221

Dose-escalation/confirmation results of ENCORE 601, a Phase 1b/2, open-label study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with non–small cell lung cancer (NSCLC)

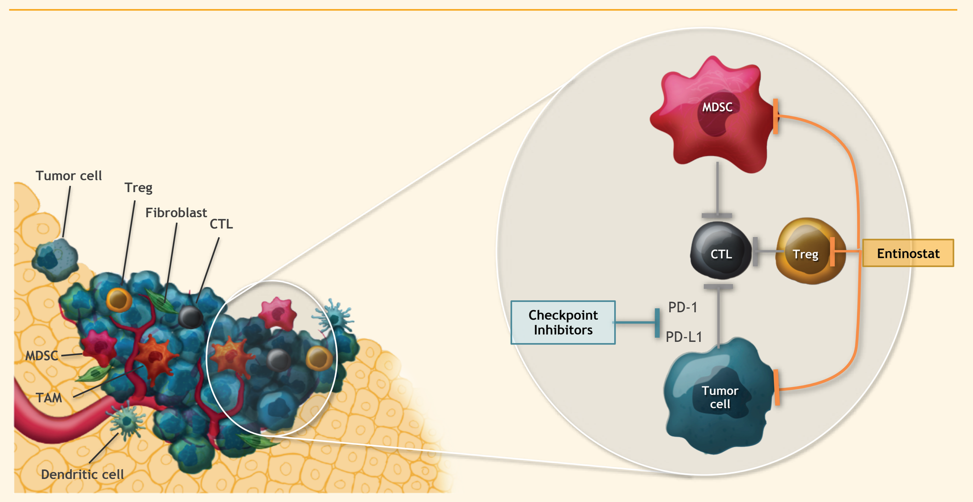
Melissa L. Johnson,[1] Alex A. Adjei,[2] Mateusz Opyrchal,[3] Suresh Ramalingam,[4] Pasi A. Jänne,[5] George Dominguez,[6] Dmitry Gabrilovich,[6] Rachel Sorensen,[7] Jeannette Hasapidis,[7] Scott J. Diede,[8] Peter Ordentlich,[7] Scott Cruickshank,[7] Michael L. Meyers,[9] Matthew D. Hellmann[10]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Mayo Clinic, Rochester, MN, USA; [3]Roswell Park Cancer Institute, Buffalo, NY, USA; [4]Emory University, Atlanta, GA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]The Wistar Institute, Philadelphia, PA, USA; [7]Syndax Pharmaceuticals, Inc., Waltham, MA, USA; [8]Merck & Co., Inc., Kenilworth, NJ, USA; [9]Syndax Pharmaceuticals, Inc., New York, NY, USA; [10]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

BACKGROUND

- Entinostat is an oral, class I selective histone deacetylase (HDAC) inhibitor with well-established activity as an epigenetic modulator as well as a radiosensitizer. It has also recently been shown to reduce immunosuppressive myeloid-derived suppressor cells (MDSCs) in cancer patients.[1]
- When combined with immune checkpoint inhibition, preclinical studies demonstrate that ENT reduces both MDSCs and regulatory T cells (Tregs), thereby resulting in synergistic anti-tumor responses (**Figure 1**).[2,3]
- ENCORE 601 is a Phase 1b/2 study designed to evaluate ENT plus PEMBRO in patients with advanced NSCLC (NCT02437136).
- The objective of the Phase 1b dose-escalation/confirmation portion was to determine the recommended Phase 2 dose (RP2D).

Figure 1. **Immune checkpoint inhibitors and entinostat target complementary immunosuppressive mechanisms in the tumor microenvironment**



CTL = cytotoxic T lymphocyte; MDSC = myeloid-derived suppressor cell; TAM = tumor-associated macrophage; Treg = regulatory T cell.

METHODS

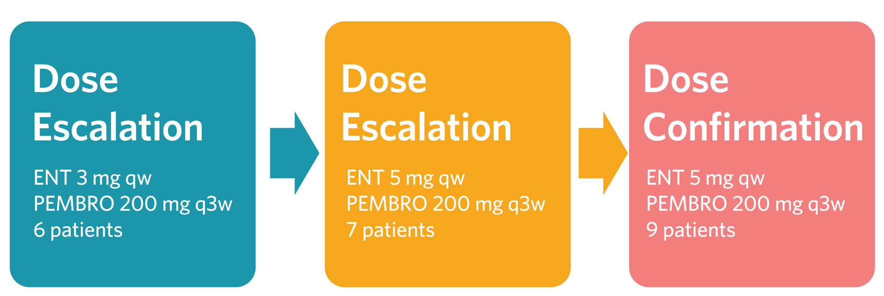
Patients and Study Design

- Patients with Stage III/IV NSCLC (previous anti-PD-1/L1 therapy was permitted) were enrolled in a 3+3 dose-escalation phase.
- Key eligibility criteria included age ≥18 years of age; recurrent or metastatic NSCLC; ≥1 measurable lesion; ≥1 prior line of therapy; ≥1 line of platinum-doublet chemotherapy; Eastern Cooperative Oncology Group performance status 0 or 1; no autoimmune disease; no immunodeficiency; no steroid or immunosuppressive therapy within 7 days prior to the first dose of study drug; no interstitial lung disease.
- Patients with *EGFR*-sensitizing mutation or *ALK* translocation were required to have had prior treatment with the appropriate therapy.

Treatment and Assessments

- ENT 3 mg and 5 mg qw PO + PEMBRO 200 mg q3w IV in 21-day cycles were explored in an initial 3+3 standard dose-escalation protocol to determine the safety, dose-limiting toxicity (DLT), maximum tolerated dose, and/or RP2D, followed by a dose-confirmation cohort (n=9) (**Figure 2**).
- Response was assessed by RECIST v1.1 and irRECIST every 6 weeks.
- Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
- Peripheral blood and tumor tissue were collected for correlative studies (tumor PD-L1 expression and phenotypic and functional evaluation of immune cell subsets).

Figure 2. **Phase 1b study schema**

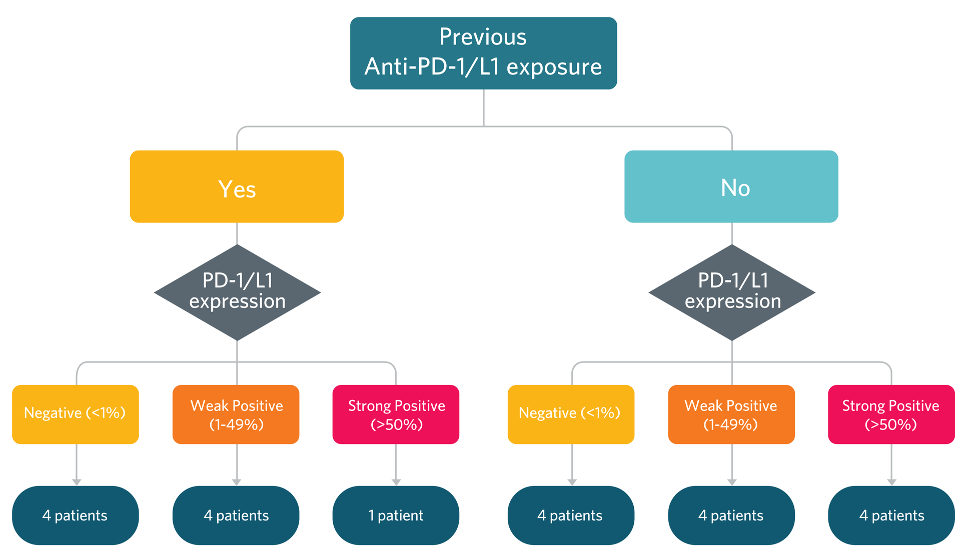


Standard dose escalation:
- <33% of patients without a DLT, proceed to next highest dose.
- ≥33% of patients without a DLT, add additonal 3 patients.

RESULTS

- Baseline demographic data are summarized in **Table 1**.
- A total of 22 patients were enrolled in Phase 1b. In the dose-escalation phase, 6 patients were treated with ENT 3 mg and 7 patients with ENT 5 mg. Nine patients were treated with ENT 5 mg during the dose-confirmation phase.
- Prior exposure to anti-PD-1/L1 therapy and PD-L1 expression are represented in **Figure 3**.
- Median follow-up was 1.8 months.

Figure 3. **Patient status of PD-1/L1 exposure and PD-L1 expression levels**



1 patient not included above due to lack of PD-L1 expression data.

Table 1. **Baseline demographic data**

Characteristic	Total (N=22)
Sex, n (%)	
Male	14 (64%)
Female	8 (36%)
Age, median (range), years	67 (46-85)
Race, n (%)	
White	18 (82%)
Asian	1 (5%)
Black or African American	1 (5%)
Other	2 (9%)
Baseline ECOG status, n (%)	
0	11 (50%)
1	11 (50%)
Smoking status, n (%)	
Current	0 (0%)
Former	19 (86%)
Never	3 (14%)
Previous anti-PD-1/L1 therapy, n (%)	
No	13 (59%)
Yes	9 (41%)
PD-L1 expression, n (%)	
Negative (<1%)	8 (36%)
Weak positive (1-49%)	8 (36%)
Strong positive (>50%)	5 (23%)
Not available	1 (5%)
Current stage of disease, n (%)	
IV	20 (91%)
IIIA	1 (5%)
IIIB	1 (5%)
Number of prior courses of systemic treatments, median (range)	2 (1-5)
Prior EGFR therapy, n (%)[a]	2 (9%)
Prior ALK therapy, n (%)[a]	0 (0%)

[a]1 unreported.
ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; PD-L1 = programmed death ligand.

SAFETY

- During the ENT 3-mg dose-escalation phase, we observed a Grade 3 DLT of immune-mediated hepatitis in 1 patient. This patient had been previously treated with anti-PD-1 therapy for 7 months.
- No other DLTs were observed with ENT 5 mg during the escalation phase; therefore, this dose was chosen for the dose-confirmation phase.
- During the dose-confirmation phase, we observed a Grade 3 DLT of hypophosphatemia in 1 patient.
- In total, 2 DLTs were observed across all 22 patients.
- A total of 22 (100%) patients experienced a treatment-emergent AE (TEAE); 14 (64%) patients experienced a Grade ≥3 TEAE; 3 (14%) patients discontinued because of either a PEMBRO- or ENT-related TEAE. The 3 TEAEs leading to discontinuation were acute respiratory failure, autoimmune hepatitis, and hypercalcemia.
- All grade ≥3 AEs are summarized in **Table 2**.
- All related AEs of any grade occurring in ≥2 patients are summarized in **Table 3**.

Table 2. **Summary of grade ≥3 AEs (any relation/causality)**

Preferred term, n (%)	PEMBRO + ENT 3 mg (n=6)	PEMBRO + ENT 5 mg (n=16)	Total (N=22)
Patients with TEAE with severity Grade ≥3	5 (83%)	9 (56%)	14 (64%)
Lung infection/pneumonia	3 (50%)	0 (0%)	3 (14%)
Embolism	1 (17%)	1 (6%)	2 (9%)
Hypophosphatemia	0 (0%)	2 (13%)	2 (9%)
Acute respiratory failure	0 (0%)	1 (6%)	1 (5%)
Anemia	0 (0%)	1 (6%)	1 (5%)
Atrial fibrillation	0 (0%)	1 (6%)	1 (5%)
Autoimmune hepatitis	1 (17%)	0 (0%)	1 (5%)
Fatigue	0 (0%)	1 (6%)	1 (5%)
Hypercalcemia	0 (0%)	1 (6%)	1 (5%)
Hemiparesis[a]	0 (0%)	1 (6%)	1 (5%)
Neutropenia	1 (17%)	0 (0%)	1 (5%)
Peripheral edema	0 (0%)	1 (6%)	1 (5%)
Pericardial effusion	1 (17%)	0 (0%)	1 (5%)
Pleural effusion	1 (17%)	0 (0%)	1 (5%)
Pulmonary hemorrhage	0 (0%)	1 (6%)	1 (5%)
Urinary tract obstruction	1 (17%)	0 (0%)	1 (5%)

[a]Related to brain metastases.

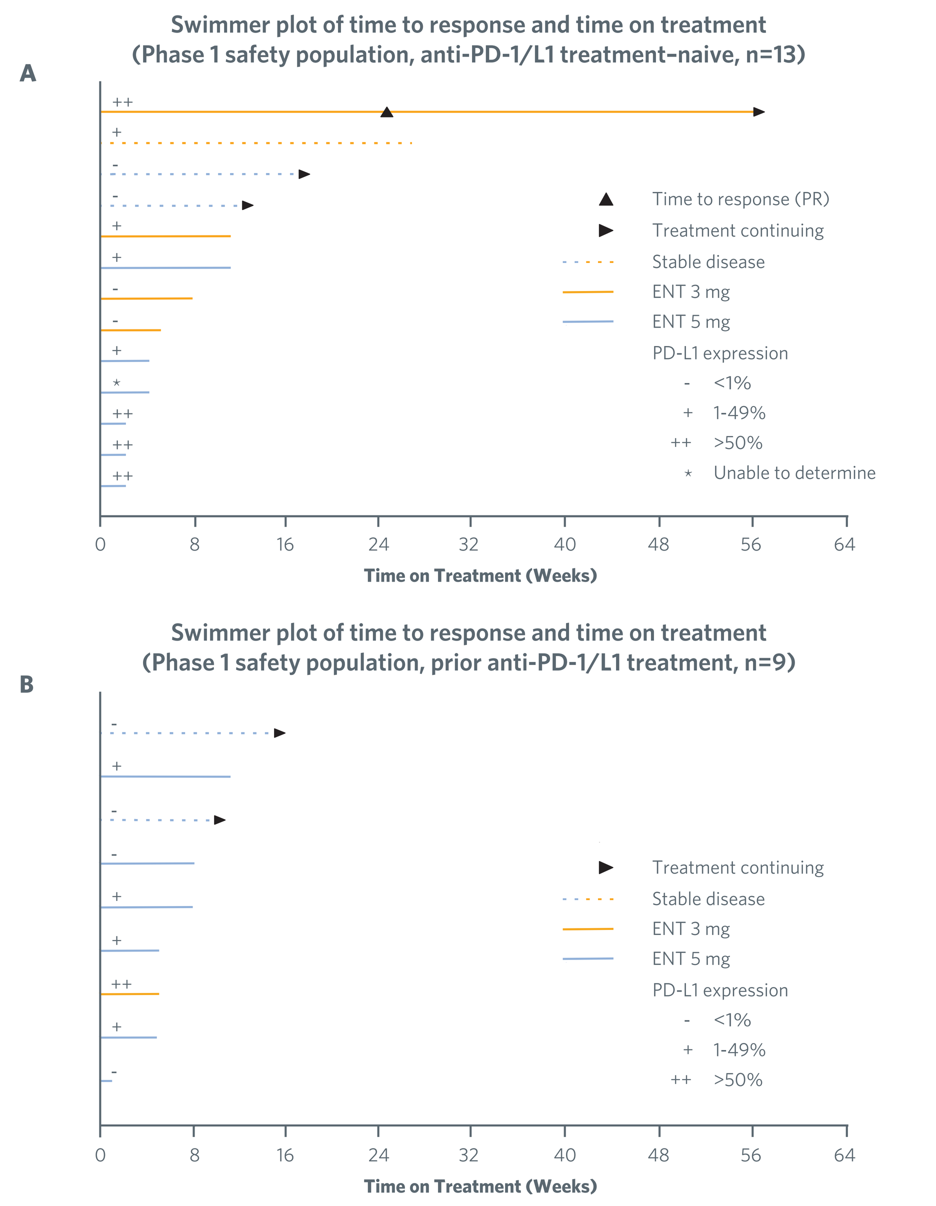
Table 3. **All related AEs of any grade occurring in ≥2 patients**

Preferred term, n (%)	PEMBRO + ENT 3 mg (n=6)	PEMBRO + ENT 5 mg (n=16)	Total (N=22)
Patients with any grade AE related to study treatment	5 (83%)	13 (81%)	18 (82%)
Fatigue	1 (17%)	10 (63%)	11 (50%)
Pruritus	1 (17%)	4 (25%)	5 (23%)
Decreased appetite	0 (0%)	4 (25%)	4 (18%)
Diarrhea	2 (33%)	2 (13%)	4 (18%)
Hypophosphatemia	0 (0%)	4 (25%)	4 (18%)
Myalgia	0 (0%)	4 (25%)	4 (18%)
Nausea	1 (17%)	3 (19%)	4 (18%)
Anemia	0 (0%)	3 (19%)	3 (14%)
Vomiting	1 (17%)	2 (13%)	3 (14%)
Dry mouth	0 (0%)	2 (13%)	2 (9%)
Dry skin	0 (0%)	2 (13%)	2 (9%)
Dyspnea	0 (0%)	2 (13%)	2 (9%)
Mucosal inflammation	1 (17%)	1 (6%)	2 (9%)
Peripheral edema	0 (0%)	2 (13%)	2 (9%)
Rash, maculopapular	1 (17%)	1 (6%)	2 (9%)

EFFICACY

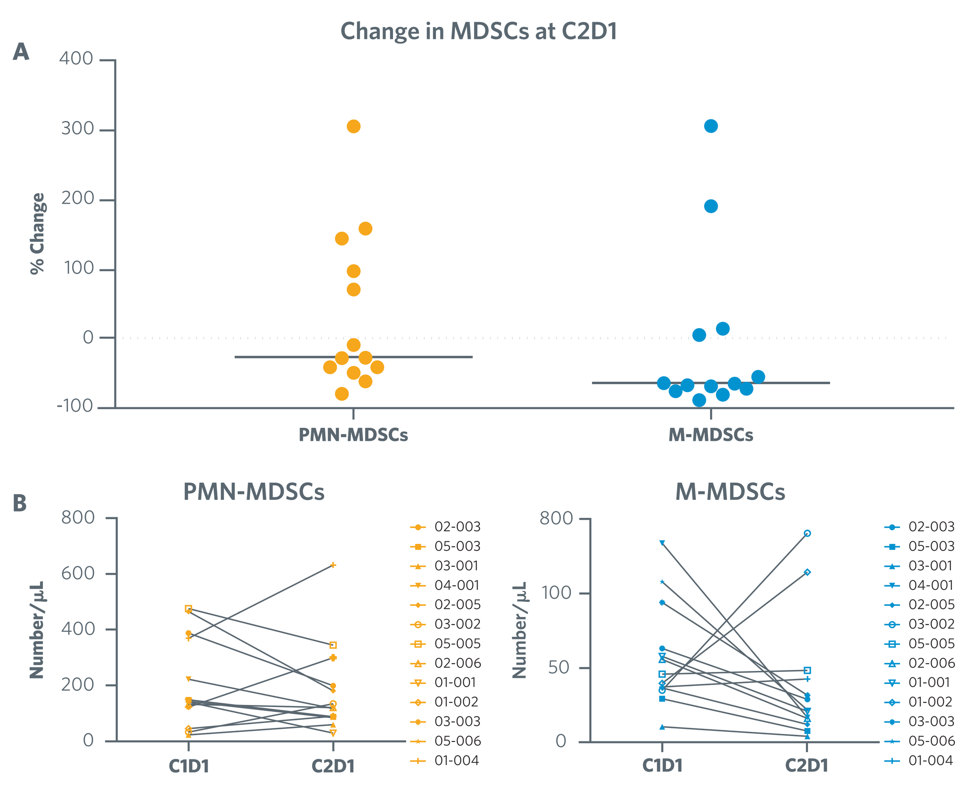
- Of 13 patients not previously treated with anti-PD-1/L1 therapy, 1 patient had a best response of partial response and 3 patients had stable disease. Of 9 patients with prior anti-PD-1/L1 therapy exposure, 2 patients had a best response of stable disease.
- Efficacy data are still maturing in patients enrolled in the confirmation phase.
- Swimmer plots of time to response and time on treatment are shown in **Figure 4** for anti-PD-1/L1 treatment-naive (**A**) and anti-PD-1/L1 treatment-exposed (**B**).
- A general trend in decreased MDSCs was observed at Cycle 2, Day 1; however, the small sample size (n=13) and lack of control arm preclude a direct association of MDSC changes with ENT treatment (**Figure 5**).

Figure 4. **Patient response and time on treatment**



A. Anti-PD-1/L1 treatment–naive patient responses; **B.** Anti-PD-1/L1 treatment–exposed patient responses. PR = partial response. Time to response represents first time point of response that was subsequently confirmed. Response is based on the treating investigator's assessment using RECIST v.1.1.

Figure 5. **Immune correlates**



A. Change in numbers of PMN-MDSCs and M-MDSCs at C2D1; **B.** MDSC paired numbers at C1D1 and C2D1. PMN = polymorphonuclear; M = monocytic.

CONCLUSIONS

- ENT 3 and 5 mg PO weekly can be safely combined with PEMBRO 200 mg IV every 3 weeks.
- Based on the manageable safety profile, ENT 5 mg was selected for the dose-confirmation and Phase 2 portions.
- The Phase 2 portion of the study is ongoing, where efficacy of the combination is being formally evaluated in 3 different patient populations: patients with NSCLC (not previously treated with a PD-1/L1 blocking antibody), patients with NSCLC (previously treated with a PD-1/L1 blocking antibody), and patients with melanoma (previously treated with a PD-1/L1 blocking antibody).

References

1. Tomita Y, et al. *Oncoimmunology*. 2016. 10.1080/2162402X.2016.1219008 **2.** Kim K, et al. *Proc Natl Acad Sci U S A*. 2014;111:11774-11779; **3.** Shen L, et al. *PLoS ONE*. 2012;7:e30815.

Acknowledgments

This study was sponsored by Syndax Pharmaceuticals, Inc., in collaboration with Merck & Co., Inc., Kenilworth, NJ. Writing assistance provided by Kate Revill, PhD, Health Science Communications, New York, and funded by Syndax Pharmaceuticals, Inc.

Poster presented at the Society for the Immunotherapy of Cancer Annual Meeting, November 9-13, 2016, National Harbor, Maryland.