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ENCORE-601: Phase 1b/2 study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with non-small cell lung cancer

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Presenter disclosure information

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Background: Many factors contribute to resistance to immunotherapies

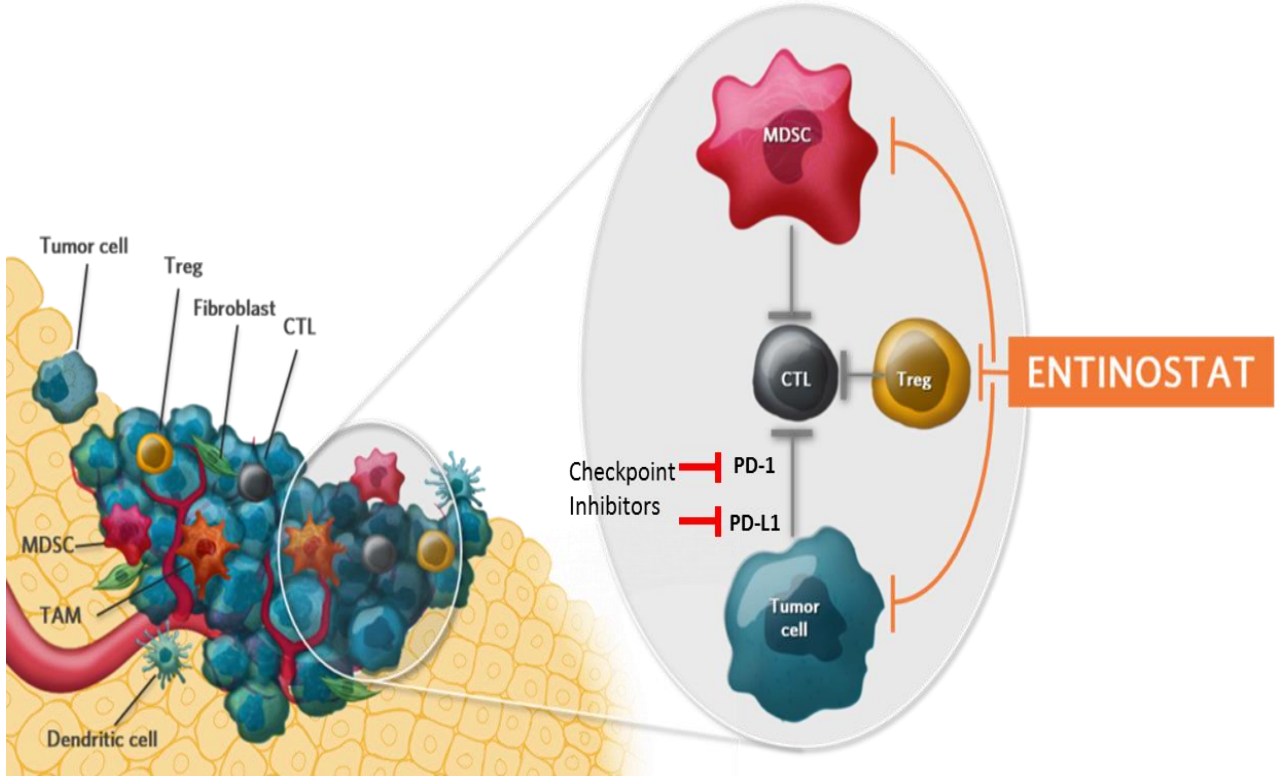
- Single-agent PD-(L)1 therapies have profoundly improved treatment options for many cancers; still, a majority of patients do not respond
- Resistance to immunotherapy may in part be due to an immunosuppressive TME in which cancer cells avoid detection and eradication by the host's immune system, mediated by:
  - Upregulation of Tregs, MDSCs, and IDO in the TME
  - Low levels of tumor-infiltrating lymphocytes (CD8+ T cells) and tumor neoantigens
  - Low expression of immune signaling molecules like PD-L1

IDO = indoleamine 2,3-dioxygenase; MDSCs = myeloid-derived suppressor cells; PD-(L)1 = programmed cell death-(ligand) 1; ROS = reactive oxygen species; TME = tumor microenvironment; Tregs = regulatory T cells.

1. Orillion A et al. *Clin Cancer Res.* 2017;23(17):5187-5201. 2. Pitt JM et al. *Immunity.* 2016;44(6):1255-1269. 3. Tkachev V et al. *J Immunol*. 2015;194(12):5789-5800.

Background: Immune checkpoint inhibitors and entinostat target complementary immunosuppression mechanisms in tumor microenvironment

- Entinostat – oral, class I selective histone deacetylase inhibitor
- Has demonstrated potent immunomodulatory activity by inhibition of myeloid-derived suppressor cell (MDSC) function
- ENCORE-601 phase 1b/2 study evaluates safety and efficacy of entinostat (ENT) plus pembrolizumab (PEMBRO) in NSCLC, melanoma, and mismatch repair-proficient colorectal cancer patients



CTL = cytotoxic T lymphocyte; NSCLC = non-small cell lung cancer; TAM = tumor-associated macrophages.
Orillion A et al. *Clin Cancer Res.* 2017;23(17):5187-5201.

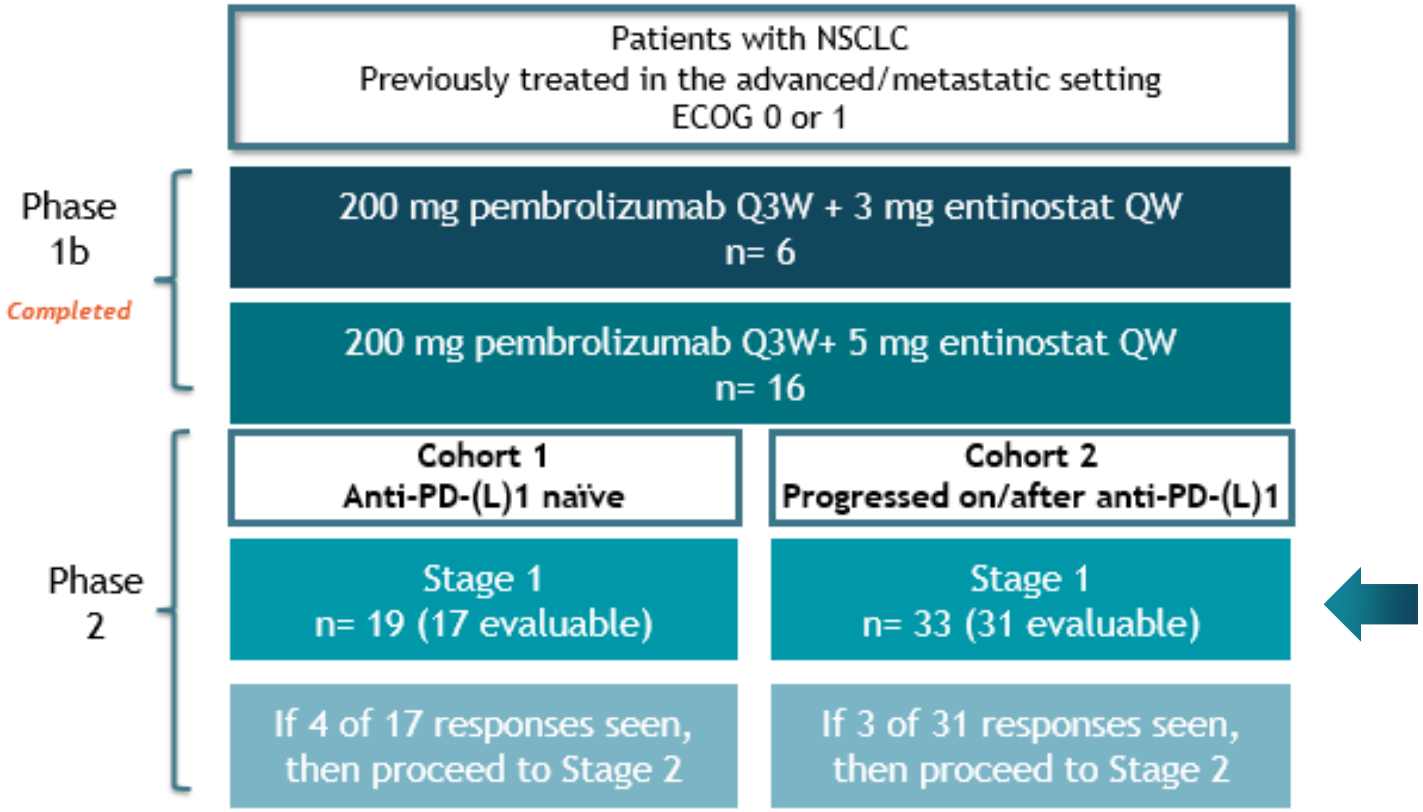
ENCORE-601 NSCLC cohort study design

Primary objectives

- Phase 1b: DLT, MTD, RP2D
- Phase 2: ORR by irRECIST

Secondary objectives

- Efficacy: CBR (CR+PR+SD at 6 months), PFS at 6 months, PFS, OS, DOR, and TTR
- Safety: AEs, laboratory parameters, and ECGs



Evaluable patients defined as patients who reached the first tumor assessment timepoint or were discontinued for progression or adverse event prior to the first tumor assessment

AEs = adverse events; CBR = clinical benefit rate; CR = complete response; DLT = dose-limiting toxicities; DOR = duration of response; ECGs = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RP2D = recommended phase 2 dose; SD = stable disease; TTR = time to response.

Baseline demographics and prior PD-(L)1 history

	Cohort 1 (n=19)	Cohort 2 (n=33)
Gender, n (%)		
Male/Female	11 (57.9) / 8 (42.1)	17 (51.5) / 16 (48.5)
Age (years)		
Median (range)	67.0 (43–78)	67.0 (48–86)
ECOG Performance Score, n (%)		
Grade 0/Grade 1	6 (31.6) / 12 (63.2)	9 (27.3) / 23 (69.7)
PD-L1 Expression, n (%)		
≥50% = Strong Positive	3 (15.8)	4 (12.1)
1%–49% = Weak Positive	5 (26.3)	13 (39.4)
<1% = Negative	6 (31.6)	15 (45.5)
Not Available	5 (26.3)	1 (3.0)
Smoking Status, n (%)		
Current	1 (5.3)	2 (6.0)
Former	13 (68.4)	29 (88.0)
Never	4 (21.0)	2 (6.0)
Missing	1 (5.3)	0

PD-(L)1 history	Cohort 2 (n=33)
Best Response on Prior PD-(L)1 Therapy, n (%)	
Partial Response	1 (3.0)
Stable Disease	18 (54.5)
Disease Progression	13 (39.4)
Unknown	1 (3.0)
Duration on Prior PD-(L)1 Therapy (days)	
Median	211.0
Duration Between Last Dose of Prior PD-(L)1 Therapy and First of Dose of ENCORE-601 Study Therapy (days)	
Median	75.0

Safety: Treatment-related adverse events (>10%)

	Cohort 1 (n=19)		Cohort 2 (n=33)		Total (N=52)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects With at Least One Related Adverse Event, n (%)	15 (78.9)	6 (31.6)	27 (81.8)	15 (45.5)	42 (80.8)	21 (40.4)
Fatigue	12 (63.2)	0	14 (42.4)	4 (12.1)	26 (50.0)	4 (7.7)
Anemia	4 (21.1)	1 (5.3)	8 (24.2)	4 (12.1)	12 (23.1)	5 (9.6)
Decreased appetite	2 (10.5)	0	7 (21.2)	0	9 (17.3)	0
Diarrhea	3 (15.8)	0	6 (18.2)	1 (3.0)	9 (17.3)	1 (1.9)
Platelet count decreased	3 (15.8)	0	5 (15.2)	0	8 (15.4)	0
Pruritus	4 (21.1)	0	3 (9.1)	0	7 (13.5)	0
Nausea	3 (15.8)	0	3 (9.1)	0	6 (11.5)	0
Pneumonitis	2 (10.5)	1 (5.3)	4 (12.1)	3 (9.1)	6 (11.5)	4 (7.7)

Safety: Grade ≥3 immune-related adverse events

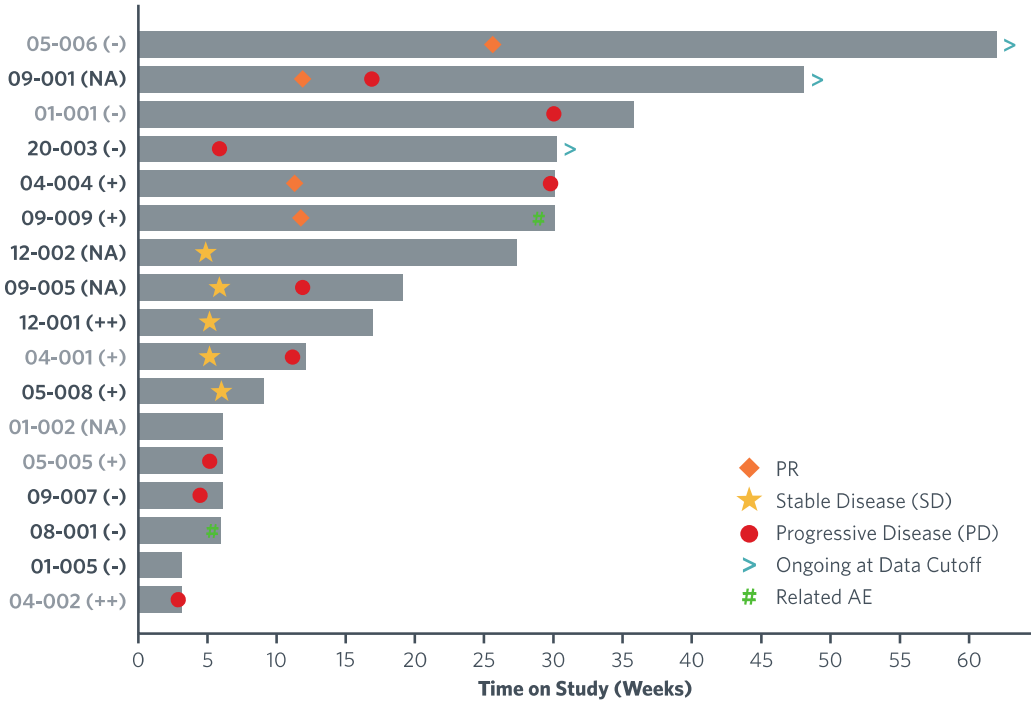
	Cohort 1 (n=19)	Cohort 2 (n=33)	Total (N=52)
Pneumonitis, n (%)	1 (5.3)	3 (9.1)	4 (7.7)
Colitis, n (%)	0	2 (6.1)	2 (3.8)
Encephalitis, n (%)	0	1 (3.0)	1 (1.9)
Hyperthyroidism, n (%)	0	1 (3.0)	1 (1.9)

- 7 patients experienced Grade ≥3 immune-related adverse event
  - 1 in Cohort 1 (5%)
  - 6* in Cohort 2 (18%)
- 5 patients discontinued due to these AEs
  - 1 in Cohort 1
  - 4 in Cohort 2

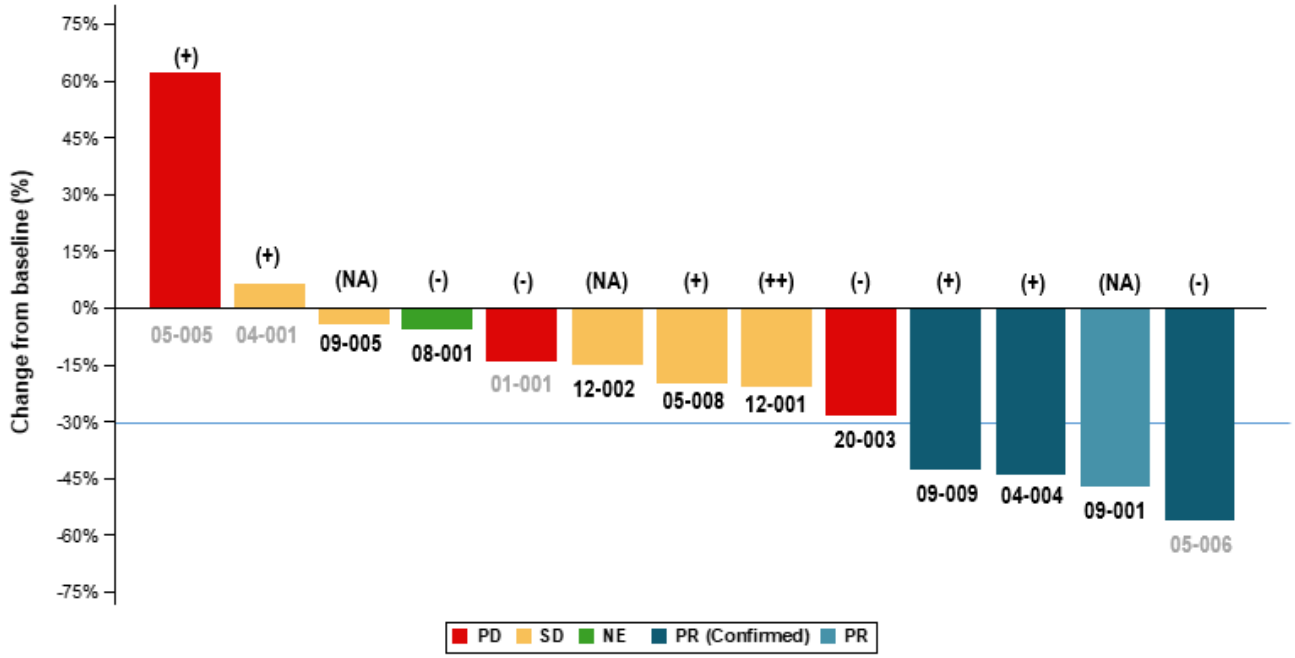
*1 patient in Cohort 2 experienced 2 immune-related adverse events

Efficacy in Cohort 1: Anti-PD-(L)1–naive group

Time to Response and Time on Treatment



Change in Tumor Size From Baseline



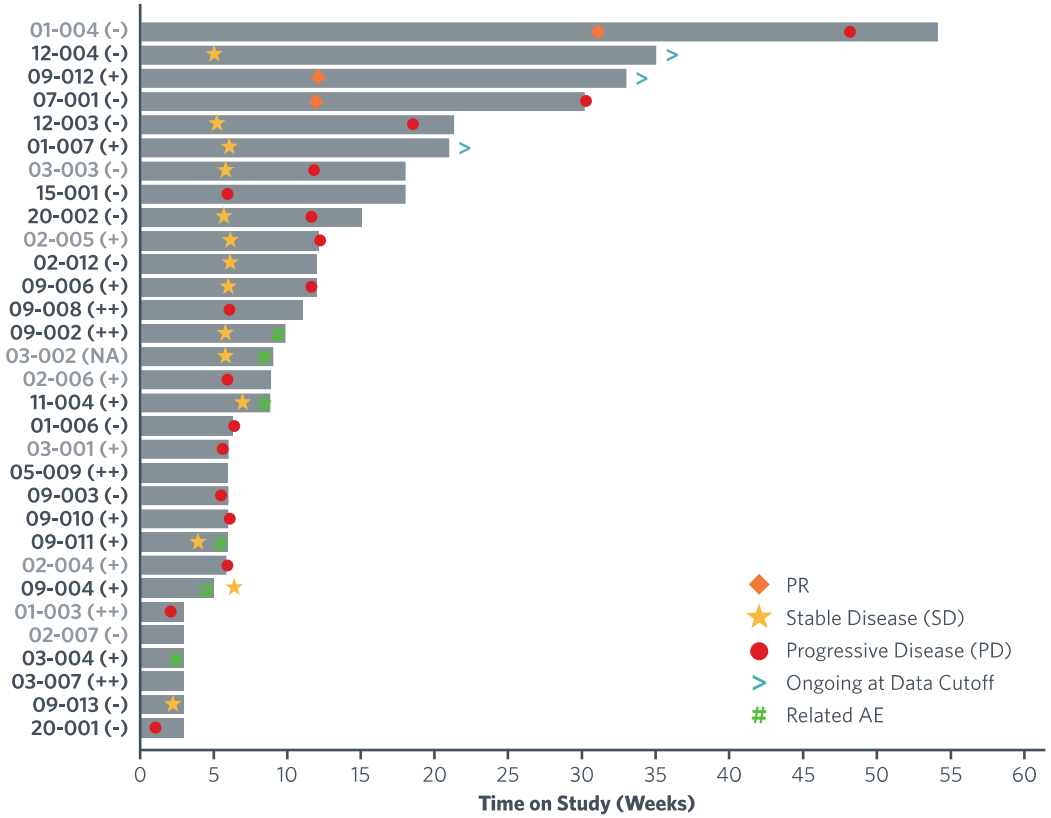
Patients not on waterfall plot did not have any post-baseline tumor measurements

- 4 PRs out of 17 evaluable patients (24% ORR, 95% CI: 7–50)
  - 3 confirmed PRs, one unconfirmed PR due to new pericardial effusion with malignant cells
  - 3 with negative or low baseline PD-L1 expression, 1 with unknown PD-L1 expression

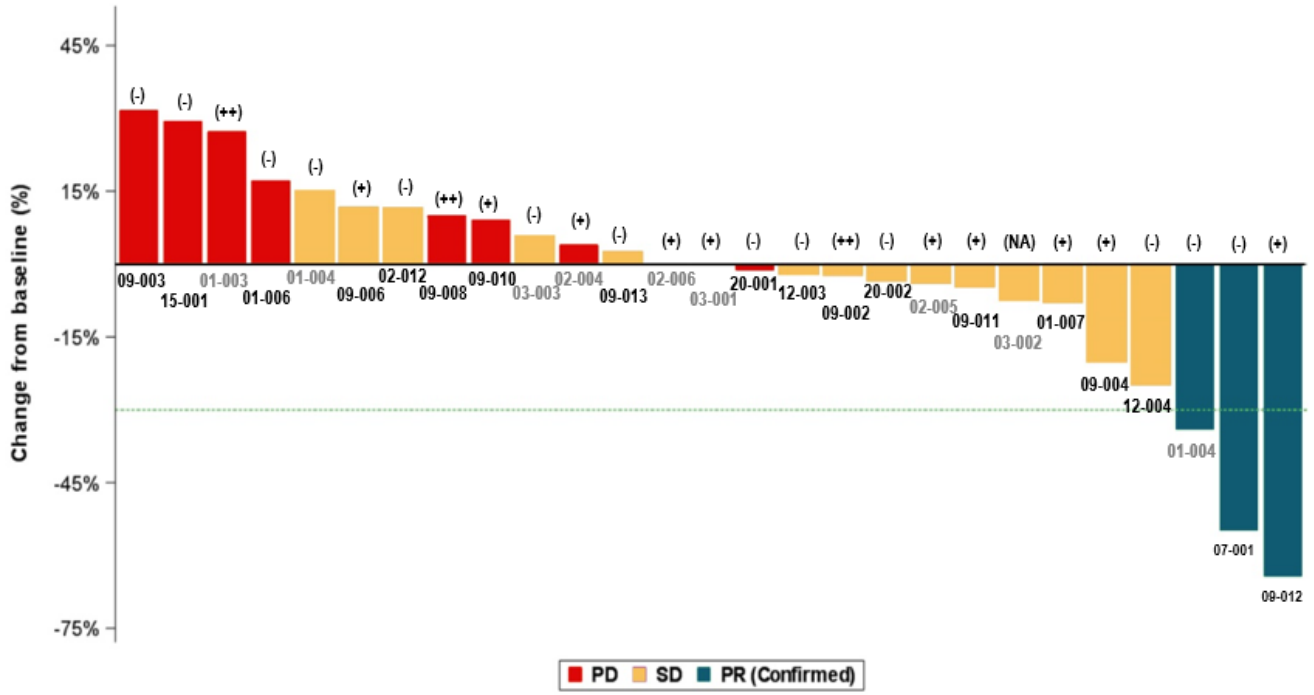
PD-L1 expression: (-) = <1%, (+) = 1%-49%, (++) = ≥50%
Phase 1 patients included in Phase 2

Efficacy in Cohort 2: Progressed on/after anti-PD-(L)1

Time to Response and Time on Treatment



Change in Tumor Size From Baseline



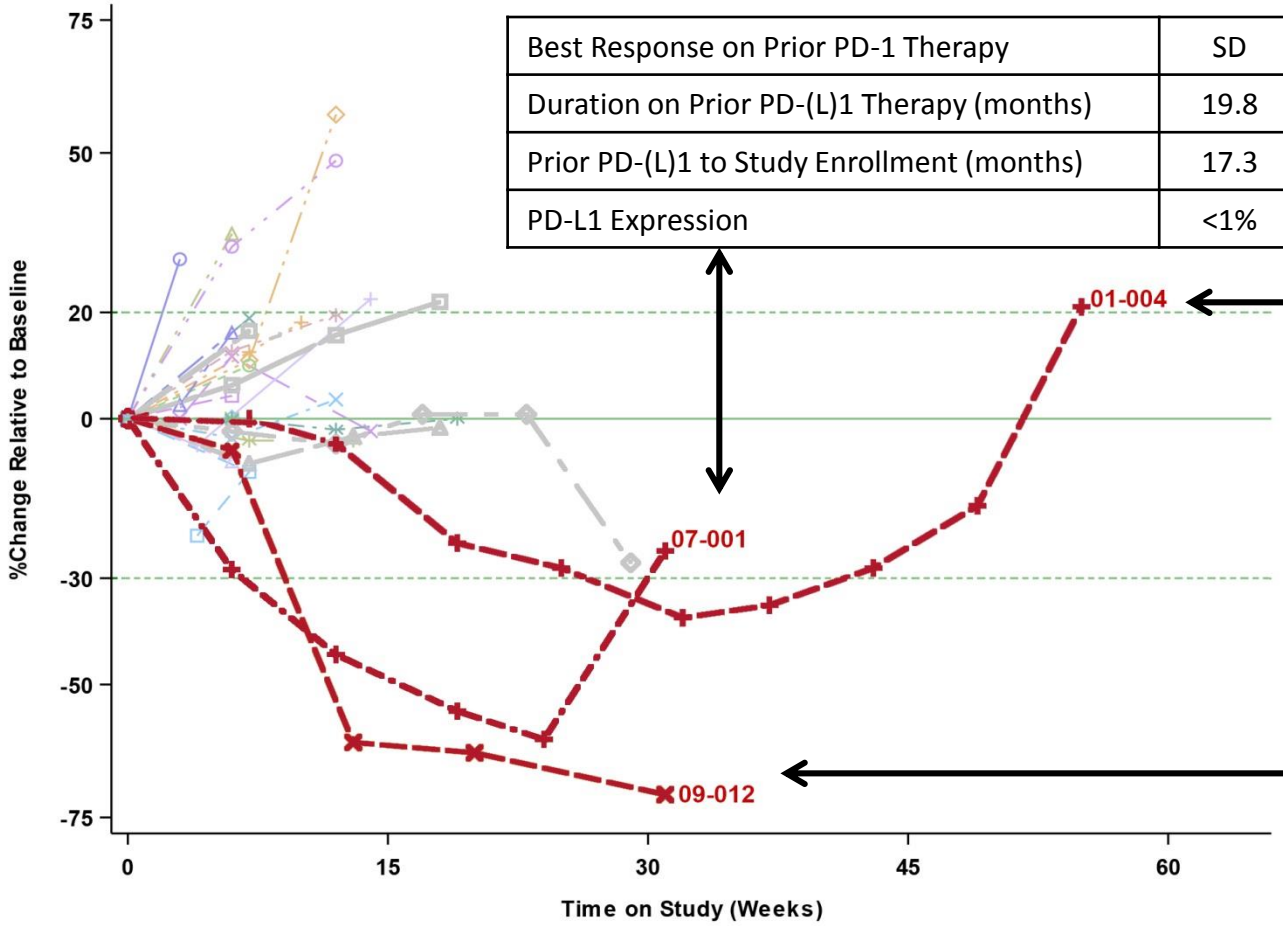
Patients not on waterfall plot did not have any post-baseline tumor measurements

- 3 PRs out of 31 evaluable patients (10% ORR, 95% CI: 2–26)
- 3 patients ongoing (1 PR, 2 SD)

PD-L1 expression: (-) = <1%, (+) = 1%-49%, (++) = ≥50%

Phase 1 patients included in Phase 2

Further details on Cohort 2 responders

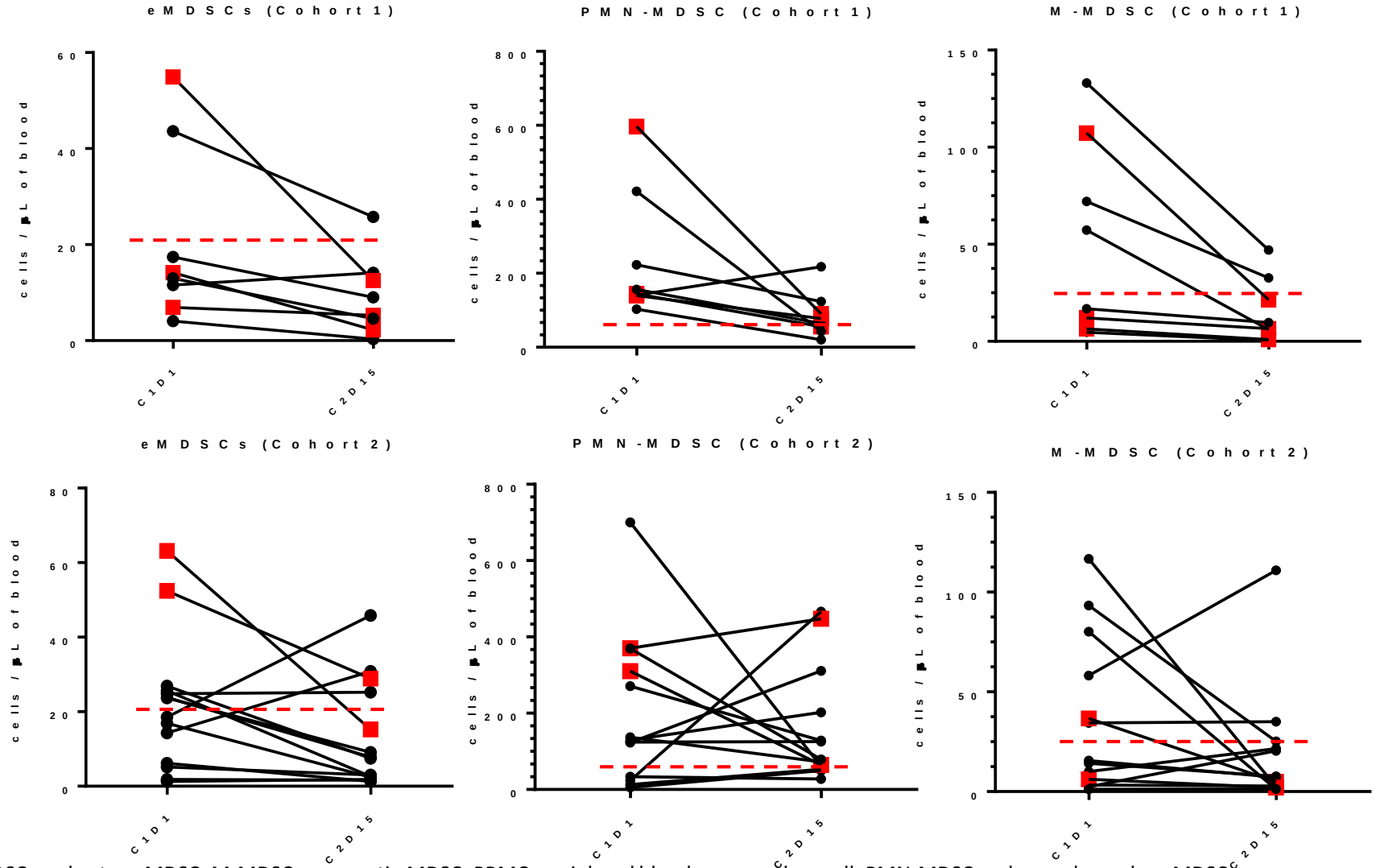


Best Response on Prior PD-1 Therapy	SD
Duration on Prior PD-(L)1 Therapy (months)	19.8
Prior PD-(L)1 to Study Enrollment (months)	17.3
PD-L1 Expression	<1%

Best Response on Prior PD-1 Therapy	Unknown
Duration on Prior PD-(L)1 Therapy (months)	7.3
Prior PD-(L)1 to Study Enrollment (months)	1.7
PD-L1 Expression	<1%

Best Response on Prior PD-1 Therapy	SD
Duration on Prior PD-(L)1 Therapy (months)	12.8
Prior PD-(L)1 to Study Enrollment (months)	1.1
PD-L1 Expression	1%–49%

Combination resulted in general decreases in MDSCs



- MDSCs were measured at cycle 1, day 1 (C1D1) and cycle 2, day 15 (C2D15) in Cohort 1 (n=8) and Cohort 2 (n=13)
- Cohort 1: all MDSC subsets decreased
  - eMDSCs (−56.5%)
  - PMN-MDSCs (−60.3%)
  - M-MDSCs (−72.3%)
- Cohort 2:
  - eMDSCs (−53.3%)
  - PMN-MDSCs (+1.0%)
  - M-MDSCs (−45.6%)
- eMDSCs and M-MDSCs decreased in all responders (5/5) and PMN-MDSCs in 4/5

Healthy donor level
Responders

eMDSC, early-stage MDSC; M-MDSC, monocytic-MDSC; PBMC, peripheral blood mononuclear cell; PMN-MDSC; polymorphonuclear-MDSC.

Conclusions

- ENT plus PEMBRO combination demonstrates antitumor activity
  - 24% ORR in anti-PD-(L)1–naive patients
  - 10% ORR in patients who progressed on prior PD-(L)1 blockade
  - Responses seen in patients with negative to low PD-L1 expression
- Acceptable safety in patients with NSCLC who are both naive to and have progressed on prior PD-(L)1 blockade
  - Potential increase in immune-related toxicity in those who had progressed on prior PD-(L)1 therapy. Additional data from stage 2 will further elucidate
- Reductions in circulating myeloid-derived suppressor cells were observed following treatment
- Cohort 2 has advanced to stage 2 and is currently enrolling
  - Additional patients are not being enrolled in Cohort 1 at this time

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