ENCORE 601: A Phase 2 study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with melanoma

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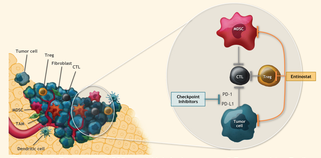
BACKGROUND

- ENT is an oral, class I selective histone deacetylase inhibitor shown preclinically to enhance the activity of immune checkpoint blockade through the reduction of functionally immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells (**Figure 1**).[1-3]
- Increases in MDSC number have been demonstrated to be associated with lack of clinical efficacy of checkpoint inhibitors in melanoma and may serve as a marker of treatment outcome.[4]
- Despite several immunotherapies now available for the treatment of advanced/metastatic melanoma, a majority of patients will progress on or following an immunotherapy (PEMBRO median progression-free survival [PFS] 5.5 months; nivolumab median PFS 5.1 months) and approximately 25% with an objective response will progress within a median of 21 months.[5-7]
- Viable treatment options for patients progressing on anti-PD-1/PD-L1 therapy (with or without prior ipilimumab) is an area of unmet need.
- ENCORE 601 is a Phase 1b/2 study designed to evaluate the combination of ENT plus PEMBRO (NCT02437136).
  - Phase 1b identified ENT 5 mg PO weekly and PEMBRO 200 mg IV every 3 weeks as the recommended Phase 2 dose.[8]

Figure 1. **Immune Checkpoint Inhibitors and Entinostat Target Complementary Immunosuppressive Mechanisms in the Tumor Microenvironment**



CTL = cytotoxic T lymphocyte; MDSC = myeloid-derived suppressor cell; Treg = regulatory T cell.

METHODS

Patients and Study Design

- The Phase 2 expansion phase of ENCORE 601 utilizes a Simon 2-stage design to assess activity across 4 cohorts: 1) anti-PD-1/L1–naive NSCLC patients, 2) NSCLC patients previously progressing on or after anti-PD-1/L1 treatment, 3) melanoma patients previously progressing on or after anti-PD-1/L1 treatment, and 4) anti-PD-1/L1–naive colorectal cancer (mismatch repair-proficient).
- For cohort 3:
  - Key eligibility criteria included age ≥18 years; recurrent or metastatic melanoma; ≥1 measurable lesion; previously treated with anti-PD-1/PD-L1 therapy and experienced progressive disease by irRECIST; progressive disease with a BRAF-inhibitor if BRAF V600–mutation positive; 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.
  - Thirteen patients with recurrent or metastatic melanoma were enrolled into the first stage of the Phase 2 study (**Figure 2**); results of the first stage of cohort 3 are reported.

Treatment and Assessments

- Patients received ENT 5 mg QW PO + PEMBRO 200 mg Q3W IV in 21-day cycles until disease progression or discontinuation for other reasons.
- 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 (version 4.03).
- Peripheral blood and tumor tissue were collected for correlative studies as detailed in **Table 1**.

Figure 2. **Phase 2 Simon 2-Stage Design**

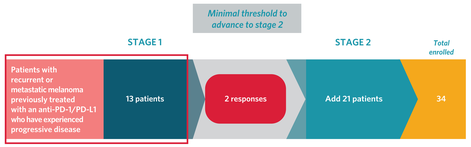


Table 1. **Collection and Planned Analysis of Peripheral Blood and Tumor Tissue**

	ENCORE 601	
Analysis	**Blood Sample***	**Tumor Tissue†**
Protein lysine acetylation‡	Yes	Yes
MDSCs	Yes	Yes
T cells (CD8, CD4, Treg)	Yes	Yes
B cells	Yes	Yes
Dendritic cells	Yes	Yes
Natural killer cells	Yes	Yes
PD-L1	-	Yes
Macrophage	-	Yes
Gene expression – NanoString; RNA-Seq	-	Yes

*Samples are collected C1D1, C2D1 and C2D15.
†Samples are collected C1D1 and C2D15; analyses of markers prioritized based on tissue availability.
‡Samples are collected C1D1, C1D15 and C2D15.
CD = cluster of differentiation; C1D1 = cycle 1, day 1; C1D15 = cycle 1, day 15; C2D1 = cycle 2, day 1; C2D15 = cycle 2, day 15.

RESULTS

- Baseline demographic data are summarized in **Table 2**.
- All patients received a prior anti-PD-1, 8 patients also received prior ipilimumab and 2 patients received a prior BRAF inhibitor.
- Details on response and duration of prior line of anti-PD-1 therapy are included in Table 2.

Table 2. **Baseline Demographic Data**

Characteristic	**Total (N=13)**
Sex, n (%)	
Male	9 (69%)
Female	4 (31%)
Age, median (range), years	62 (38-86)
Race, n (%)	
White	13 (100%)
Baseline ECOG status, n (%)	
0	8 (62%)
1	5 (38%)
PD-L1 expression, n (%)	
Negative	4 (31%)
Positive	6 (46%)
Not evaluable	3 (23%)
Baseline LDH (>ULN)	
Yes	3 (23%)
No	4 (31%)
Not available	6 (46%)
Site of metastases, n (%)	
Visceral	6 (46%)
Non-visceral	7 (54%)
Prior BRAF inhibitor therapy, n (%)	2 (15%)
Prior ipilimumab therapy, n (%)	8 (62%)
Prior PEMBRO therapy, n (%)	7 (54%)
Best response on prior anti-PD-1 therapy	
Complete response	1 (8%)
Partial response	0 (0%)
Stable disease	7 (54%)
Disease progression	5 (38%)
Duration on prior anti-PD-1 therapy (months)	
Median (range)	6.48 (2.79-20.29)
Duration between last dose of prior anti-PD-1 therapy and first of dose of ENT study therapy (months)	
Median (range)	1.77 (0.72-28.8)

ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal.

SAFETY

- Thirteen (100%) patients experienced a treatment-emergent adverse event (TEAE); 8 (62%) patients experienced a Grade ≥3 TEAE, and of these, 4 patients experienced a Grade ≥3 TEAE related to either study drug.
- One (8%) patient discontinued because of a TEAE. This was an event of autoimmune hepatitis deemed probably related to PEMBRO.
- All Grade ≥3 AEs are summarized in **Table 3**.
- All related AEs of any grade occurring in ≥2 patients are summarized in **Table 4**.

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

Preferred Term, n (%)	**Total (N=13)**
Patients with TEAE with severity Grade ≥3	8 (62%)
Alanine aminotransferase/aspartate aminotransferase increased	2 (15%)
Atrial flutter	1 (8%)
Blood bilirubin increased	1 (8%)
Cellulitis	1 (8%)
Fatigue	1 (8%)
Hyponatremia	1 (8%)
Hypovolemia	1 (8%)
Nausea	1 (8%)
Rash	1 (8%)
Sepsis	1 (8%)
Urinary tract infection	1 (8%)

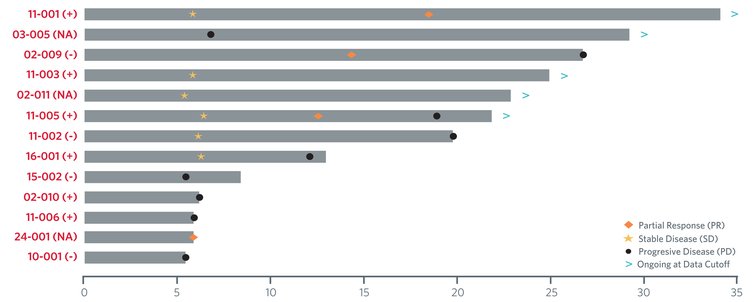
Table 4. **All Related AEs of Any Grade Occurring in ≥2 Patients**

Preferred Term, n (%)	**Total (N=13)**
Patients with any grade AE related to study treatment	10 (77%)
Nausea	7 (54%)
Diarrhea	3 (23%)
Pruritus	3 (23%)
Fatigue	2 (15%)

EFFICACY

- Of 13 patients with advanced melanoma previously progressing on or following anti-PD-1 therapy, 4 patients had a partial response by RECIST v1.1 and irRECIST (3 confirmed, 1 unconfirmed) for an overall response rate of 31% (95% CI: 9-61%).
  - Of the 4 responders, 2 had SD and 2 had PD as best response to the prior anti-PD-1 therapy, with a median duration on prior anti-PD-1 therapy of 4.9 months (range 2.7-12.5). Three of the 4 entered this study within 10 months (range 1.8-10.4) of last dose of prior anti-PD-1 therapy. An exception is patient 11-001, whose last dose was 28.8 months prior to study start.
  - Of note, 1 patient with a confirmed PR converted from a PD-L1 negative, non-inflamed gene signature in a pre-treatment tumor biopsy to PD-L1 positive, inflamed gene signature post-treatment. Analyses for the other responders are ongoing.
- Four patients (31%) had a best response of stable disease; 2 of these patients are ongoing.
- Response, time to response and time on treatment are shown in **Figure 3**, and best percent change from baseline is shown in **Figure 4**.

Figure 3. **Patient Response and Time on Treatment**



irRECIST patient responses by investigator assessment. PD-L1 expression status is denoted in parenthesis. Notes: 11-005 had a PR at Week 6 by central review. 03-005 had progressive disease at Week 6; however, the patient continued in the study because of clinical benefit as determined by the investigator.

Figure 4. **Change in Tumor Size From Baseline**

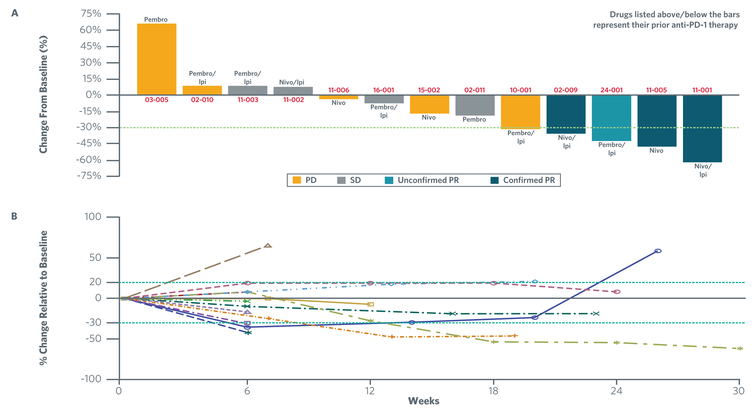


Figure 4A) Waterfall plot of percentage change in tumor size from baseline (sum of diameters of target lesions).
Figure 4B) Spider plot of percentage change in tumor size relative to baseline by weeks from start of study (sum of diameters of target lesions).

CONCLUSIONS

- In this anti-PD-1–experienced melanoma population where current treatment options are lacking, ENT plus PEMBRO shows promising activity with an overall response rate of 31%.
- This combination has an acceptable toxicity profile.
- Enrollment is ongoing in stage 2.
- Correlative analysis of peripheral blood and tumor tissue is ongoing.

References

1. Tomita Y, et al. *Oncoimmunology.* 2016;5:e1219008; **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; **4.** Kitano S, et al. *J Clin Oncol.* 2012;30:abstr 2518; **5.** KEYTRUDA® (pembrolizumab) Prescribing Information; revised 03/2017; **6.** OPDIVO® (nivolumab) Prescribing Information; revised 04/2017; **7.** Zaretsky JM, et al. *N Engl J Med.* 2016;375:819-829; **8.** Johnson ML, et al. *J Immunother Cancer.* 2016;4(suppl 1):73.

Acknowledgments

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