Efficacy and Safety of Entinostat (ENT) and Pembrolizumab (PEMBRO) in Patients With Melanoma Previously Treated With Anti-PD-1 Therapy

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Relevant Disclosures

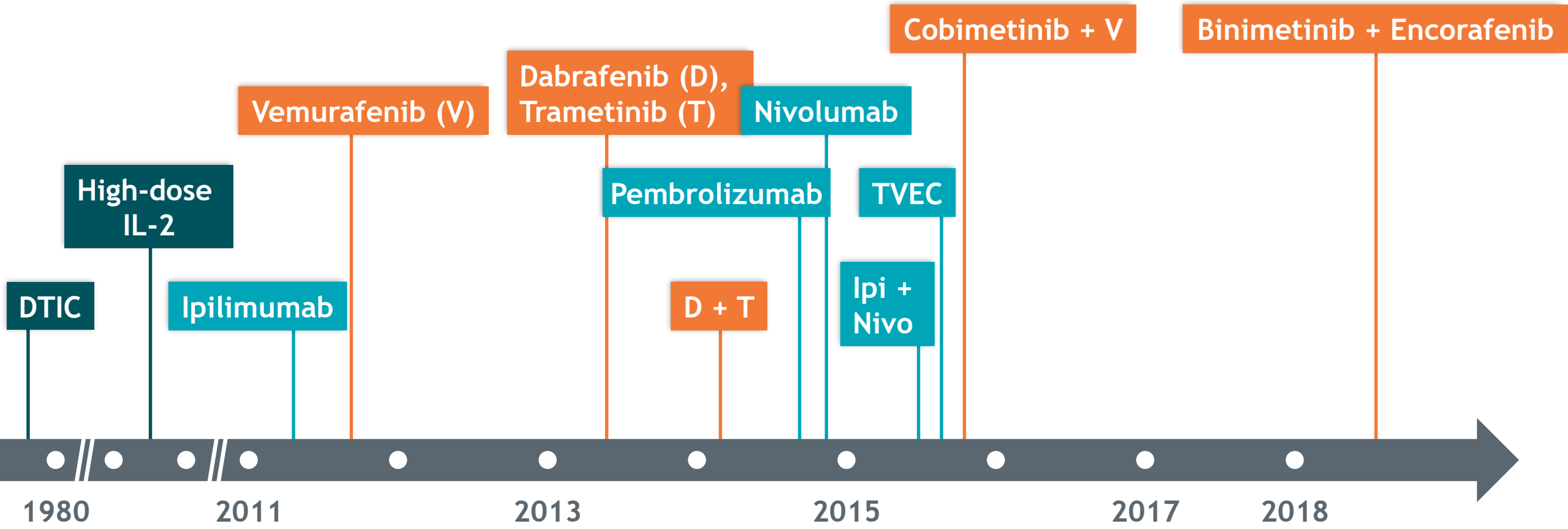
Advisory Board/Consulting:

- Novartis
- Amgen
- Merck
- Array
- Syndax
- Replimune
- Bristol-Myers Squibb

Research Sponsorship:

- Amgen
- Merck

Advanced Melanoma Treatment Landscape 2019



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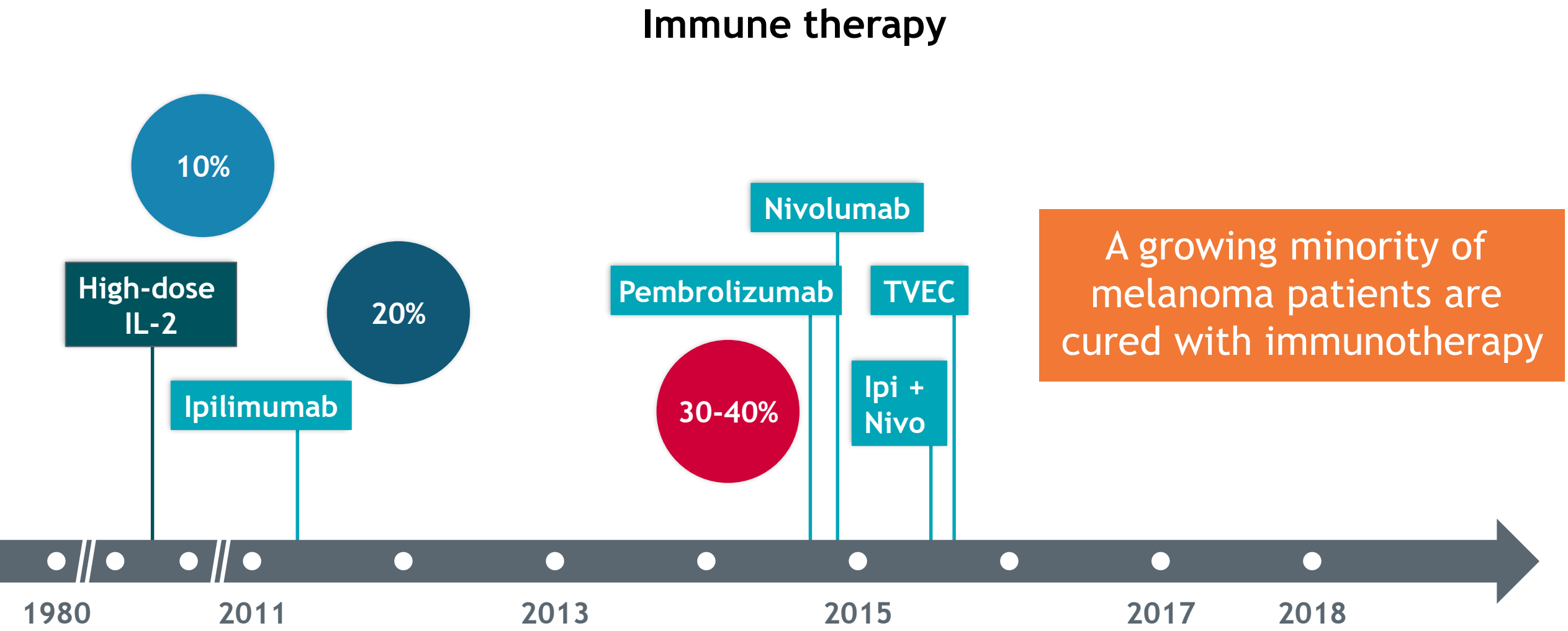
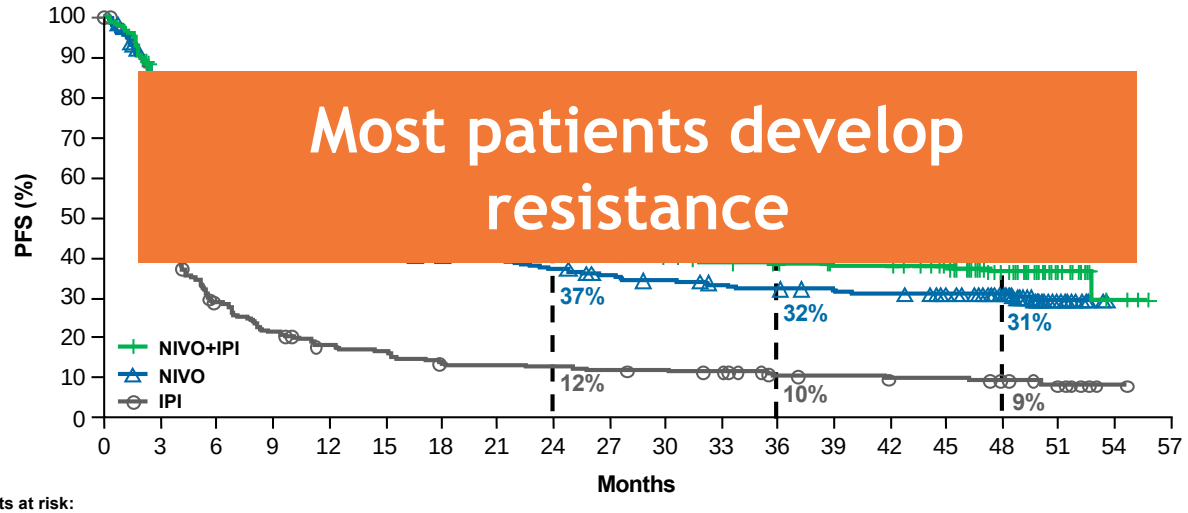


A growing minority of melanoma patients are cured with immunotherapy

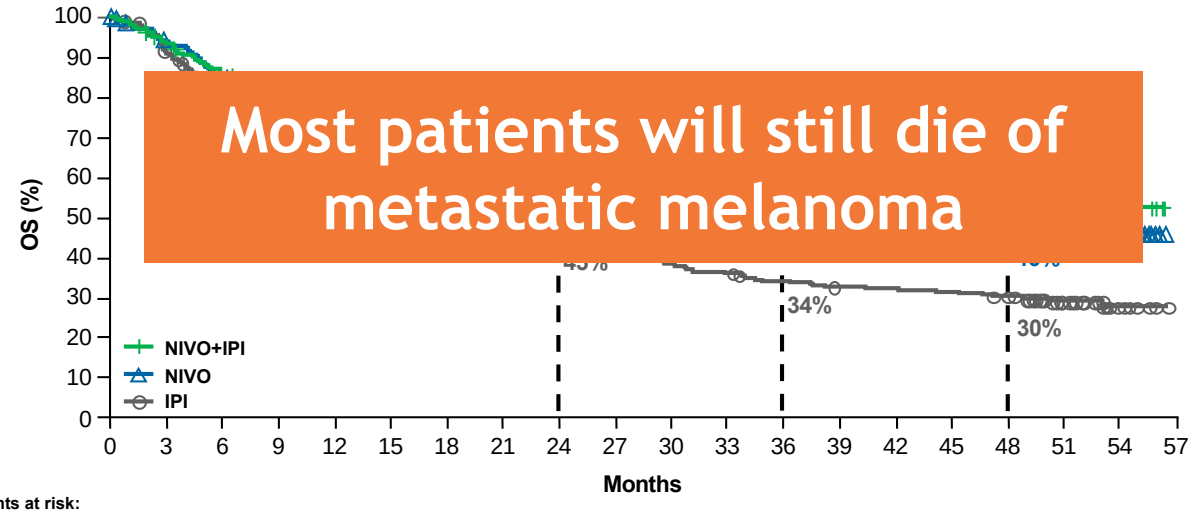
And Yet…



Most patients develop resistance

Patients at risk:

NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0



Most patients will still die of metastatic melanoma

Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

Hodi et al. ESMO 2018; Hodi FS, et al. *Lancet Oncol*. 2018;19(11):1480-1492.

What Is The Unmet Need?

We need a better therapeutic approach

How Do We Address Unmet Need?

1. Improve our understanding of mechanisms of therapeutic resistance
2. Develop more effective therapies (eg, combinations)
    a. Frontline
    b. Post-PD-1 setting

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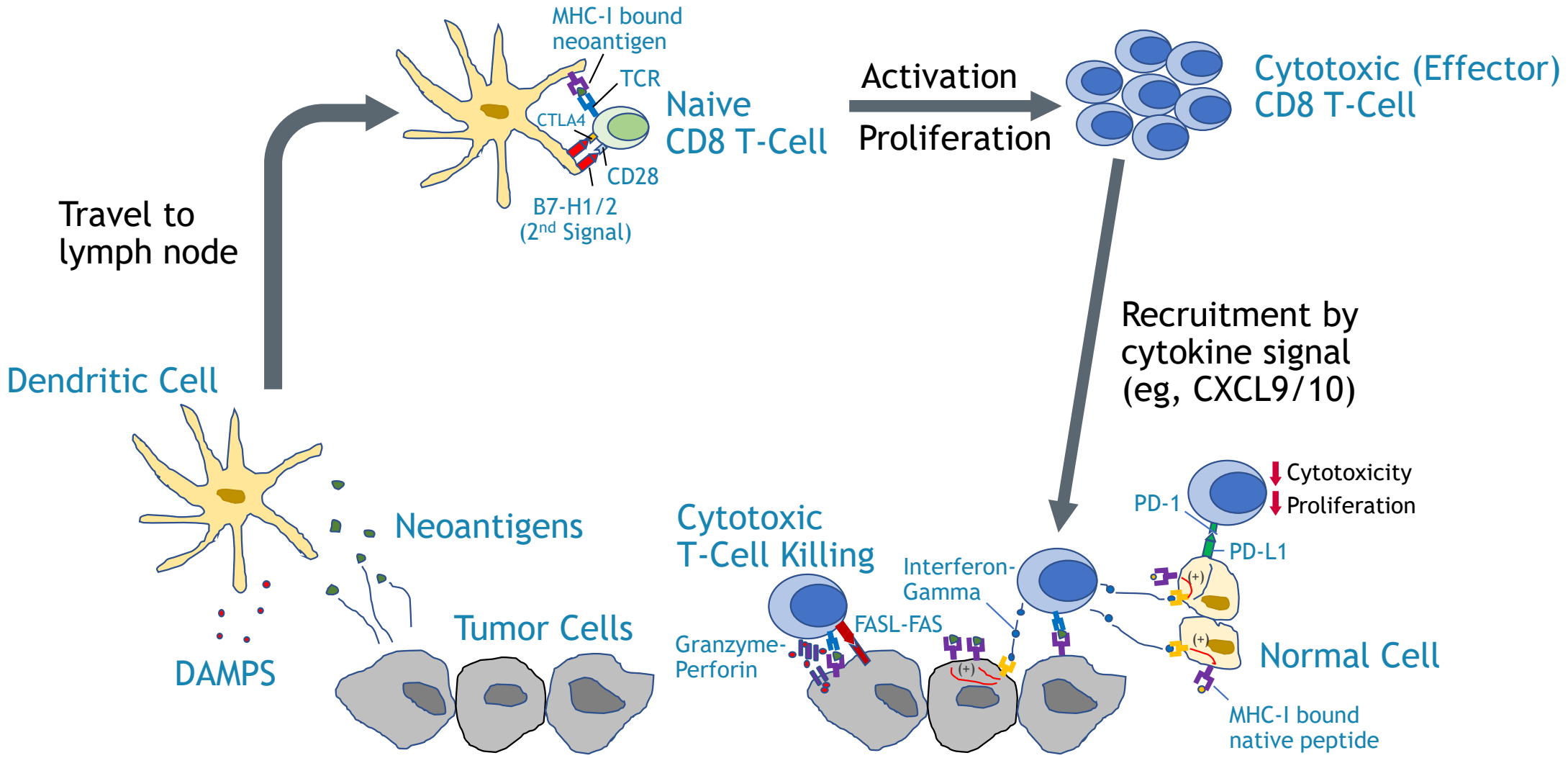
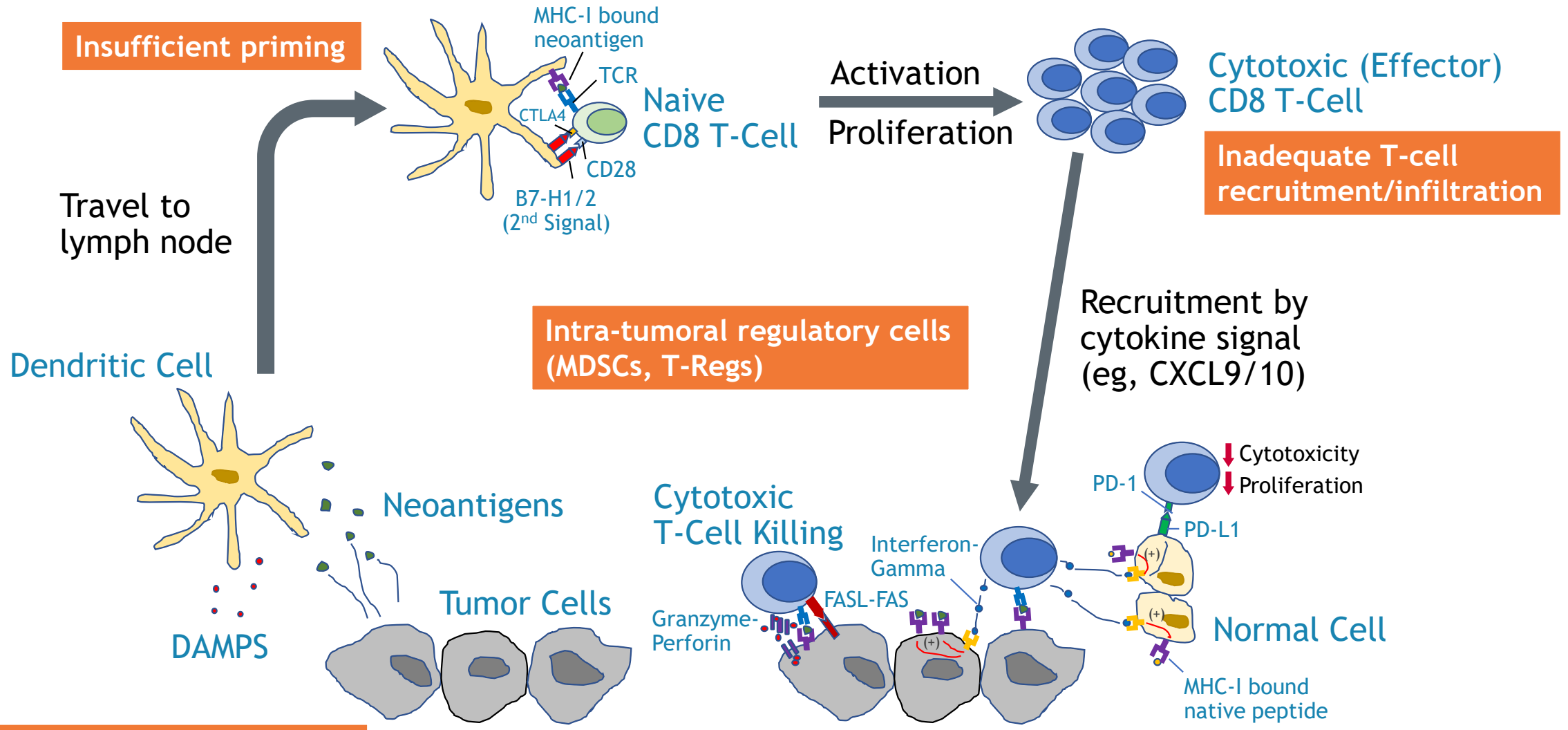
Why Does Therapy Fail?



CTLA4, cytotoxic T-lymphocyte-associated protein 4; DAMPS, damage-associated molecular patterns; FASL, FAS ligand; MHC-I, class-I major histocompatibility complex; TCR, T-cell receptor.
Liu D, Jenkins RW, Sullivan RJ. *Am J Clin Dermatol*. 2019;20(1):41-54.

Why Does Therapy Fail?



Liu D, Jenkins RW, Sullivan RJ. *Am J Clin Dermatol*. 2019;20(1):41-54.

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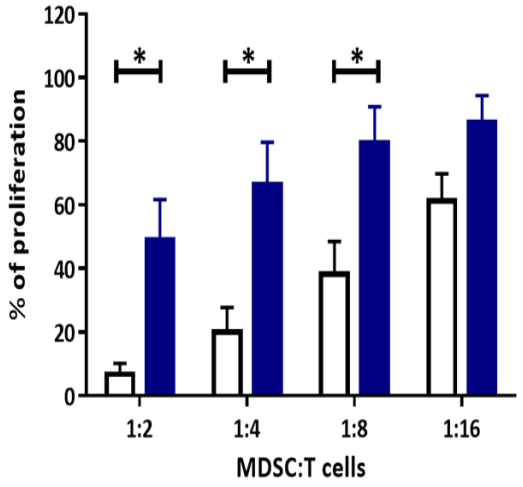
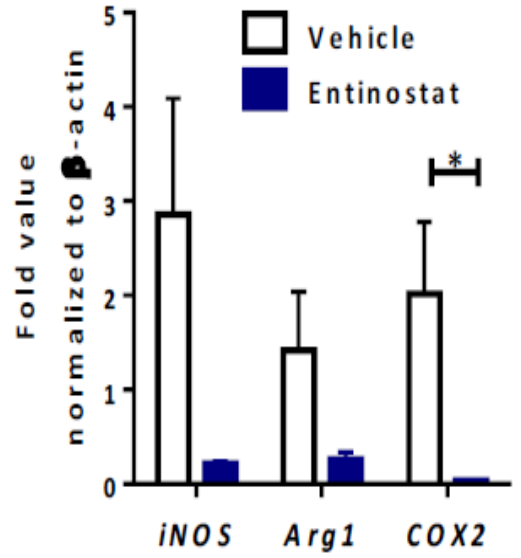
Rationale for Entinostat in Combination with anti-PD-(L)1 Therapy

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD-1 inhibition in preclinical models

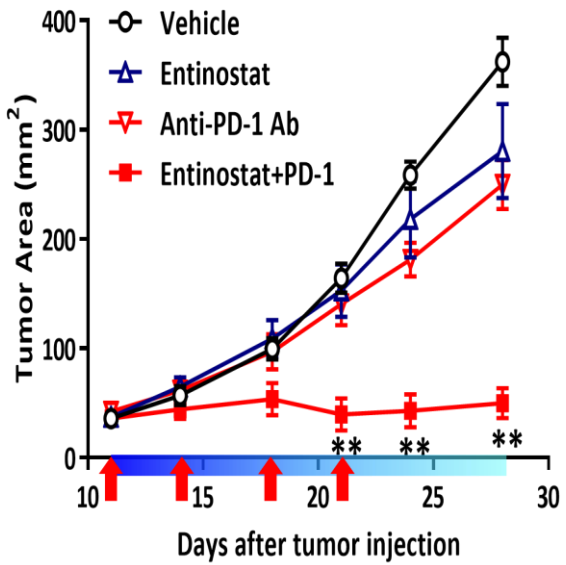
MDSC function[1†]



MDSC mRNA expression[1†]



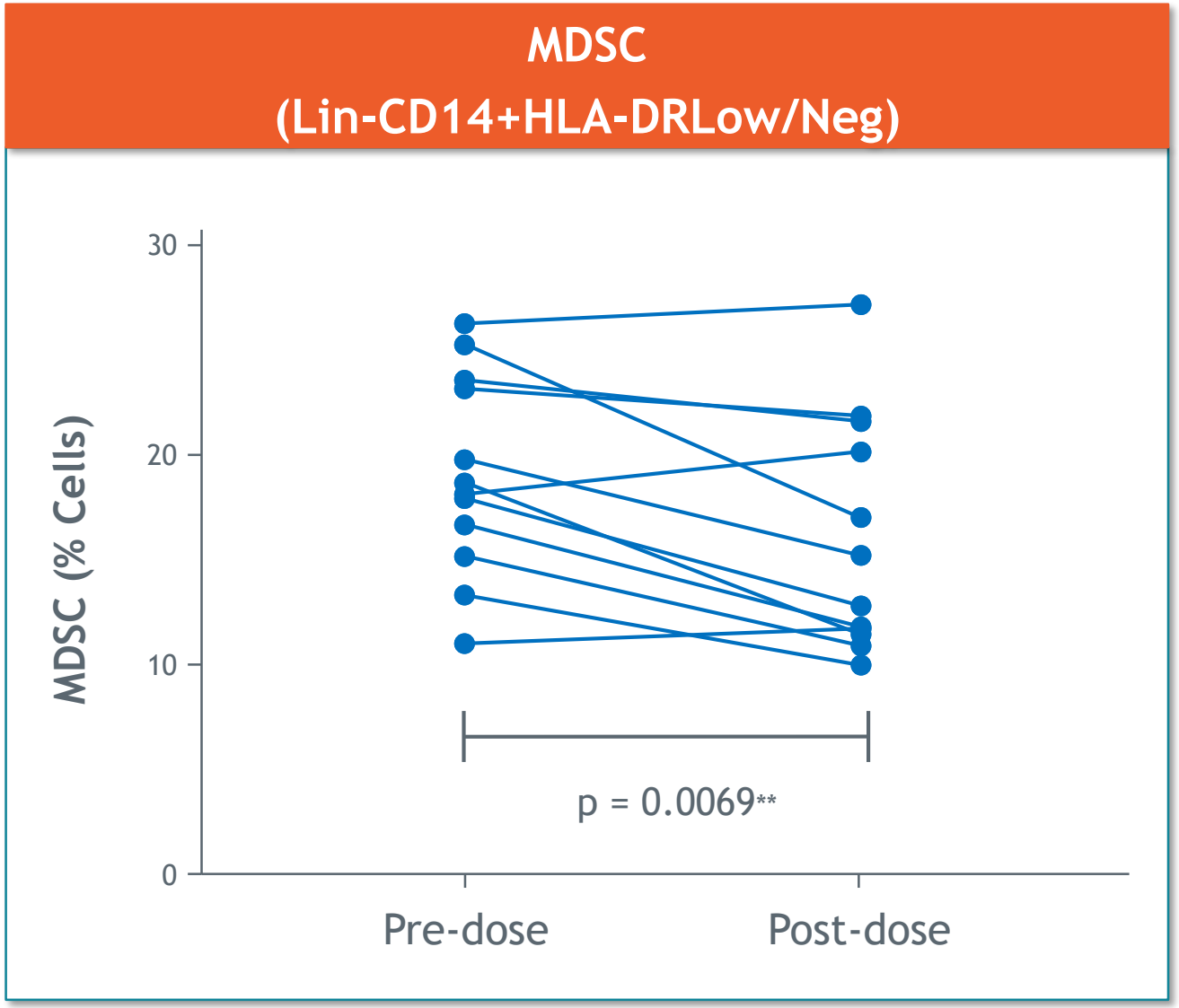
Tumor growth[1†]



† *In vivo* and *in vitro* studies were performed using Lewis Lung Carcinoma (LLC) cells. ***P*<0.001. **P*<0.05.
Ab, antibody; Arg1, arginase 1; COX2, cytochrome oxidase subunit 2; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells.
Orillion A, et al. *Clin Cancer Res*. 2017;23(17):5187-5201.

Changes in MDSCs Observed After Entinostat Treatment in Cancer Patients

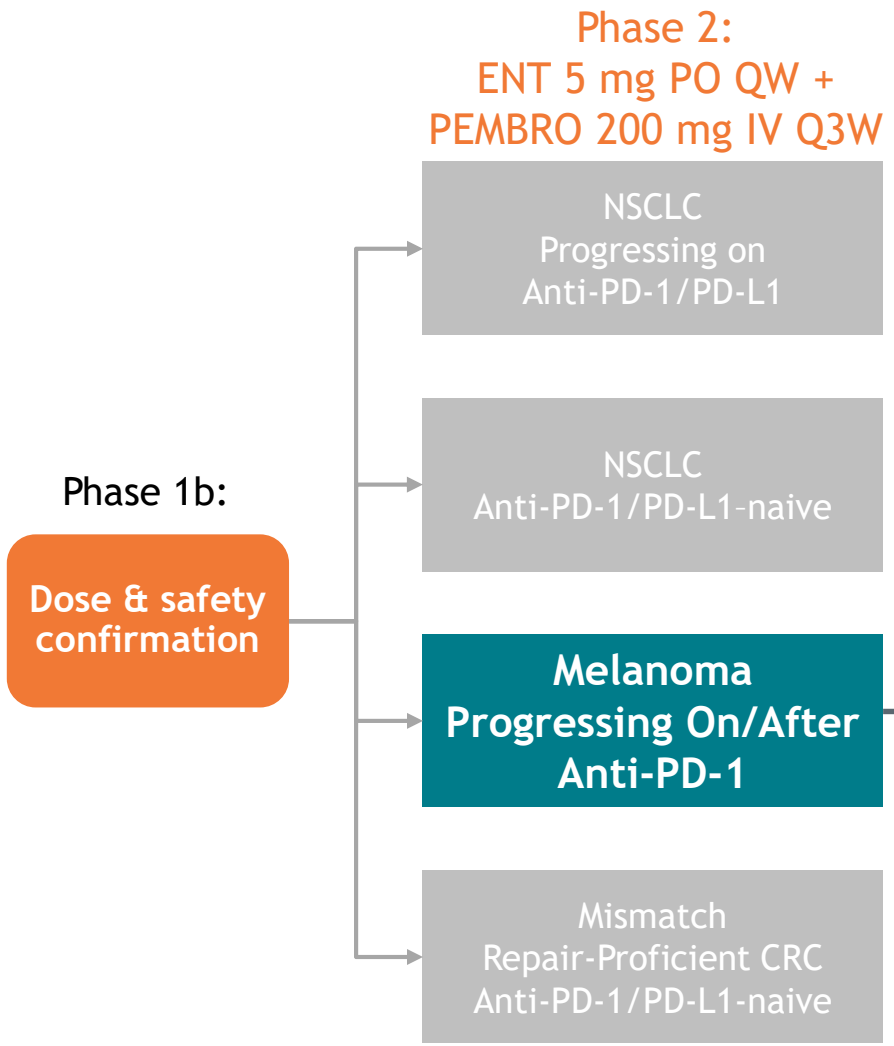
In patients with advanced solid tumors, MDSC cell frequency was significantly decreased at Day 14 after a single entinostat dose



** Paired t-test

Tolcher A, et al. Presented at AACR 2019. Abstract CT179

ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy



Inclusion Criteria:

- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint

- ORR (irRECIST)

Secondary Endpoints

- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

CBR, clinical benefit rate; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; QW, once a week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

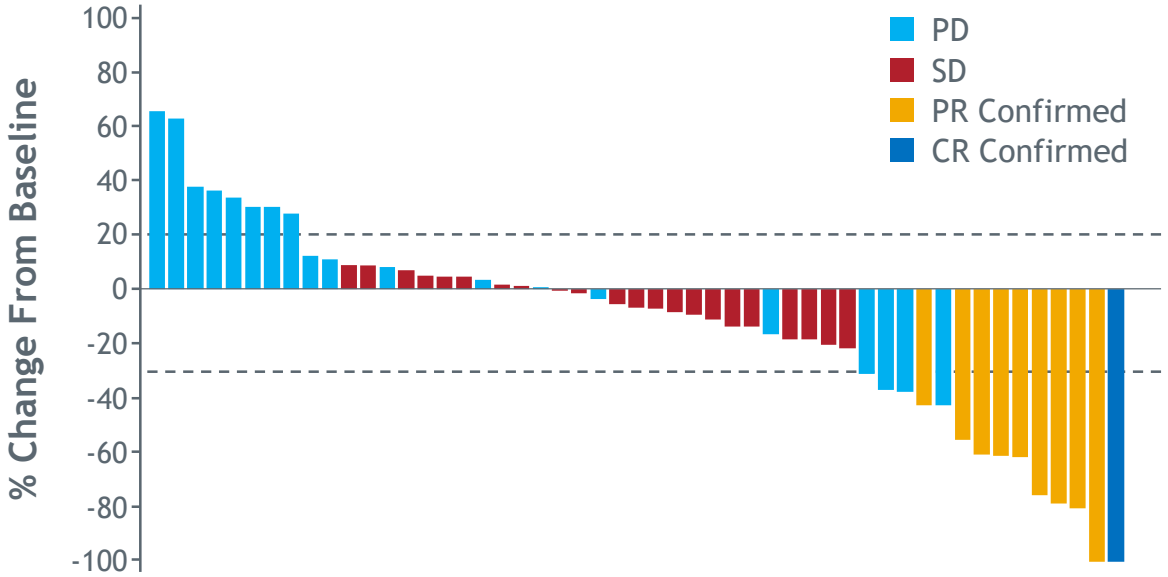
Patient Baseline Demographics and PD-1 History

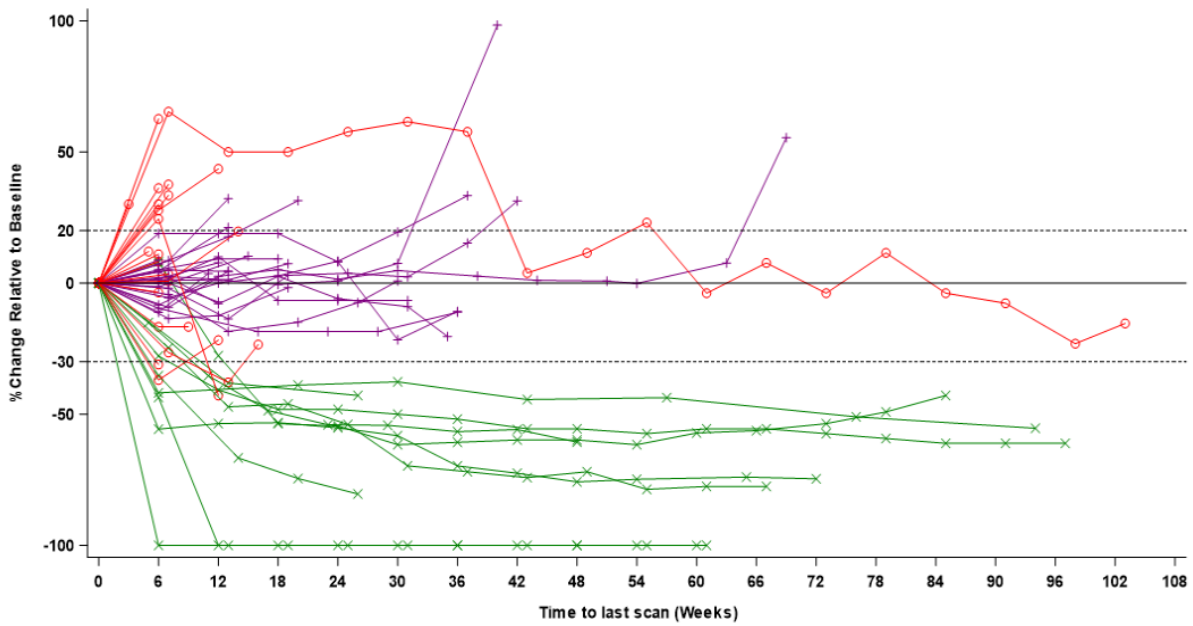
Demographics	N=53
Male, n (%)	32 (60%)
Median age (range)	62.0 (20-86)
Race, n (%)*	
White/ Other	47 (89%) / 6 (11%)
ECOG Performance Status, n (%)	
0 / 1	29 (55%) /24 (45%)
PD-L1 expression, n (%)	
Negative	11 (21%)
Positive	28 (53%)
Not Evaluable	10 (19%)
Visceral metastases, n (%)	
Yes / No	34 (64%) / 19 (36%)
Baseline LDH (%>ULN)	
Yes	19 (36%)

Prior therapy	N = 53
Prior treatment with Ipi & PD-1	37 (70%)
Prior treatment with BRAF/MEK	12 (23%)
PD-1 history	
Best response on prior PD-1 therapy, n (%)	
CR	1 (2%)
PR	6 (11%)
SD	20 (38%)
PD	22 (42%)
Unknown	4 (7%)
Duration of latest PD-1 therapy	
Median months (range)	5.2 (0.72-23.1)
Duration between prior PD-1 therapy and first dose	
Median months (range)	2.6 (0.66-37.1)

*Rounding may produce values that do not add up to 100%.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; Ipi, ipilimumab; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper limit of normal.

Change in Tumor Volume and Change in Tumor Volume Over Time per irRECIST in ENCORE-601

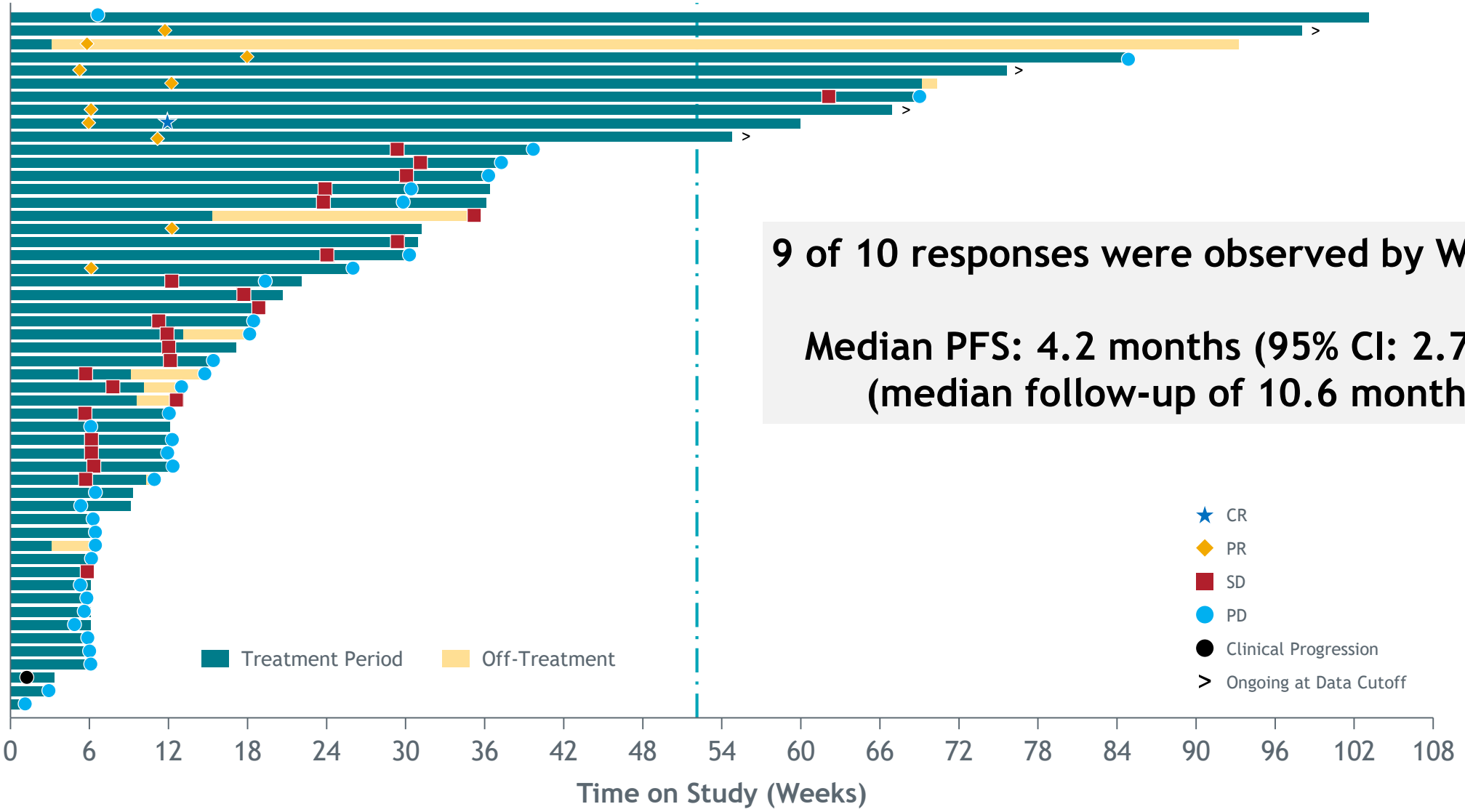




- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Time to Response and Time on Treatment in ENCORE-601

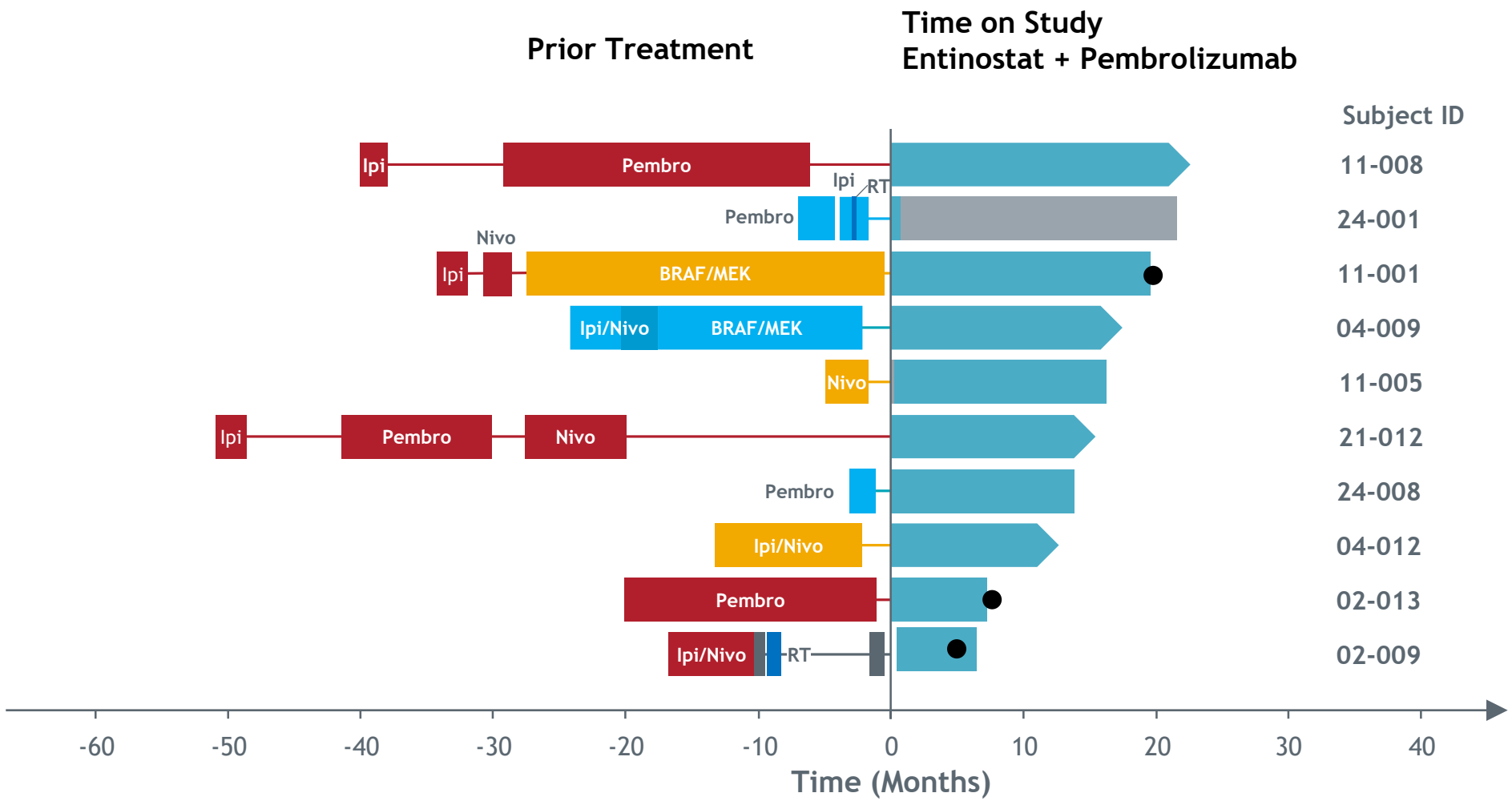


9 of 10 responses were observed by Week 12

Median PFS: 4.2 months (95% CI: 2.7-7.0)
(median follow-up of 10.6 months)

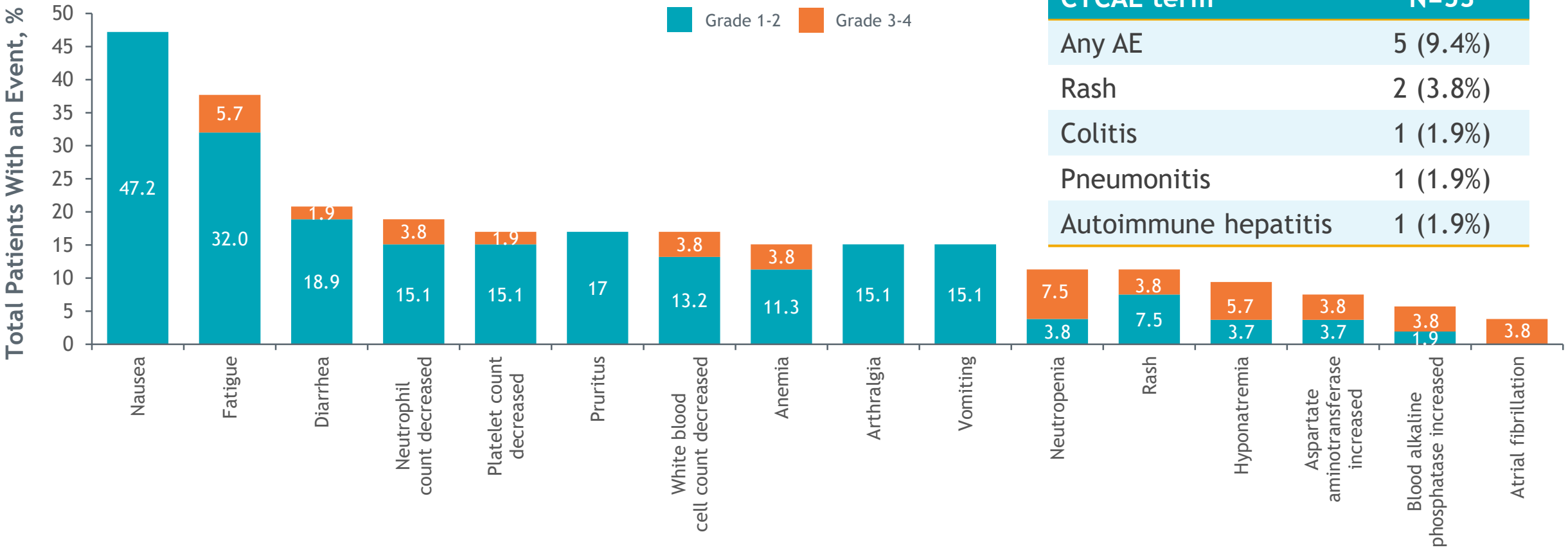
CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Responses Observed Regardless of Prior Treatment History



Ipi, ipilimumab; Nivo, nivolumab; RT, radiotherapy.

Safety: Treatment-Related Adverse Events Occurring in ≥15% of Patients for All Grade or ≥2 Patients for Grade 3/4



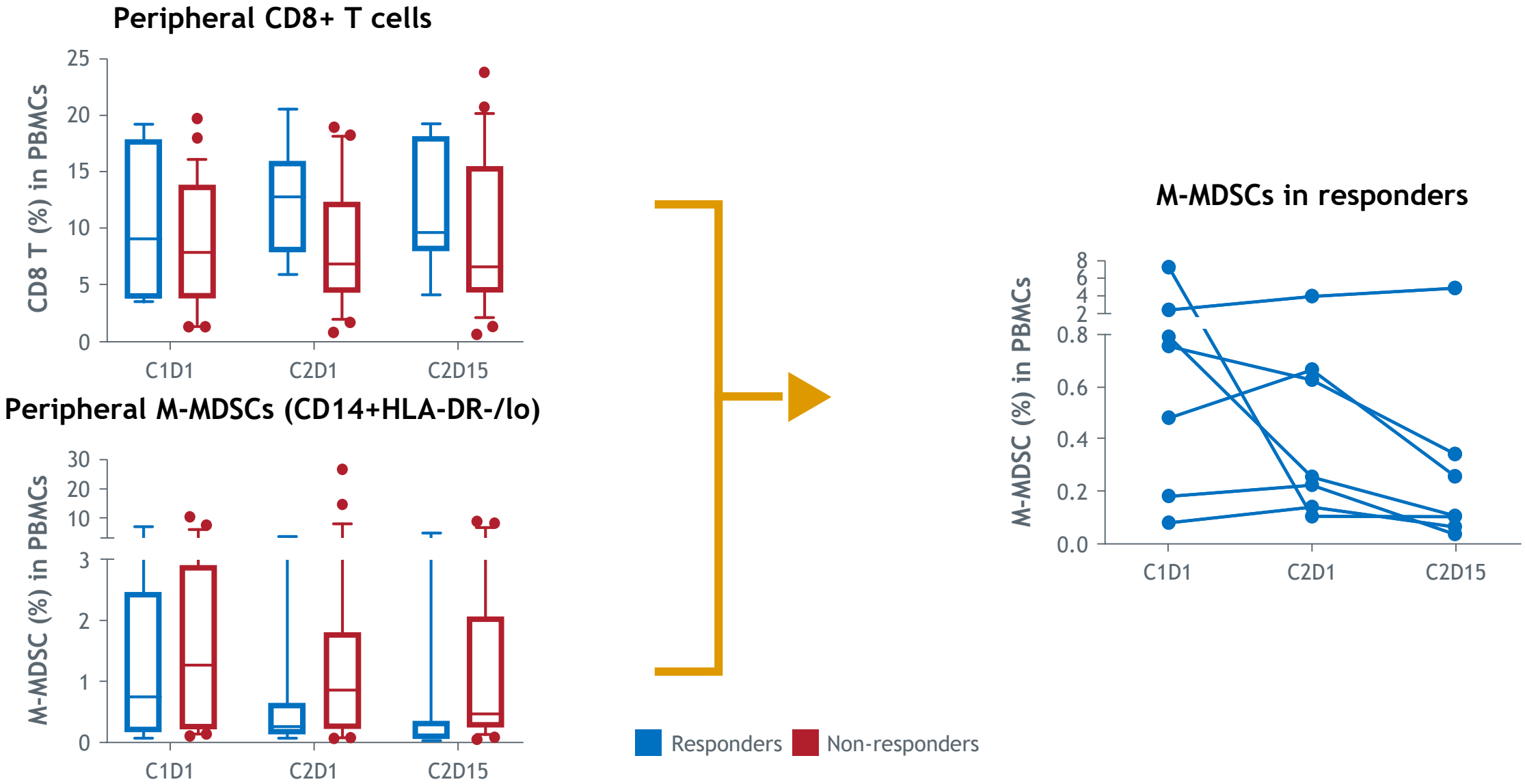
Grade 3/4 Immune-Related AEs

CTCAE term	N=53
Any AE	5 (9.4%)
Rash	2 (3.8%)
Colitis	1 (1.9%)
Pneumonitis	1 (1.9%)
Autoimmune hepatitis	1 (1.9%)

- 6 pts discontinued due to related AEs:
  increased bilirubin, mucosal inflammation, neutropenia, pneumonitis, constipation and autoimmune hepatitis

AE, adverse event; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

Changes in Peripheral CD8+ T-cell and M-MDSC Levels Associated With Response (n = 49)



M-MDSC, monocytic myeloid-derived suppressor cells; MDSC, myeloid-derived suppressor cell; PBMC, peripheral blood mononuclear cell.

Gene Signatures (RNA seq) Enriched in Responders (n=4) vs Non-Responders (n=4) and Post-treatment vs Pre-Treatment for Responders

Responders vs non-responders

Hallmark Pathways up	NES
TNFA_SIGNALING_VIA_NFKB	2.72
INFLAMMATORY_RESPONSE	2.34
EPITHELIAL_MESENCH_ TRANS	2.11
HYPOXIA	2.1
MYOGENESIS	1.92

Hallmark Pathways down	NES
E2F_TARGETS	-1.93
G2M_CHECKPOINT	-1.68
OXIDATIVE_PHOSPHORYLATION	-1.55
FATTY_ACID_METABOLISM	-1.45

*Top 5 and bottom 5 enriched pathways with adjusted p-value <0.05 (there were only 4 pathways with negative normalized enrichment score and adjusted p value <0.05).

NES (normalized enrichment score)

Post vs pre in responders

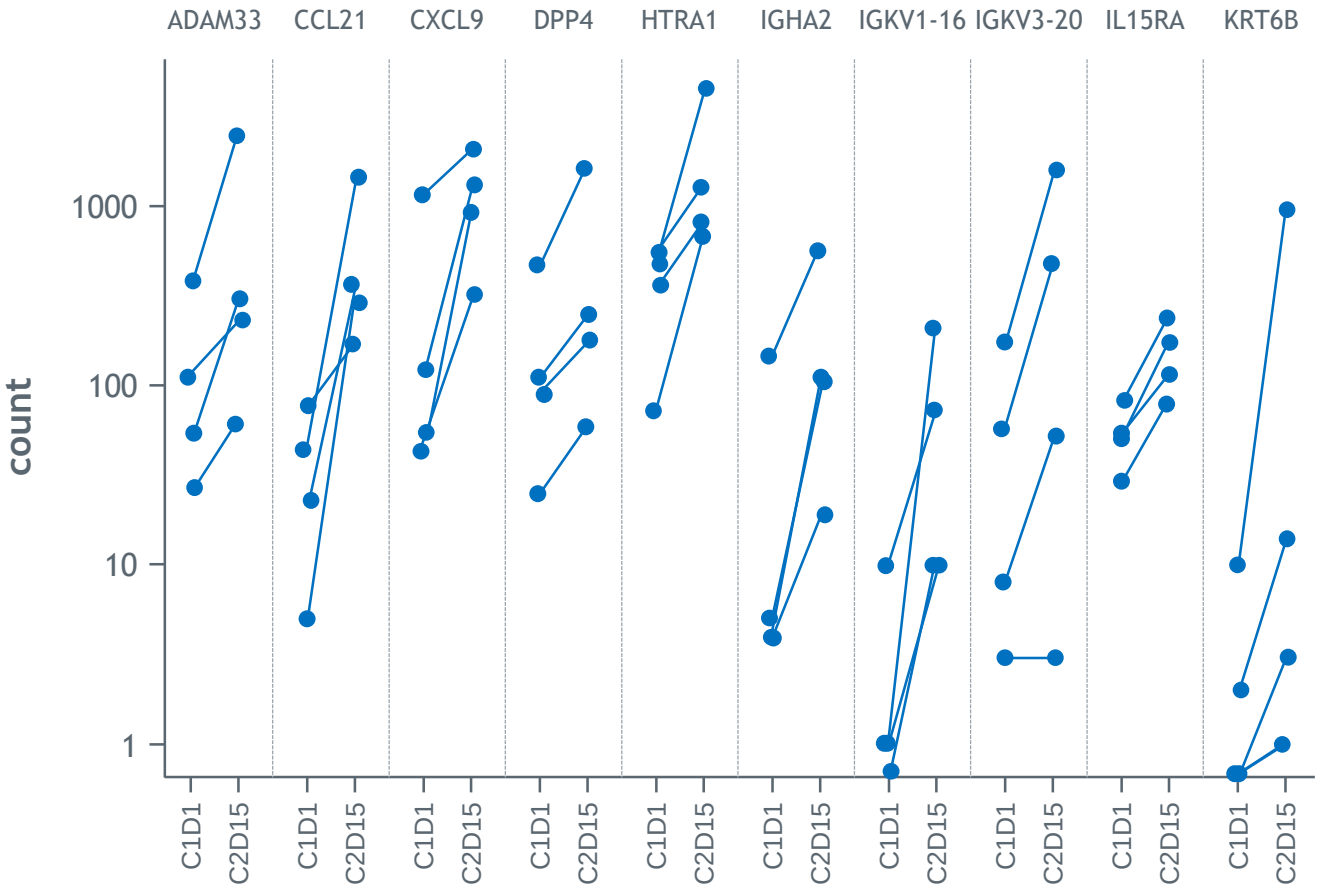
Hallmark Pathways up	NES
EPITHELIAL_MESENCH_TRANS	2.51
ALLOGRAFT_REJECTION	2.4
INTERFERON_GAMMA_RESPONSE	2.36
IL6_JAK_STAT3_SIGNALING	2.11
UV_RESPONSE_DN	2.1

Hallmark Pathways down	NES
E2F_TARGETS	-2.57
G2M_CHECKPOINT	-2.54
MYC_TARGETS_V2	-2.13
OX_PHOSPH	-1.98
MYC_TARGETS_V1	-1.71

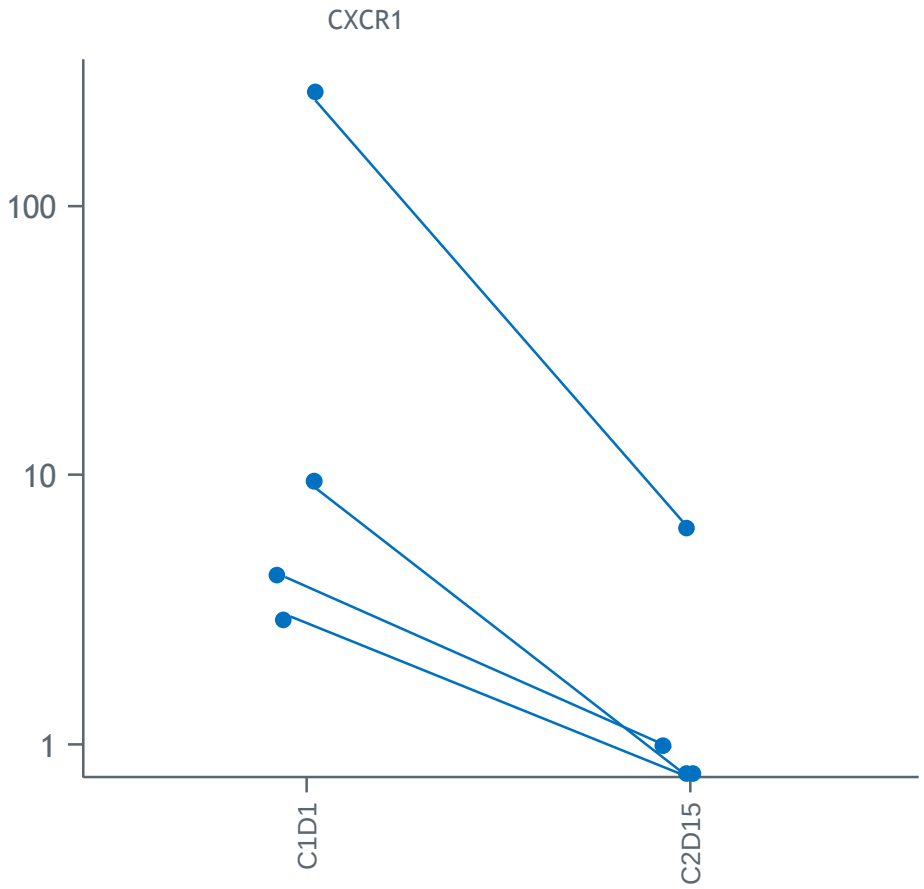
*Top 5 and bottom 5 enriched pathways with adjusted p-value <0.05.

Individual Gene Changes Post-Treatment vs Pre-treatment in Responders

Paired C1D1-vs-C2D15 for responders top up genes



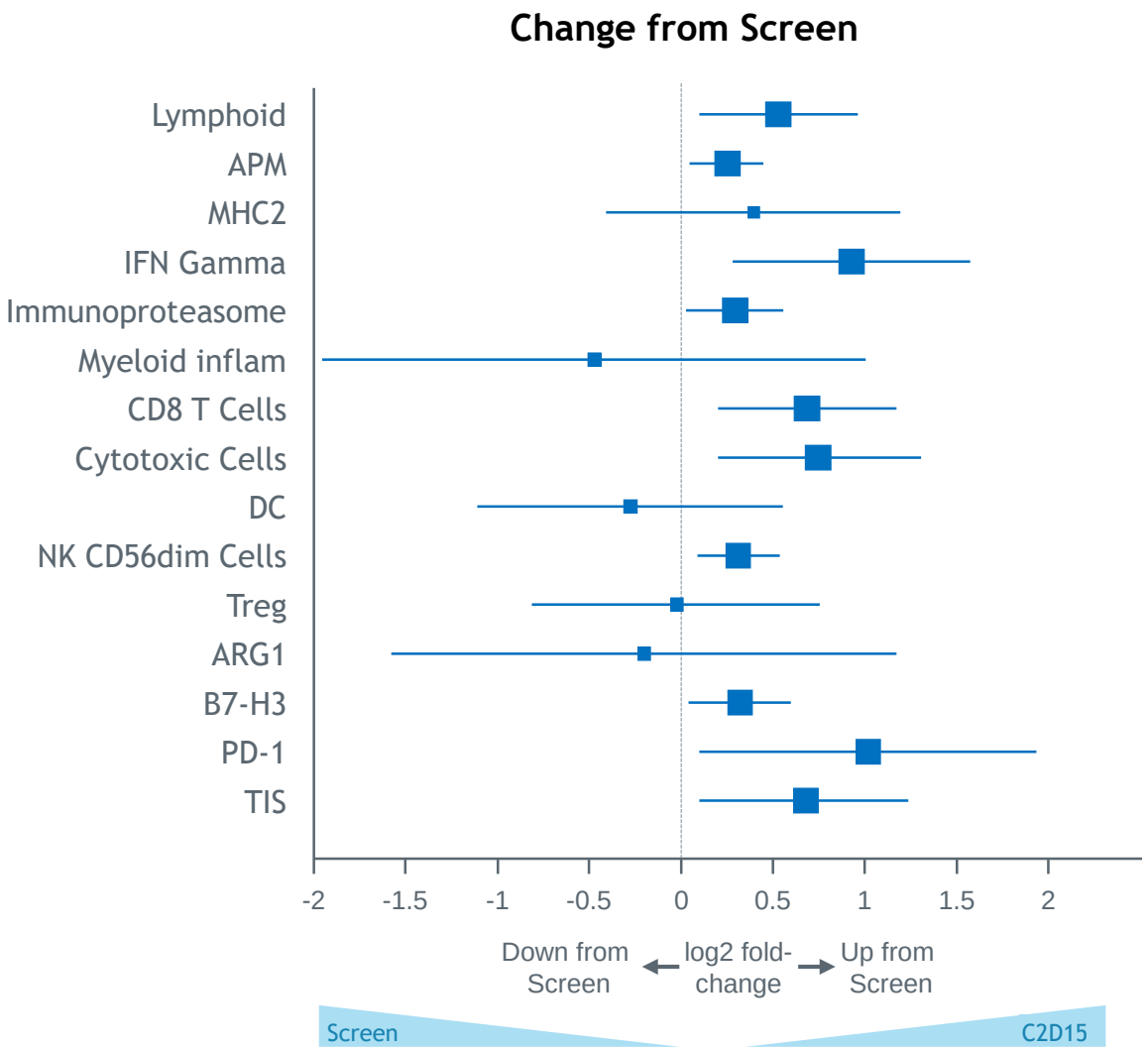
Paired C1D1-vs-C2D15 for responders top down genes

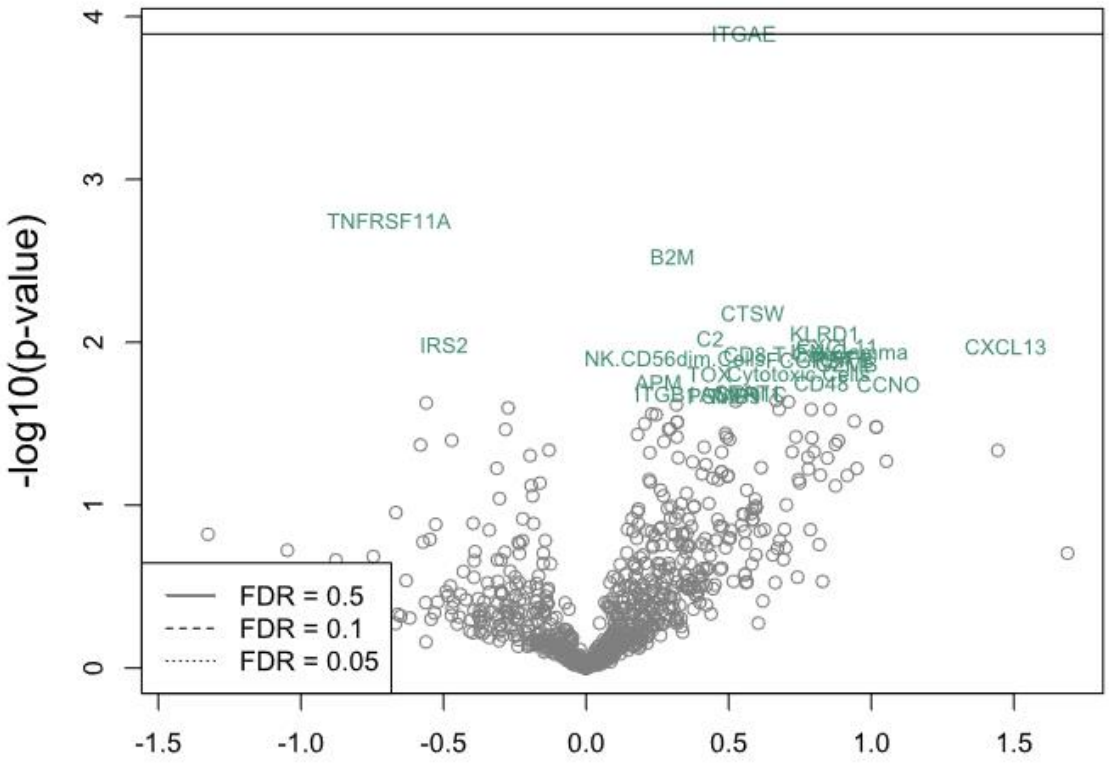


Batch 1

*Top 10 and bottom 10 gene with adjusted p-value < 0.05.
C, cycle; D, day.

Many Immune Signatures (n=7) Including Those Associated With Increased TIL and IFN Signaling Increase Following Treatment (NanoString)





log2 fold-change: Time= C2D15 vs. Screen

C, cycle; D, day; IFN, interferon; TIL, tumor infiltrating lymphocyte.

Conclusions

- In patients with progressing melanoma on prior PD-1 blockade and both prior PD-1/CTLA-4 blockade, a group with limited treatment options, ENT + PEMBRO demonstrate significant anti tumor activity
- ENT + PEMBRO was safe and tolerable
- Dominant toxicity with ENT + PEMBRO appeared to be related to ENT, with no apparent increase in irAEs with the combination
- Preliminary biomarker analysis demonstrated findings consistent with the mechanism of action of ENT:
  - Reduction in circulating MDSCs
  - Tumor specific increases in (pre/on) and enriched in (R/NR) inflammatory pathways

ENT, entinostat; PEMBRO, pembrolizumab.

Acknowledgments

The authors thank the patients and their families

Co-Investigators and study staff

Rancho BioSciences: Dan Rozelle

NanoString: Amy Sullivan, Sarah Church

The Wistar Institute: Fang Wang, Dmitry Gabrilovich

This study was sponsored by Syndax Pharmaceuticals, Inc., in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Editorial assistance was provided by BluPrint Oncology, LLC. This assistance was funded by Syndax Pharmaceuticals, Inc.