ENCORE 601: A phase 2 study of entinostat in combination with pembrolizumab in patients with microsatellite stable metastatic colorectal cancer.

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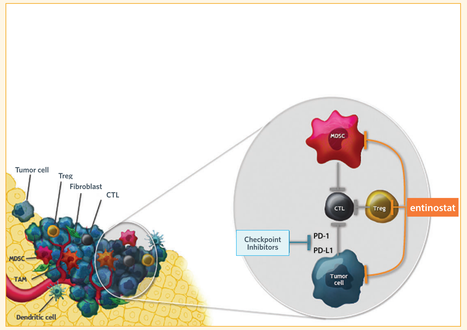
BACKGROUND

In studies reported to date, no objective responses to single agent PD-1 inhibitors have been observed in advanced/metastatic CRC (mCRC) patients with microsatellite stable (MSS)/mismatch repair proficient (pMMR) tumors[1]. Since most patients with mCRC have MSS/pMMR tumors, additional strategies are needed to improve effectiveness of immunotherapies in these patients[2].

Entinostat (ENT), an oral, class I-selective histone deacetylase inhibitor, enhances anti-PD-1 activity by downregulation of immunosuppressive cell types (eg, Tregs and MDSCs) in the tumor microenvironment in vivo[3] and has shown promising activity with pembrolizumab (PEMBRO) in patients with melanoma and lung cancer[4-6]. **Figure 1** describes the targets of entinostat and pembrolizumab in modulating immunosuppression.

This study evaluates the safety and efficacy of ENT + PEMBRO in patients with MSS/pMMR mCRC.

Figure 1. **Entinostat and Pembrolizumab Synergize to Modulate Immunosuppression.**



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

METHODS

Key Eligibility Criteria

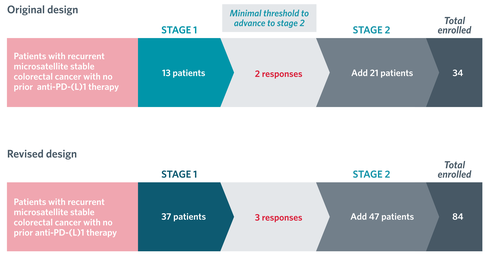
- Documented mismatch repair-proficient colon cancer as determined by either immunohistochemistry for mismatch repair proteins or PCR-based functional microsatellite instability.
- Received at least 1 chemotherapeutic regimen in the advanced/metastatic setting and experienced documented, unequivocal progressive disease by either RECIST 1.1 or clinical assessment.
- Prior treatment with a PD-1/PD-L1-blocking antibody was not permitted.
- Other eligibility criteria included ECOG Performance Status 0 or 1, measurable disease per RECIST 1.1, and adequate end organ function.

METHODS (continued)

Study Design

- The Phase 2 expansion phase of ENCORE 601 utilizes a Simon 2-stage design to assess activity. The original design is noted below **(Figure 2)**, and the original Stage 1 patients reported here. The cutoff date for the analysis reported here was April 24, 2018.
- Based on emerging data regarding the minimal level of activity of PD-L1 inhibitors in MSS/pMMR CRC patients, the study was amended prior to completion of Stage 1 to expand Stage 1 enrollment to a total of 37 patients. Three responses of 37 are required to advance to Stage 2, at which point an additional 47 patients would be enrolled.
- The primary endpoint is objective response rate (ORR) as assessed by irRECIST assessed every 6 weeks.

Figure 2. **Simon 2-Stage Study Design.** The first 16 patients from stage 1 are reported



Treatment Assessments

- Patients received entinostat 5 mg QW PO + pembrolizumab 200 mg Q3W IV in 21-day cycles until disease progression or discontinuation for other reasons.
- Peripheral blood and tumor tissue were collected for correlative studies are described in **Table 1**.

Table 1: Correlative 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
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.

PATIENT DEMOGRAPHICS

- For the first 16 patients, the first patient enrolled August 2017 and last patient enrolled September 2017.
- Patient demographics are listed in **Table 2**.

Table 2: Demographics	Total (N=16)
Sex	
Male	8 (50%)
Female	8 (50%)
Age (years)	
Median	58.0
Range	36 to 69
Race	
White	14 (88%)
Black or African American	1 (6%)
Other	1 (6%)
Baseline ECOG Performance Score	
0	7 (44%)
1	8 (50%)
Stage of Disease at Initial Diagnosis	
IIA	1 (6%)
IIIA	3 (19%)
IIIB	2 (13%)
IVA	4 (25%)
IVB	5 (31%)
Baseline LDH (> ULN)	
Yes	5 (31%)
No	11 (69%)
Baseline CEA (> ULN)	
Yes	8 (50%)
No	2 (13%)
Not Reported	6 (38%)
Tumor Location at Initial Diagnosis	
Left side	2 (13%)
Right side	5 (31%)
Rectum	4 (25%)
Transverse	1 (6%)
Not specified	4 (25%)
Lines of Prior Therapy	
1	3 (19%)
2	4 (25%)
3	2 (13%)
4	4 (25%)
>4	3 (19%)

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

EFFICACY

- One patient of the first 16 had an objective response, resulting in an ORR of 6% (95% CI: 0-30).
- The patient with a partial response is ongoing, as shown in **Figure 3** and **Figure 4**. Additional details of this patient are as follows:
  - 68 year old, male, with right sided primary, CEA at baseline = 9.8 ng/mL (ULN = 3.8 ng/mL), 6 lines of prior therapy in the advanced setting (best response to any of these prior therapies was stable disease), ECOG PS = 0, and sites of metastases = lung.
  - The patient entered the study 7.2 years following time of metastatic diagnosis (7.4 years from initial diagnosis).
  - MSS status confirmed by Foundation One.
  - Mutation burden = intermediate 10 muts/Mb
- Two patients (14-006 and 26-002) exhibited pseudoprogression at the first tumor assessment, as seen in **Figure 5**.
- Median time on treatment was 12.28 weeks, with the patient with a partial response being on treatment for over 30 weeks and ongoing.
- Nine patients experienced stable disease as best response **(Figure 3)**.
- Two of the nine experienced stable disease for 4 months or longer shown in **Figure 4**.
- Median progression-free survival was 86 days (95% CI, 46-134).

EFFICACY (continued)

Figure 3. **Percentage Change in Tumor Size from Baseline (Sum of Diameters of Target Lesions).** One partial response has been observed to date. Three patients did not have post-baseline measurements.

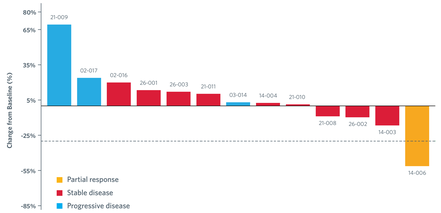


Figure 4. **Patient Response and Time on Treatment.** irRECIST patient response by investigator assessment. Nine of 16 patients exhibited stable disease and one patient remains on treatment.

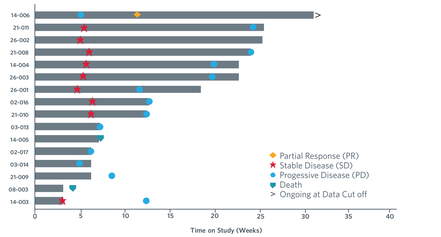
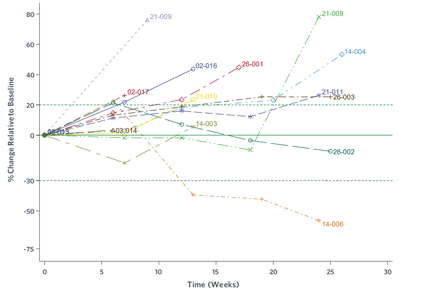


Figure 5. **Change in Tumor Size from Baseline Over Time.** Two patients exhibited pseudoprogression.



SAFETY

- Table 3 shows treatment-emergent adverse events related to entinostat or pembrolizumab or both in >10% of patients, or Grade ≥3 TEAE in any patient.
- TEAEs Grade 3 or higher occurred in 11/16 patients.
  - One patient experienced a Grade 3/4 related irAE (pneumonitis). Seven other patients experienced Grade 3/4 AEs with only anemia and blood alkaline phosphatase increase occurring in more than one patient (2 patients each).
- 2 (13%) patients discontinued due to a treatment-related AE. These events included liver enzyme increase and pneumonitis.

Table 3: Safety	Any Grade (N=16)	Grade ≥3 (N=16)
Subjects With At Least One Treatment-Emergent Adverse Event Related to Study Treatment	**16 (100.0)**	**8 (50.0)**
Gastrointestinal disorders		
Nausea	5 (31.3)	
Diarrhea	4 (25.0)	1 (6.3)
Vomiting	4 (25.0)	
Constipation	3 (18.8)	
Gastroesophageal reflux disease	2 (12.5)	
Pancreatitis	1 (6.3)	1 (6.3)
General disorders and administration site conditions		
Fatigue	8 (50.0)	1 (6.3)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	2 (12.5)	1 (6.3)
Skin and subcutaneous tissue disorders		
Pruritus	3 (18.8)	
Rash maculo-papular	2 (12.5)	
Investigations		
Blood alkaline phosphatase increased	6 (37.5)	2 (12.5)
Aspartate aminotransferase increased	5 (31.3)	1 (6.3)
Platelet count decreased	3 (18.8)	
Lymphocyte count decreased	1 (6.3)	1 (6.3)
Neutrophil count decreased	1 (6.3)	1 6.3)
White blood cell count decreased	1 (6.3)	1 (6.3)
Metabolism and nutrition disorders		
Decreased appetite	3 (18.8)	
Hypoalbuminemia	2 (12.5)	
Hyperglycemia	1 (6.3)	1 (6.3)
Hypophosphatemia	1 (6.3)	1 (6.3)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (25.0)	
Myalgia	4 (25.0)	
Endocrine disorder		
Hypothyroidism	2 (12.5)	
Blood and lymphatic system disorders		
Anemia	4 (25.0)	2 (12.5)
Thrombocytopenia	2 (12.5)	
Nervous system disorder		
Headache	2 (12.5)	
Hepatobiliary disorder		
Cholangitis	1 (6.3)	1 (6.3)

CONCLUSIONS

- ENT + PEMBRO demonstrates acceptable safety and encouraging preliminary activity in a small cohort of MSS/pMMR CRC patients, a patient population in which clinical benefit has not been observed with PD-(L)1 monotherapy.
- Additional analyses are ongoing to identify biomarkers that can predict clinical benefit in this population.
- The decision to proceed to Stage 2 will be based on the analyses of the amended Stage 1 cohort. Enrollment is currently ongoing.

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Acknowledgments

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