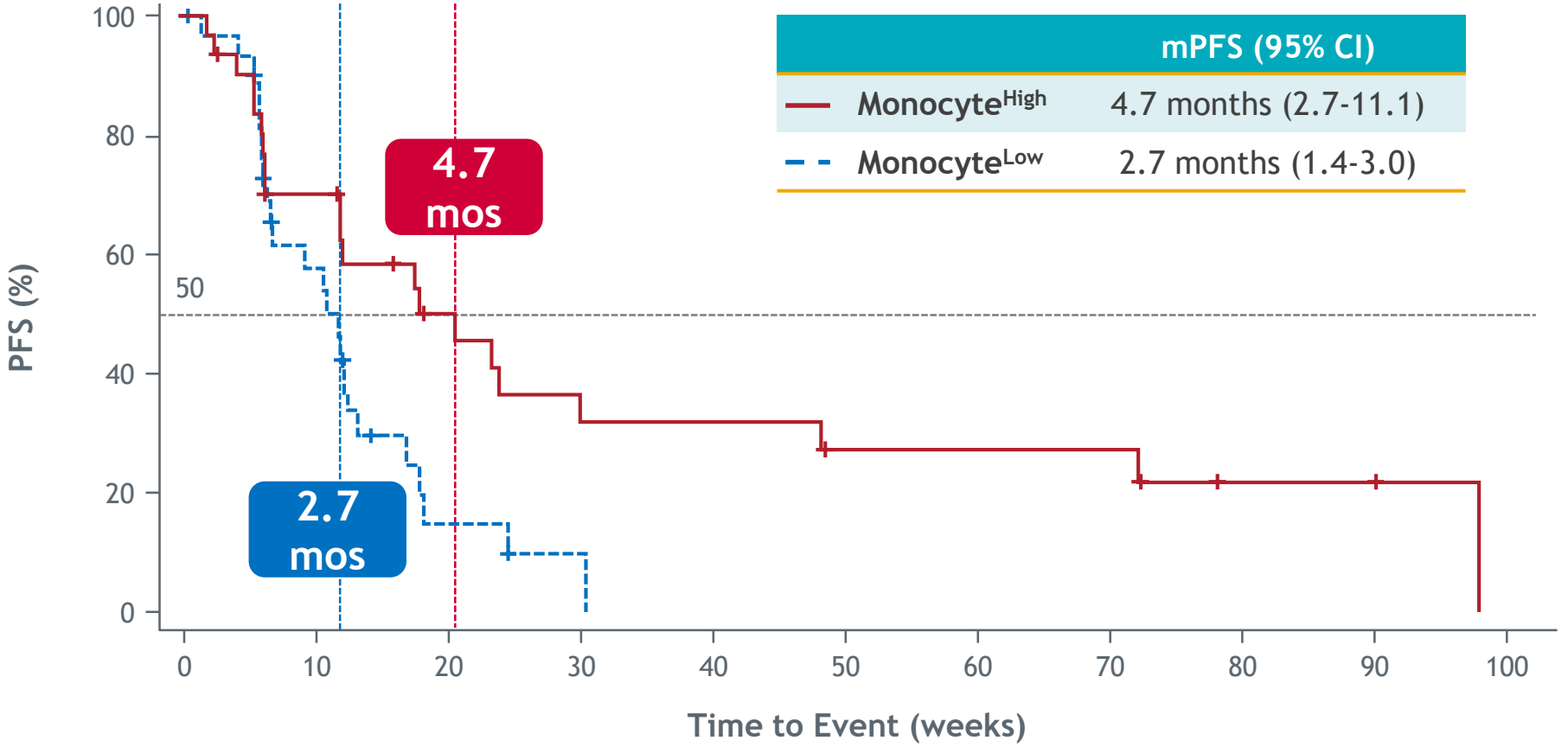


A key finding of Krieg et al was to associate baseline levels of CD14+CD16-HLA-DRHi classical monocytes with clinical benefit to nivolumab in melanoma patients

* Age, sex, ECOG and visceral involvement.

Krieg C, et al. *Nat Med*. 2018;24:144-153.

Baseline Peripheral Classical Monocytes May Predict Clinical Benefit in NSCLC Cohort



	mPFS (95% CI)
Monocyte^{High}	4.7 months (2.7-11.1)
Monocyte^{Low}	2.7 months (1.4-3.0)

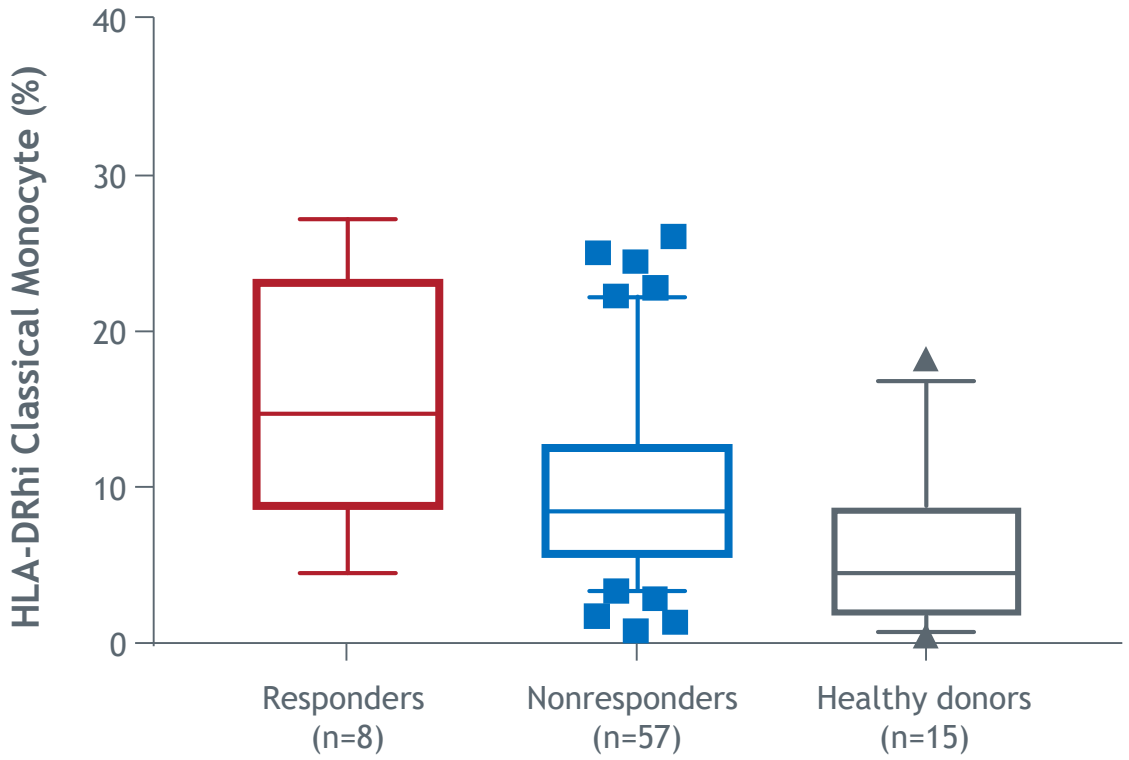
High*	33	19	11	7	7	5	5	5	2	2	0
Low*	32	15	3	1	0						

Patients with high levels of monocyte at baseline experienced a significantly longer PFS benefit from ENT + PEMBRO

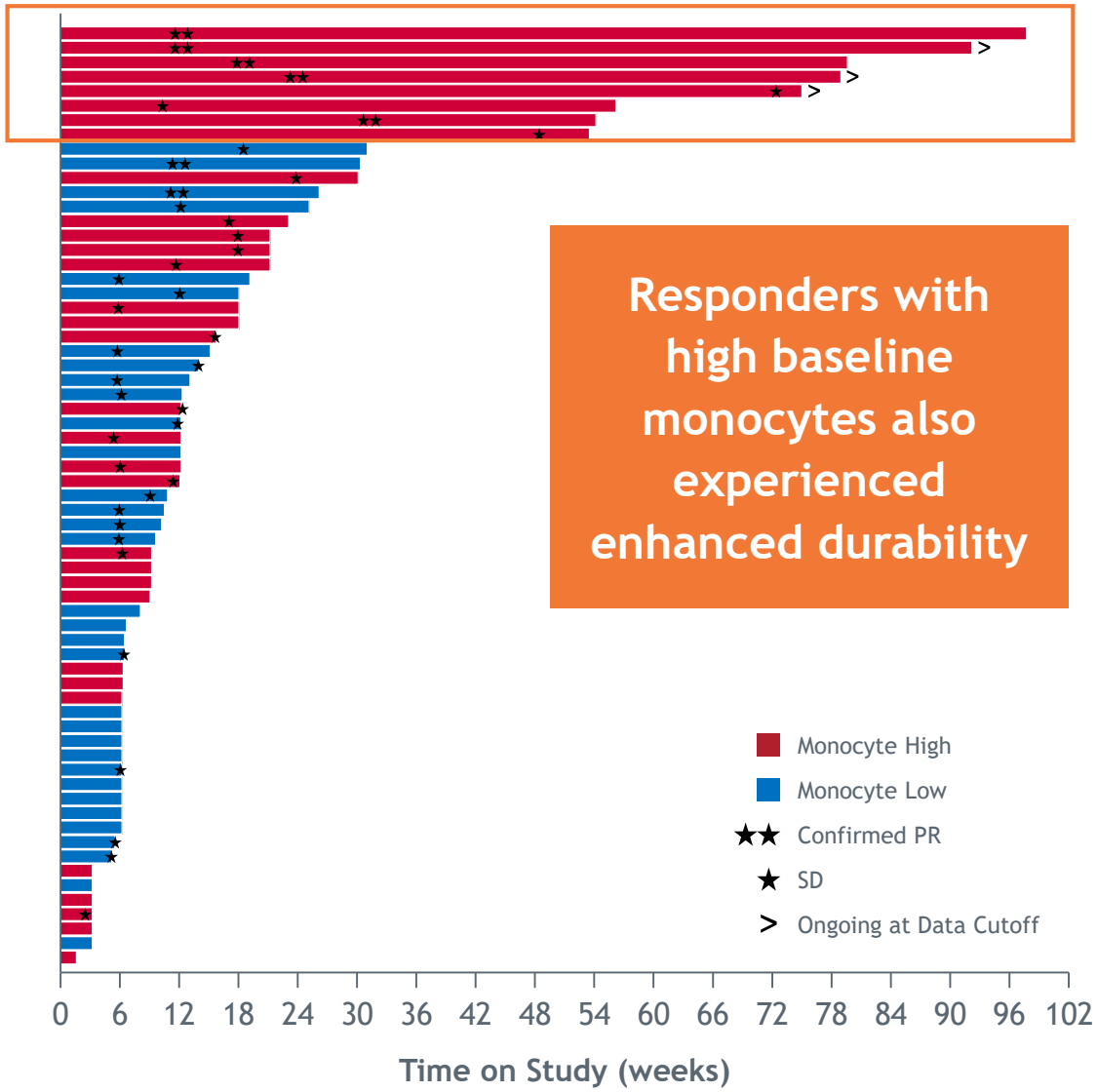
* High / low defined by the median (9% of live PBMCs/ml) of peripheral monocyte values from available samples (n = 65).
CI, confidence interval; PBMCs, peripheral blood mononuclear cells; mPFS, median progression-free survival.

Majority of Responders Had High Monocytes at Baseline

Pretreatment classical monocytes (NSCLC)



The percentage of HLA-DRhi classical monocytes (CD14+CD16-HLA-DRhi in PBMC) before start of the treatment



Responders with high baseline monocytes also experienced enhanced durability

PBMCs, peripheral blood mononuclear cells; PR, partial response; SD, stable disease.

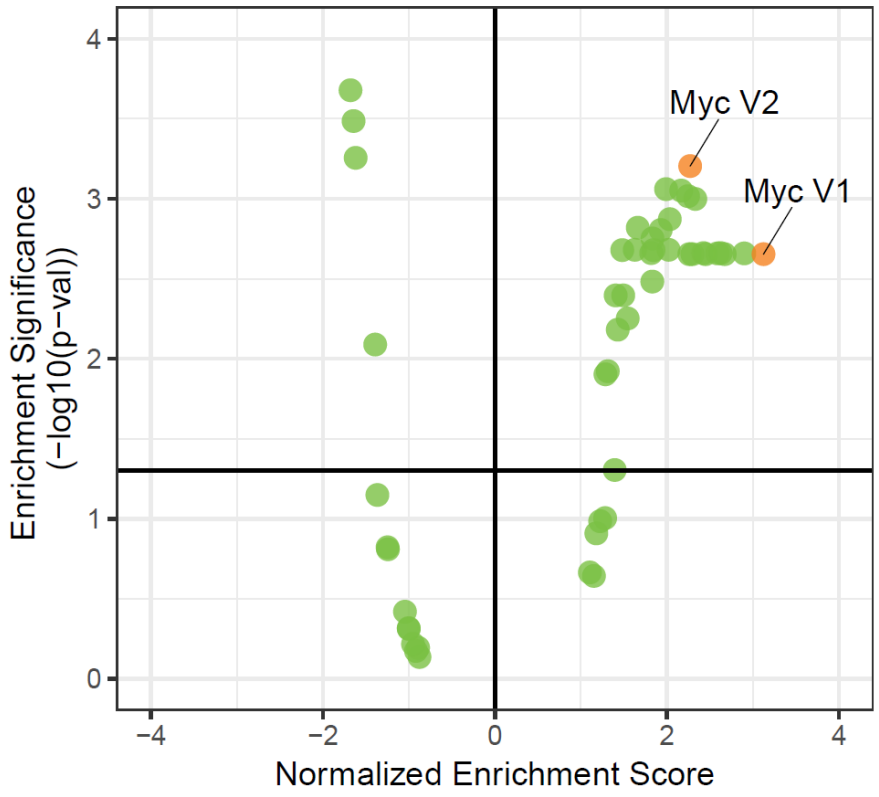
Evaluation of Baseline Tumor Tissue

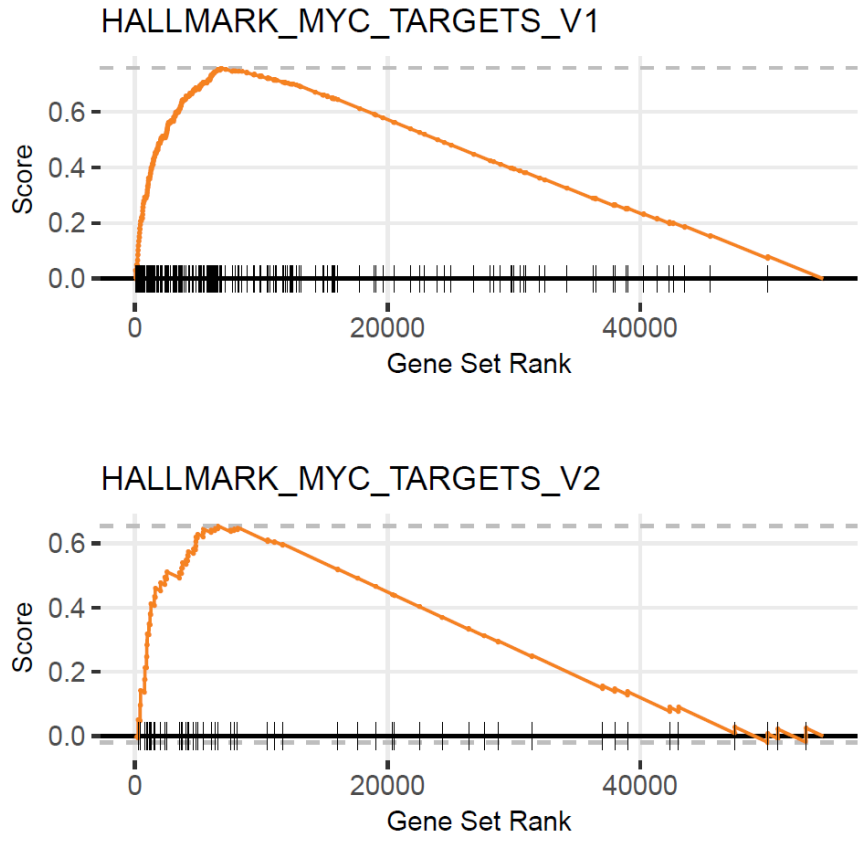
- Gene expression analyses of pre-treatment tumor biopsies to identify signatures associated with response
- RNAseq / Nanostring available for ~60% of patients
- Geneset enrichment analysis identifying pathways of interest including signaling pathways tied to entinostat MOA

MOA, mechanism of action; RNAseq, RNA sequencing.

MYC Signaling Enriched in Responders

Enrichment of MYC Hallmark genesets in pre-treatment tumors from anti-PD-1 pretreated NSCLC patients responding to pembrolizumab plus entinostat





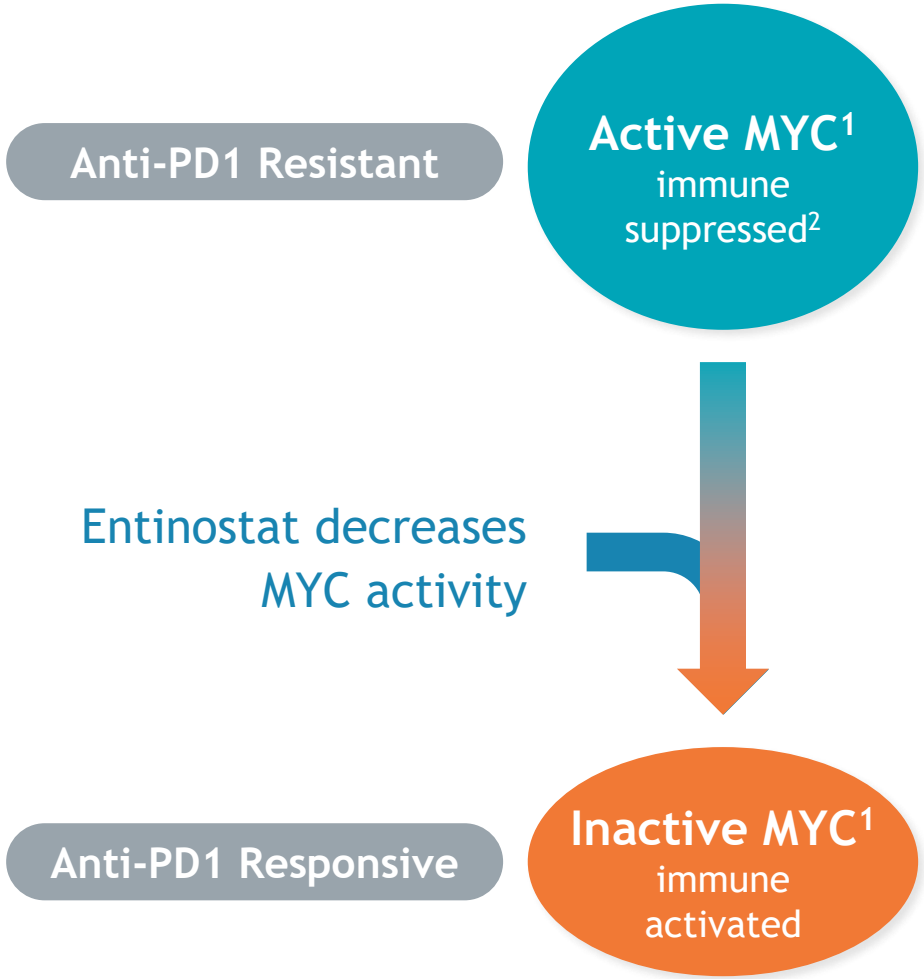
Gene Expression Analysis on Tumor Biopsies Identified High Baseline MYC Activity in ENCORE-601 Responders

High MYC activity leads to PD-(L)1 resistance and immune suppressed TME through:[1,2]

- Increased PD-L1 expression
- Decreased Type I IFN
- Exclusion of lymphocytes

Entinostat known to decrease MYC activity[3-6]

ENCORE-601 responders found to have high MYC activity prior to treatment[7]



IFN, interferon; TME, tumor microenvironment.

1. Topper MJ, et al. *Cell*. 2017;171(6):1284-1300. 2. Kortlever RM, et al. *Cell*. 2017;171(6)1301-1315. 3. Simmons JK et al. *Mol Cancer Ther*. 2017;16(9):2008-2021. 4. Nebbioso A, et al. *Clin Cancer Res*. 2017;23(10):2542-2555. 5. Merino VF, et al. *Breast Cancer Res*. 2018;20(1):145. 6. Tanioka et al. *Genome Med*. 2018;10(1):86. 7. Syndax Pharmaceuticals, Inc. Unpublished results.

Conclusions

- ENT + PEMBRO demonstrated durable antitumor activity (ORR 10%) in patients with NSCLC who have progressed on prior PD-(L)1 blockade
- Exploratory biomarker analyses identified baseline levels of peripheral classical monocytes as potential predictors of clinical benefit
  - Patients with high levels of monocyte at baseline experienced a longer PFS benefit
- Gene expression analysis on tumor biopsies identified high baseline MYC activity in responders
- Future trial designs should prospectively incorporate biomarkers for patient selection

Acknowledgments

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