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Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti–PD-(L)1 Therapy

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ABSTRACT

Purpose: New therapies are needed to treat immune checkpoint inhibitor–resistant non–small cell lung cancer (NSCLC) and identify biomarkers to personalize treatment. Epigenetic therapies, including histone deacetylase inhibitors, may synergize with programmed cell death-1 (PD-1) blockade to overcome resistance. We report outcomes in patients with anti-programmed cell death ligand-1 [PD-(L)1]–resistant/refractory NSCLC treated with pembrolizumab plus entinostat in ENCORE 601.

Patients and Methods: The expansion cohort of ENCORE 601 included patients with NSCLC who previously experienced disease progression with immune checkpoint inhibitors. The primary endpoint for the phase II expansion cohort is overall response rate (ORR); safety, tolerability, and exploratory endpoints are described.

Results: Of 76 treated patients, 71 were evaluable for efficacy. immune-regulated RECIST–assessed ORR was 9.2% [95% confidence interval (CI): 3.8–18.1], which did not meet the prespecified threshold for positivity. Median duration of response was 10.1 months (95% CI: 3.9–not estimable), progression-free survival (PFS) at 6 months was 22%, median PFS was 2.8 months (95% CI: 1.5–4.1), and median overall survival was 11.7 months (95% CI: 7.6–13.4). Benefit was enriched among patients with high levels of circulating classical monocytes at baseline. Baseline tumor PD-L1 expression and *IFNγ* gene expression were not associated with benefit. Treatment-related grade ≥3 adverse events occurred in 41% of patients.

Conclusions: In anti–PD-(L)1–experienced patients with NSCLC, entinostat plus pembrolizumab did not achieve the primary response rate endpoint but provided a clinically meaningful benefit, with objective response in 9% of patients. No new toxicities, including immune-related adverse events, were seen for either drug. Future studies will continue to evaluate the association of monocyte levels and response.

Introduction

Anti-programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) immunotherapy administered as monotherapy or combined with chemotherapy has significantly improved outcomes for patients with non–small cell lung cancer (NSCLC) and has led to the approval of nivolumab and atezolizumab in the metastatic setting, durvalumab in the locally advanced setting, and pembrolizumab in both the metastatic and locally advanced settings (1–5). Despite this success, a substantial proportion of patients do not experience a response to initial PD-1 therapy or eventually develop acquired resistance (6). Effective therapeutic approaches that circumvent resistance to PD-1 blockade and patient selection strategies to identify those who may benefit from mechanistically driven combinations are critically needed. Although a major effort to address these clinical needs has been underway, few successes have been found to date (7, 8).

To help inform rational therapeutic development to address resistance to PD-1 blockade, mechanisms of primary and acquired resistance have been explored. Resistance is likely to be multifactorial and may be generated through genetic and epigenetic changes in the cancer cell and immune cell populations (9). Key mechanisms of immune evasion identified in preclinical studies and patient samples include neoantigen loss, poor immune cell infiltration, effector cell exhaustion and dysfunction, and upregulation of regulatory pathways that lead to an immunosuppressive microenvironment (10–13). For example, epigenetic changes in NSCLC cell lines were shown to induce aberrant activation of gene expression pathways, such as *MYC* signaling, and loss of antigen presentation leading to anti–PD-(L)1 resistance (8, 14–16). Epigenetic repression of neoantigen expression may also be a mechanism of immune evasion (16). These data and others demonstrating impact of epigenetic factors on immunosuppressive myeloid cell populations (8, 14–16) suggest that the combination of immune checkpoint inhibitors plus epigenetic therapy could lead to increased activation of the IFN pathway, increased T-cell attraction, and decreased proliferation of tumor cells (15).

Targeting histone deacetylases (HDAC) is one approach to preventing and normalizing epigenetic changes. HDAC inhibition has been demonstrated preclinically to improve immune competency

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Despite improved outcomes for patients with non–small cell lung cancer (NSCLC) with single-agent anti–programmed cell death-1 (anti–PD-1) immunotherapy, some patients do not respond to treatment, and resistance occurs in other patients. New therapeutic strategies to overcome resistance are needed, as well as biomarkers to drive insight and personalize treatment. To help address these obstacles, we performed a clinical trial of the anti–PD-1 inhibitor pembrolizumab combined with the histone deacetylase (HDAC) inhibitor entinostat in patients with PD-1 axis inhibitor–resistant NSCLC and examined predictive biomarkers for response. Preclinical results suggest that HDAC inhibition may enhance the efficacy of immunotherapy through multiple mechanisms. Here we show that this combination provides clinical benefit in a subset comprising 9% of patients. No new toxicities, including immune-related adverse events, were seen for either drug. We also report that benefit is enriched in patients with increased circulating baseline classical monocytes.

through increased MHC presentation and tumor antigen expression and reduced number and function of immunosuppressive cells (15, 17–21), particularly myeloid-derived suppressor cells (MDSC; refs. 21, 22). Entinostat is a selective inhibitor of class I HDACs that has been shown to be effective in combination with PD-1 blockade in multiple tumor models, including lung carcinoma mouse models, which exhibited significant tumor growth reduction (20). Building on preclinical data, a recent correlative analysis of patients with breast cancer treated with entinostat plus an estrogen modulator (ENCORE 301) demonstrated monocytic and granulocytic MDSCs as specific targets of entinostat (22).

On the basis of these data, we hypothesized that the combination of entinostat plus the PD-1 inhibitor pembrolizumab could be effective for patients with NSCLC whose disease had previously progressed despite PD-1 blockade. In addition, we predicted that evaluation of pretreatment circulating levels of monocytic cells or their derivatives or changes in expression of selected genes in pretreatment tumor tissue may provide a means to identify biomarkers for future selection of subjects for treatment by entinostat in combination with immunotherapy. To explore these hypotheses, ENCORE 601 was a multicenter, single-arm, open-label study designed to assess the safety and efficacy of entinostat and pembrolizumab in patients with metastatic NSCLC resistant to anti–PD-(L)1 therapy.

Patients and Methods

Study design and participants

ENCORE 601 is a phase Ib/II, open-label, dose-escalation study of entinostat in combination with pembrolizumab in patients with NSCLC, with expansion cohorts in patients with NSCLC, melanoma, and mismatch repair–proficient colorectal cancer. This study was approved by the institutional review board or independent ethics committee at each center and conducted in accordance with Good Clinical Practice guidelines defined by the International Conference on Harmonization. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki. This report focuses on patients with refractory NSCLC (cohort 2) enrolled in the single-arm, multicenter expansion phase (phase II) of ENCORE-601.

Eligible patients had recurrent or metastatic NSCLC, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and were previously treated with at least one chemotherapeutic regimen for advanced or metastatic NSCLC and developed unequivocal progressive disease by either RECIST 1.1 (23) or clinical assessment. Patients originally diagnosed with early-stage disease (stage I–III) must have recurred after definitive therapy or developed distant metastatic disease to be eligible. Patients must also have been previously treated for at least 6 weeks with a PD-1/PD-L1 blocking antibody and experienced documented radiographic progression by immune-related RECIST (irRECIST) (24) or similar criteria during or within 12 weeks after the last dose. Patients with EGFR mutation–positive or anaplastic lymphoma kinase (ALK) translocation–positive disease must have previously been treated with an appropriate targeted therapy. Pretherapy tumor biopsies were required, and on-treatment biopsies were optional. Pretherapy PD-L1 expression was assessed retrospectively and was not used to determine eligibility for enrollment. Patients were excluded whether they had immunodeficiency or active autoimmune disease or were on immunosuppressive therapy. Treatment continued up to 2 years or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or if a study investigator or sponsor decided to discontinue treatment.

Procedures

Patients were enrolled to receive entinostat 5 mg by mouth on cycle days 1, 8, and 15 in combination with pembrolizumab administered intravenously at a dose of 200 mg on day 1 of each cycle for a maximum of 35 21-day cycles.

Tumor response was assessed using irRECIST 1.1 criteria for evaluation of contrast-enhanced CT or contrast-enhanced MRI performed at screening and then every 6 weeks until documented progressive disease. Complete response (CR) and partial response (PR) were initially assessed by a study investigator and confirmed by a center core radiologic laboratory.

Adverse events (AE), including immune-related AEs (irAE), were graded according to the NCI Common Terminology Criteria for Adverse Events v4.03.

Outcomes

The primary endpoint of phase Ib (dose escalation/confirmation cohorts) was to determine the dose-limiting toxicities (DLT) and MTD or recommended phase II dose (RP2D) of entinostat in combination with pembrolizumab (25). The primary endpoint of phase II (expansion cohorts) was to evaluate the efficacy of entinostat at the RP2D in combination with pembrolizumab in patients with anti–PD-(L)1–resistant NSCLC as determined by overall response rate (ORR), per irRECIST.

The secondary endpoints were safety and the tolerability of entinostat in combination with pembrolizumab (based on clinical AEs, laboratory parameters, and electrocardiogram results). Secondary measures of efficacy included clinical benefit rate, progression-free survival (PFS) rate at 6 months, PFS, overall survival (OS), and duration of response (DOR) and time to response in patients who experienced a response to treatment (i.e., CR or PR). These endpoints were evaluated using RECIST 1.1 and irRECIST.

Exploratory endpoints include measurement of pretreatment and posttreatment changes in immune cell subtypes and gene expression analysis of mandated pretreatment tumor biopsies. Pharmacokinetics and pharmacodynamics of entinostat when given in combination with pembrolizumab were also evaluated, in addition to exploring the exposure-safety response of entinostat in combination

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with pembrolizumab. The correlation of clinical benefit and multiple parameters at pretherapy were analyzed to explore potential predictive biomarkers (method further described in the Supplementary Appendix).

Pharmacodynamic analysis

Whole-blood samples were collected in cell preparation tubes with sodium citrate (BD Biosciences). Peripheral blood mononuclear cells (PBMC) were obtained by centrifugation and viably frozen until analysis. PBMCs were thawed, washed with flow buffer (5% BSA, 2 mmol/L EDTA in PBS), and incubated with LIVE/DEAD Fixable Aqua Dead Cell Stain (Life Technologies), Fc receptor blocking agent (Miltenyi Biotec) and stained with surface antibodies [CD3 clone OKT3, CD4 clone RPA-T4, CD8 clone SK1, CD14 clone HCD14, CD19 clone HIB19, CD25 clone BC96, inducible T-cell costimulatory (ICOS) clone C398.4A, human leukocyte antigen-DR isotype (HLA-DR) clone L243, PD-1 clone 29F.1A12, all from BioLegend] for 20 minutes at 4°C. For Foxp3 and Ki67 staining, cells were fixed and permeabilized using a Fix/Perm buffer (eBiosciences) according to the manufacturer's instructions, then stained with anti-Foxp3 (clone 206D, BioLegend) or anti-Ki67 antibody (clone B56, BD Biosciences).

For global protein acetylation analysis, after surface staining, cells were fixed with 0.4% paraformaldehyde (Thermo Fisher Scientific), permeabilized in Triton X-100 (Sigma-Aldrich) and subsequently stained with anti-acetylated lysine antibody (clone 15G10, BioLegend).

Statistical analysis

As previously reported, the initial phase Ib was designed to determine the DLT and the R2PD of entinostat to be given in combination with pembrolizumab (25). The expansion phase (phase II) of the trial was designed using a Simon optimal two-stage design; two responses in 20 patients were observed in stage I, meeting the criteria to expand to stage II and enroll up to 36 patients. Before enrollment was completed, the study was further revised to accrue up to 70 patients to increase statistical power from 80% to 90% and decrease type 1 error (one-sided significance level of 5%), allowing for more patients to be treated while making an informed decision based on an earlier analysis with appropriate control of type 1 error. The alternative hypothesis in the NSCLC cohort was a 15% ORR, and the cohort was sized to rule out the lower bound of 5% using a single proportion binomial test.

ORR and two-sided 95% confidence intervals (CI) were calculated on the basis of the proportion of patients with a CR or PR by irRECIST criteria. DOR, PFS, and OS were summarized descriptively using the Kaplan–Meier method with 95% CIs. PFS rates at 6 months and corresponding 95% CIs were estimated using the Kaplan–Meier method. The Greenwood formula was used to calculate the SEs of the Kaplan–Meier estimates and upper and lower limits of the 95% CIs.

Gene expression data were evaluated by principal component analysis, and additional analyses were performed using R-statistical software (version 3.5.1) with Bioconductor 3.8. Differentially expressed genes with estimated fold changes >1.5 and Benjamini–Hochberg (bh)-adjusted $P \leq 0.05$ were considered significant. Preranked gene set enrichment analysis (GSEA) was performed using the fast preranked GSEA (1.8.0) Bioconductor package. Fold-change estimates from DESeq2 were used to calculate a rank_metric [$-\log_{10}(P)^*$sign(estimate)], and genes were sorted and tested for enrichment against all human Molecular Signatures Database (MSigDB) collections (msigdbr, 6.2.1) using the following parameters (min_gs_size = 3, max_gs_size = 10,000, permutations = 10,000). Gene sets showing a positive normalized enrichment score and a Benjamini–Hochberg (bh)-adjusted $P \leq 0.05$ were considered to be significantly enriched for a gene set. Subselected heatmaps (pheatmap, 1.0.12) displaying normalized enrichment scores were generated from filtered results of interest, including Hallmark, c2 curated, or c7 immunologic gene sets. Some further subselected heatmaps were specifically filtered to show only gene sets that contained the *MYC* gene as a defined leading-edge member.

High/low monocyte levels were defined on the basis of the median percentage (8.64%) of human leukocyte antigen-DR isotype high ($HLA\text{-}DR_{hi}$) classical monocytes among total PBMCs from available samples.

Role of the funding source

The funders provided the study drugs and worked with the investigators to design the study and to collect, analyze, and interpret the data. All authors, including those employed by the sponsor of the study, contributed to the interpretation of the data. All drafts of the report were prepared by the corresponding author with input from all coauthors and editorial assistance from professional medical writers, funded by the sponsor. The corresponding author had final responsibility for the decision to submit for publication.

Results

Patients

Between May 17, 2015 and December 13, 2017, 110 patients from 14 centers and hospitals within the United States were screened for eligibility. In total, 77 patients were enrolled, 76 patients were treated (1 patient had anemia prior to treatment on cycle 1 day 1 (C1D1) that limited eligibility), and 71 were evaluable for efficacy (5 patients discontinued because of unrelated AEs or withdrew consent before the week 6 scan assessment).

The median age of patients was 66 years (range, 29–85 years), 53% were male, 54 (71%) had an ECOG status of 1, and 88% were either current or former smokers (**Table 1**). PD-L1 expression data from pretreatment biopsies were available for 62/76 patients: 25 (33%) were PD-L1 negative, 37 (49%) were positive (**Table 1**).

All patients had received ≥1 chemotherapy regimen and anti–PD-(L)1 therapy at some point prior to enrollment. Anti–PD-(L)1 therapy was the most recent systemic treatment in 47 patients (62%). Median duration of prior anti–PD-(L)1 therapy was 5.6 months (range, 0.6–27.6 months), and best response (per local investigator assessment) to prior anti–PD-(L)1 therapy was 1% CR, 9% PR, 55% stable disease, and 29% progressive disease. The median time between the last dose of prior anti–PD-(L)1 therapy and the start of study therapy was 2.3 months (range, 0.3–53.0 months; **Table 1**).

At the time of data freeze on October 2, 2019, the median duration of follow-up was 5.95 months (range, 0.4–27.0). Three patients continued to receive entinostat and pembrolizumab beyond that date. The median number of cycles started was 3 (range, 1–35).

Efficacy

The primary endpoint, irRECIST-assessed ORR, was 7 of 76 (9.2%, 95% CI: 3.8%–18.1%; **Fig. 1**). This primary endpoint did not reach the prespecified threshold for the lower bound of the 95% CI. Median DOR was 10.1 months, based on the Kaplan–Meier method (95% CI: 3.9–not estimable; **Fig. 1B** and **C**). PFS rate at 6 months was 22%, and median PFS was 2.8 months (95% CI: 1.5–4.1). Median OS was 11.7 months (95% CI: 7.6–13.4). Median time between last dose of prior PD-1/PD-L1 therapy and first of dose of therapy in ENCORE 601 was comparable between responders and nonresponders [median 1.41 months (range, 0.69–11.20) vs. 1.64 months (range, 0.03–53.03)].

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Table 1. Patient baseline demographics and anti–PD-1 treatment history.

Demographics	$N = 76$
Male, *n* (%)	40 (52.6)
Median age (range)	66 yrs (29–85)
ECOG PS, *n* (%)	
0	21 (27.6)
1	54 (71.1)
Missing	1 (1.3)
Current/former smoker, *n* (%)	67 (88.2)
Race, *n* (%)	
Asian	2 (2.6)
Black or African American	3 (3.9)
Other	5 (6.6)
White	66 (86.8)
PD-L1 expression, *n* (%)	
Negative	25 (32.9)
Positive	37 (48.7)
Not evaluable	8 (10.5)
Not done	6 (7.9)
Visceral metastases, *n* (%)	
Yes	66 (86.8)
No	8 (10.5)
Missing	2 (2.6)
Metastatic sites, *n* (%)	
Abdomen	1 (1.3)
Adrenal/kidney	6 (7.9)
Bone	22 (28.9)
CNS	14 (18.4)
Liver	13 (17.1)
Lung	43 (56.6)
Lymph nodes	40 (52.6)
Pancreas	1 (1.3)
Pleura	9 (11.8)
Other	12 (15.8)
Stage at metastatic diagnosis, *n* (%)	
I	0 (0.0)
II	0 (0.0)
IIIA	5 (6.6)
IIIB	7 (9.2)
IIIC	0 (0.0)
IV	64 (84.2)
Baseline LDH (%> ULN), *n* (%)	
No	49 (64.5)
Missing	1 (1.3)
ALK result, *n* (%)	
Negative	54 (71.1)
Missing	22 (28.9)
EGFR result, *n* (%)	
Positive	5 (6.6)
Negative	52 (68.4)
Missing	19 (25.0)
Best response on prior anti–PD-(L)1, *n* (%)	
Complete response	1 (1)
Partial response	7 (9)
Stable disease	42 (55)
Disease progression	22 (29)
Unknown	2 (3)
Duration on latest anti–PD-(L)1	
Median	5.6 months
Time from prior anti–PD-(L)1 to study therapy	
Median	2.3 months
PD-(L)1 as immediate prior therapy, *n* (%)	47 (62)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; yrs, years.

Table 2. Treatment-related adverse events.

Treatment-related adverse event ($N = 76$)[a]	Any grade	Grade ≥3
Any	62 (81.6)	31 (40.8)
Fatigue	32 (42.1)	8 (10.5)
Diarrhea	16 (21.1)	2 (2.6)
Anemia	15 (19.7)	5 (6.6)
Decreased appetite	15 (19.7)	1 (1.3)
Platelet count decreased	12 (15.8)	1 (1.3)
Hypophosphatemia	11 (14.5)	7 (9.2)
Nausea	10 (13.2)	1 (1.3)
Blood alkaline phosphatase increased	8 (10.5)	1 (1.3)
Hypoalbuminemia	7 (9.2)	0 (0.0)
Hyponatremia	7 (9.2)	4 (5.3)
Vomiting	7 (9.2)	1 (1.3)
Weight decreased	7 (9.2)	0 (0.0)
Pneumonitis	6 (7.9)	3 (3.9)
Colitis	3 (3.9)	3 (3.9)
Edema	3 (3.9)	2 (2.6)

[a]Treatment-related adverse events occurring in ≥9% of patients for all grade or ≥2 patients for grade ≥3.

Prior treatment and duration of treatment are shown in detail for responders. Responses were observed regardless of prior treatment history (**Fig. 1C**). All 7 responders were among the 67 former or current smokers enrolled in the trial, but no significant correlation between response and smoking history was identified in multivariate subset analyses. Of the 7 responders, 5 were negative for PD-L1 expression, 1 was weak positive, and 1 was strong positive.

Safety

Treatment-emergent AEs (TEAE) related to entinostat and/or pembrolizumab occurred in 82% of patients (**Table 2**). Grade ≥3 TEAEs occurred in 44 (58%) of patients; 31 (41%) had grade ≥3 TEAEs related to entinostat and/or pembrolizumab (**Table 2**). TEAEs that led to entinostat and/or pembrolizumab discontinuation occurred in 25% (19) of patients; 15% (11) of patients had a drug-related TEAE that led to entinostat and/or pembrolizumab discontinuation. Fifty-three percent of patients had at least one entinostat dose modification (dose decreased, dose delayed, dose skipped, or discontinued), and 37% of patients required pembrolizumab dose modification at least once. TEAEs not related to treatment led to death in 3 patients.

The most common any-grade TEAEs related to entinostat and/or pembrolizumab treatment were fatigue (42%), diarrhea (21%), anemia (20%), and decreased appetite (20%). Grade ≥3 TEAEs related to either treatment that occurred in 4 or more patients included fatigue (11%), hypophosphatemia (9%), anemia (7%), and hyponatremia (5%). Seven patients (9%) experienced a grade ≥3 irAE (3 events of pneumonitis, 3 events of colitis, 1 each of encephalitis, pancreatitis, and hyperthyroidism) (**Table 2**).

Pharmacodynamics

The expected pharmacodynamic impact of entinostat was observed as an increase in lysine acetylation across peripheral immune cells, including $CD3^+$ T cells, $CD19^+$ B cells, and $CD14^+$ monocytes (**Fig. 2A–C**). Increased acetylation at cycle 2 day 15 (C2D15) in $CD19^+$ B cells, as compared to pretreatment C1D1 values, was associated with improved PFS, and decreased acetylation was associated with an inferior PFS (**Fig. 2D** and **E**). Increased acetylation in T cells and monocytes was not associated with improved PFS.

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It is unclear why only acetylation in B cells would translate to a PFS difference, although acetylation in B cells was also found to exhibit the most robust PFS difference in the previously reported phase II ENCORE 301 study of entinostat combined with exemestane in ER$^+$ breast cancer (26). Additional observations associated with an activated immune response, and potentially related to the immunomodulatory activity of entinostat combined with pembrolizumab, included posttreatment C1D15 and C2D15 increases in HLA-DR expression in CD8$^+$ and CD4$^+$ T cells (Supplementary Fig. S1A–S1D), increased ICOS expression in CD4$^+$ T cells (Supplementary Fig. S1E), an increase in the proportion of Ki67$^+$/PD-1$^+$ T cells, a decrease in FoxP3 expression and intensity in CD4$^+$ regulatory T cells (Tregs; Supplementary Fig. S1F), and a decrease in the ratio of Tregs to CD8$^+$ T cells (Supplementary Fig. S1G). Furthermore, while the baseline value of T cells with a reinvigorated phenotype (Ki67$^+$/PD1$^+$ in CD4$^+$ T cells and Ki67$^+$/PD1$^+$ in CD8$^+$ T cells) did not correlate with duration of treatment, the percent of reinvigorated T cells at C1D15 correlated with duration of treatment, suggesting an association between treatment-induced reinvigorated T cells and a favorable duration of treatment (Supplementary Fig. S1H and S1I).

We found that responses were enriched among patients with high levels of classical monocytes [$n = 32$; defined as CD14$^+$/CD16$^-$/HLA-

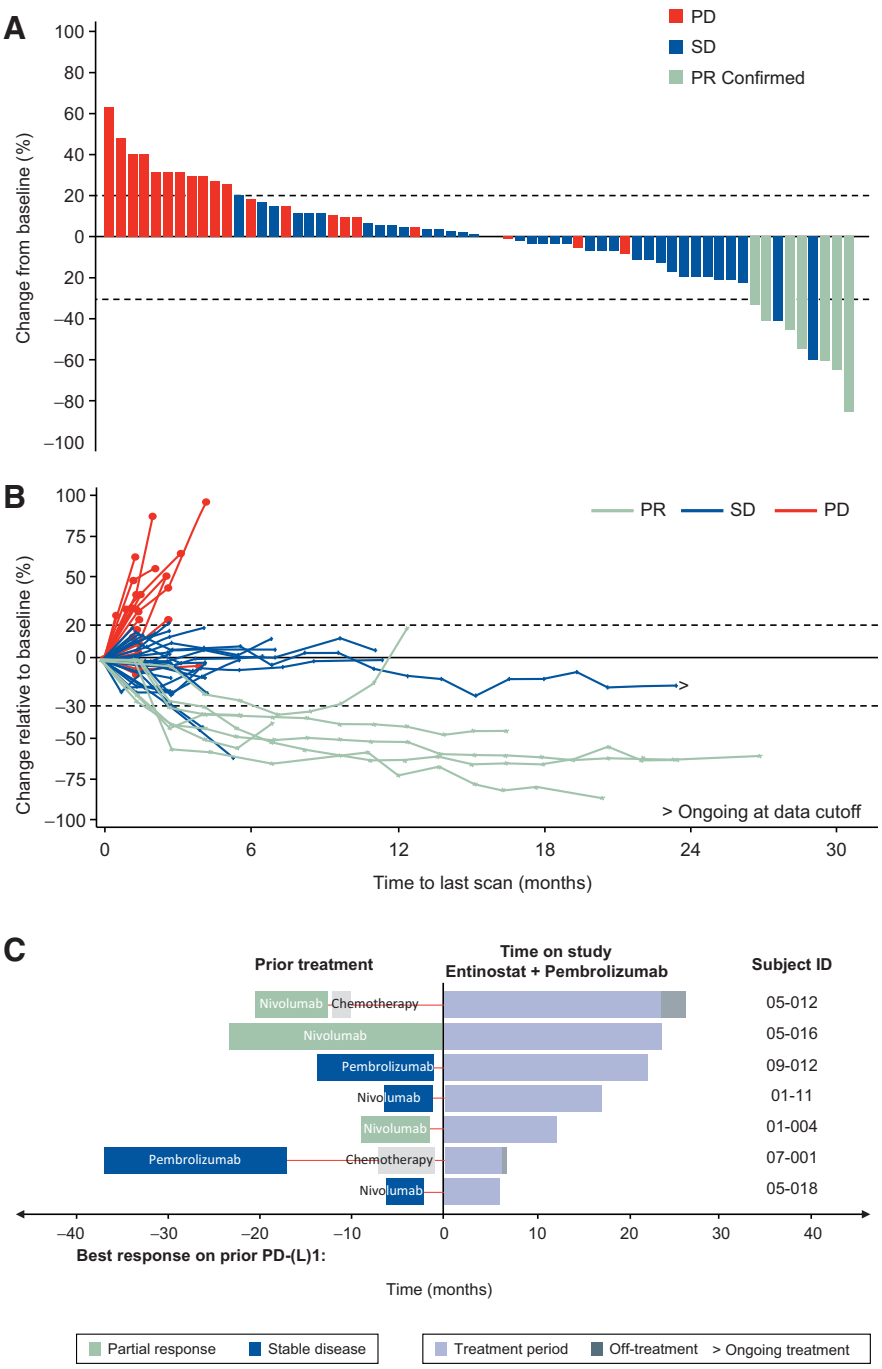

Figure 1.

Maximal tumor burden and change in tumor volume over time. Waterfall plot (**A**) and spider plot (**B**) of change in lesions over time. **C,** Prior treatment and duration of treatment for responders. Responses were observed regardless of prior treatment history or PD-L1 status.

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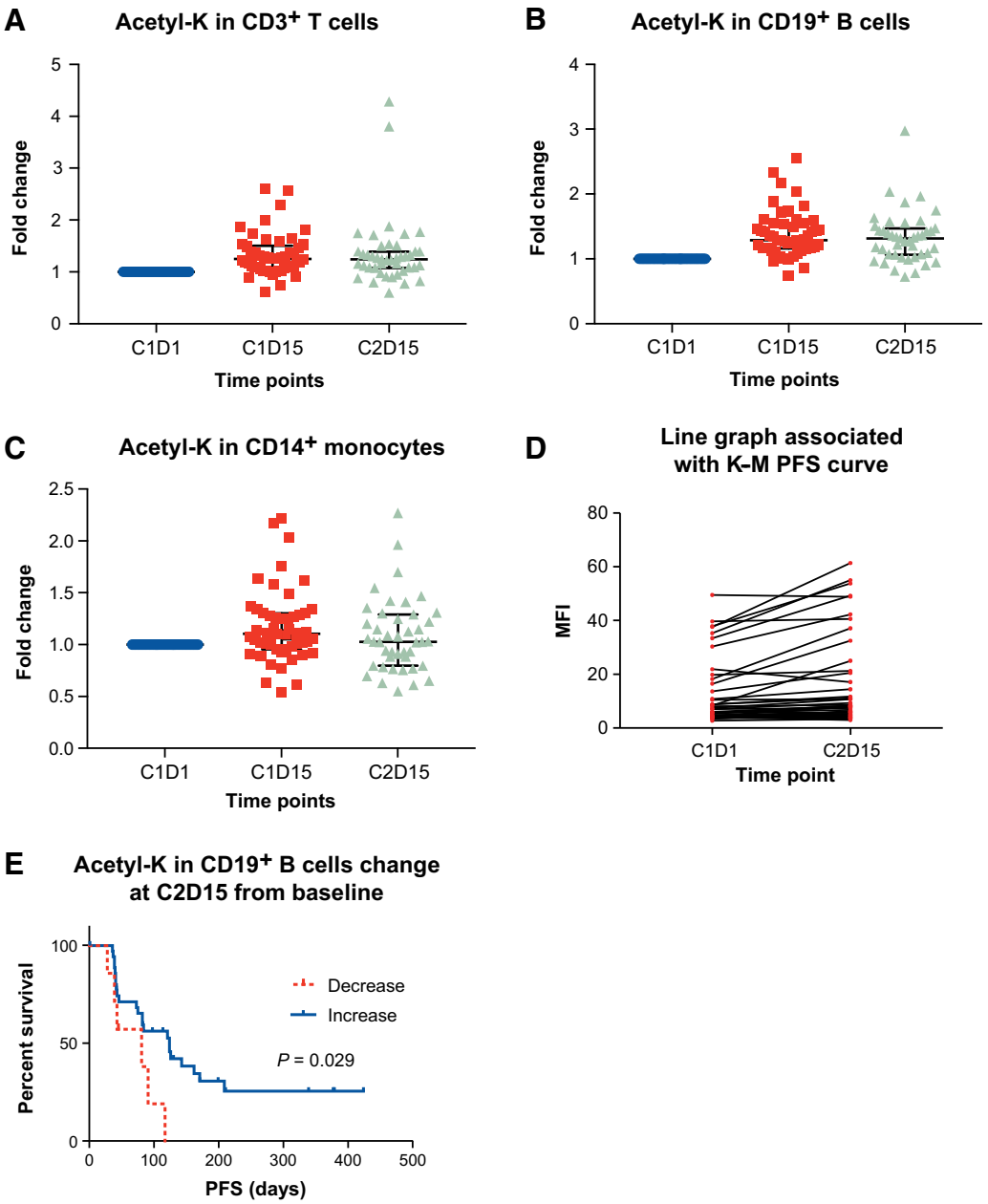

Figure 2.

Expression of acetylated lysine in peripheral immune cells after therapy. Flow cytometry was used to analyze levels of acetylated lysine in $CD3^+$ T cells (**A**), $CD19^+$ B cells (**B**), and $CD14^+$ monocytes (**C**) at cycle 1, day 1 (C1D1); cycle 1, day 15 (C1D15); and cycle 2, day 15 (C2D15). Error bars represent mean ± SD. **D,** Acetyl-lysine expression in $CD19^+$ B cells at C2D15 compared with baseline C1D1 values. **E,** Kaplan–Meier curve of PFS by increase or decrease in acetyl-lysine expression in $CD19^+$ B cells from baseline to C2D15.

DR_{hi} and split high vs. low around the median of 8.6%; ORR 14.7% (95% CI:5.0–31.1)] compared with those with lower levels of monocytes [$n = 31$; <8.6%; ORR, 5.9% (95% CI: 0.7–19.7)]. Patients with high monocytes also had longer PFS [HR, 0.44 (95% CI: 0.24–0.82); mPFS, 4.1 months (95% CI: 1.4–9.3) vs. 2.7 months (95% CI: 1.4–3.7)] and OS [HR = 0.43 (95% CI: 0.21–0.87); mOS 58.1 weeks (95% CI: 40.3–not reached) vs. 33.1 weeks (95% CI: 16.0–56.9); **Fig. 3A** and **B**].

In addition to the peripheral blood, we also examined bulk transcriptional profiles of tumors ($n = 43$; 4 responders and 39 nonresponders) to evaluate tumor-specific features associated with response. Two posttreatment biopsies were obtained, both in nonresponders, and these samples were not evaluated further. Unlike previous results in antiPD-(L)1–naïve patients, *IFNγ* expression was not associated with response to pembrolizumab plus entinostat in patients with prior antiPD-(L)1 treatment (27, 28). Instead, MYC was identified as the top pathway associated with response (Supplementary Table S1; **Fig. 4**). This observation is consistent with preclinical data showing that combination of MYC depletion with epigenetic therapy

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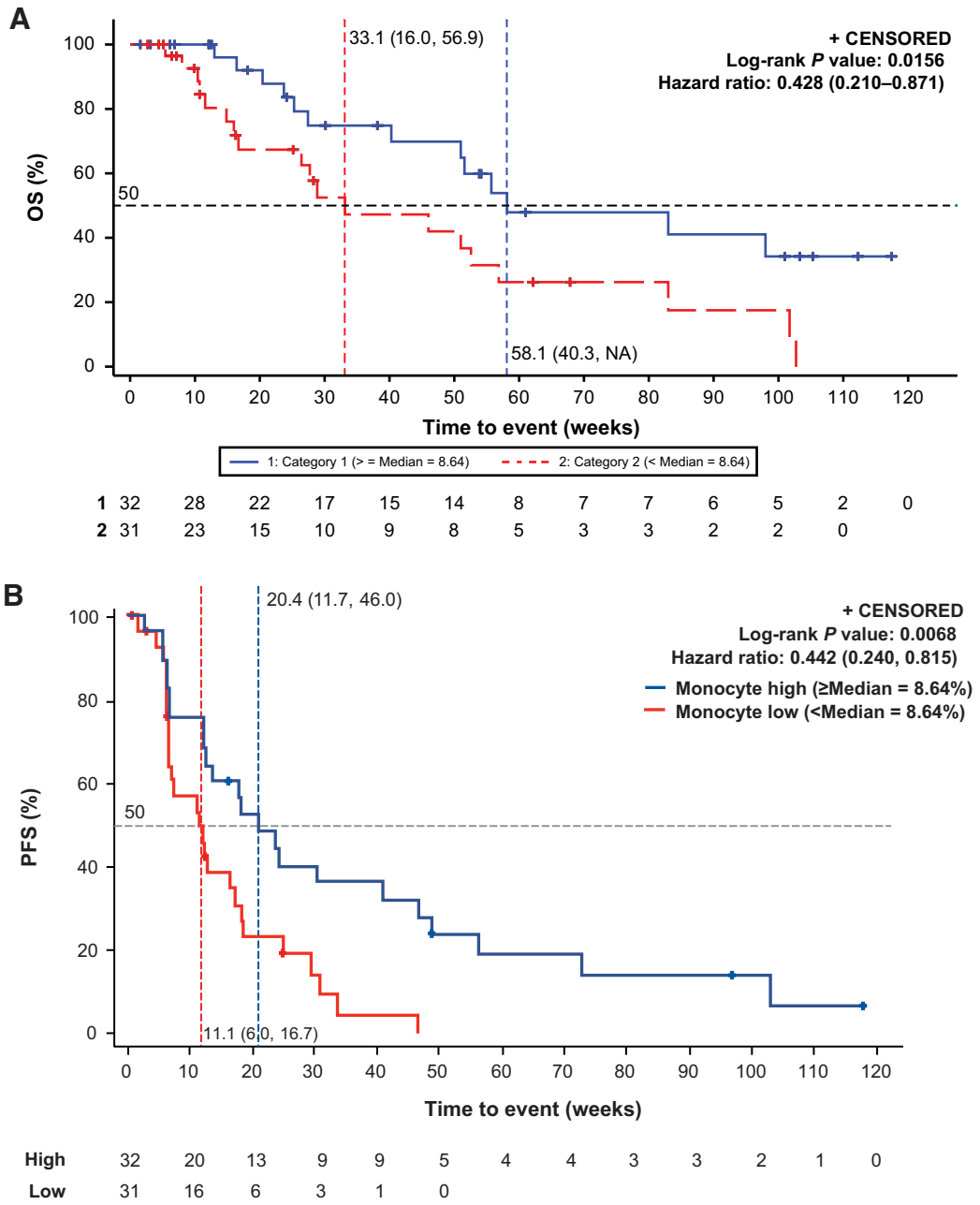

Figure 3.

Kaplan–Meier curve of PFS (**A**) and OS (**B**) by proportion of classical monocytes ($CD14^+/CD16^-/HLA\text{-}DR_{hi}$). Median PFS and median OS were increased in the monocyte high group (≥8.64%) versus the monocyte low group (<8.64%).

reversed immune evasion, potentially allowing for more effective NSCLC treatment (15).

Discussion

We report on the safety, efficacy, and pharmacodynamic results from a phase II expansion cohort of a phase Ib/II trial of the combination of entinostat plus pembrolizumab in patients with NSCLC who were previously treated with and progressed on anti–PD-(L)1–based therapy. Treatment was associated with a response rate of 9.2% (95% CI: 3.8%–18.1%). The lower bound of the 95% CI did not exceed 5%, which was considered the lowest threshold for antitumor activity that would warrant continued development in this setting. The median DOR (10.1 months; 95% CI: 3.9–not estimable) and percentage of patients with PFS at 6 months (22%) were nevertheless notable in demonstrating a meaningful clinical benefit for some patients. Of note, evaluation of PD-L1 expression in pretreatment biopsies indicated that tumors from 5 of the 7 responding patients were negative for PD-L1 expression. While the sample size is too small to associate lack of PD-L1 expression with response, particularly with the lack of

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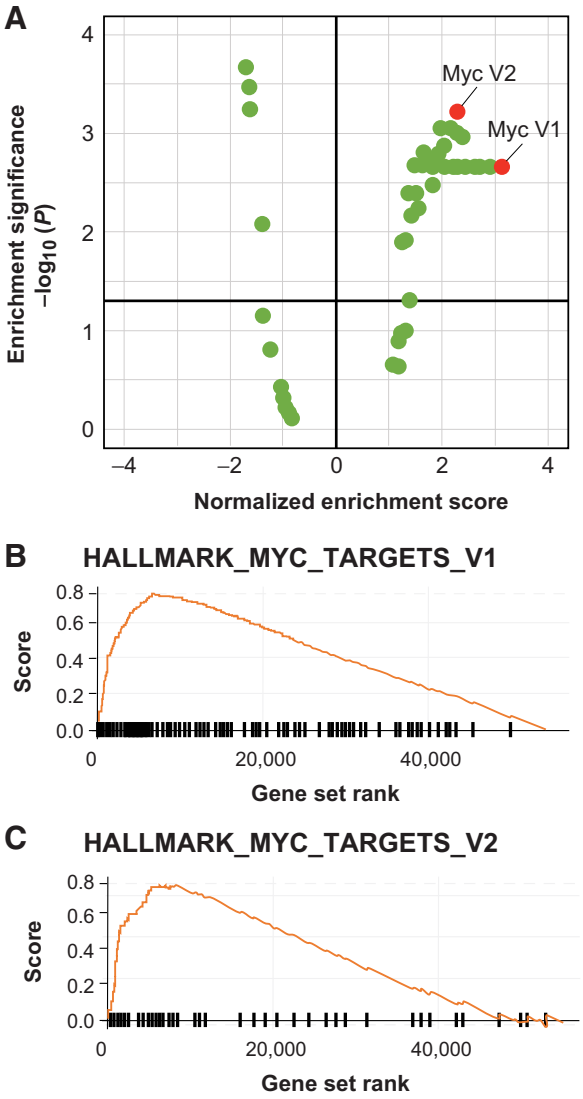

Figure 4.

Enrichment of MYC Hallmark genesets V1 and V2 in pretreatment tumors from anti–PD-1 pretreated patients with NSCLC responding to pembrolizumab plus entinostat.

response in the majority of patients with negative PD-L1 expression, these results may reflect the potential for the combination to elicit responses in a subset of patients with nonimmunogenic tumors. The response rate remains of clinical interest, particularly if correlative data can predict which patients could benefit the most from this combination. In multivariate analyses, we observed a positive correlation between high baseline HLA-DR_{hi} classical monocytes and clinical benefit in patients with NSCLC previously treated with anti–PD-(L)1 therapy. ORR was 14.7% in the monocyte high population, and mPFS was 4.1 months, and mOS was 58.1 weeks (**Fig. 3A** and **B**).

HLA-DR is a primary antigen-presenting molecule of the MHC class II pathway that is primarily expressed on antigen-presenting cells, including monocytes and, in some cases, tumor cells. The expression of HLA-DR can be upregulated by cytotoxic T cell–secreted IFNγ, and elevation of HLA-DR may be an indication of activated T cells and IFNγ-induced responses that usually mediate sensitivity to anti–PD-(L)1 therapy. Indeed, the presence of HLA-DR–expressing tumor cells in melanoma patient tumor biopsies is strongly correlated with response to immunotherapy (29), and elevated numbers of HLA-DR classical monocytes in the peripheral blood were shown to be predictive of response to anti–PD-1 therapy in patients with melanoma previously untreated with anti–PD-(L)1 therapy (30). In this study, the patients had either never responded to or had progressed after responding initially to prior immunotherapy, suggesting that HLA-DR_{hi} classical monocyte levels may also indicate sensitivity to the entinostat–pembrolizumab combination. A phase II/III study has been designed to further explore clinical outcomes of the combination of entinostat and pembrolizumab in patients with metastatic NSCLC stratified by high/low HLA-DR_{hi} monocyte count as measured by an HLA-DR_{hi} monocyte assay. This trial will evaluate the hypothesis that patients with metastatic NSCLC with elevated HLA-DR_{hi} monocytes ($CD14^+/CD16^-$/HLA-DR_{hi} ≥9%) whose disease progressed on approved standard-of-care platinum-based therapy and within 12 weeks of checkpoint inhibitor therapy will have an improved PFS with the combination of entinostat and pembrolizumab in comparison to docetaxel.

In addition to the observation that elevated levels of circulating classical monocytes were associated with clinical benefit, this study provided an opportunity to explore gene expression pathways tied to immune therapy resistance in a sizeable population of patients with anti–PD-(L)1 therapy relapsed/refractory NSCLC. Interestingly, the top five enriched pathways included MYC and E2F signaling, both of which have recently and independently been shown to coincide with an immune-suppressed tumor microenvironment and immune checkpoint therapy resistance in preclinical studies and in patient samples (15, 31–34). Entinostat has previously been shown to decrease MYC activity (34–37), which may suggest a potential mechanism for overcoming resistance to anti–PD-(L)1 therapy in addition to its ability to reduce the immunosuppressive function of MDSCs.

Toxicities with entinostat plus pembrolizumab were comparable with other studies with pembrolizumab alone or combined with chemotherapy or another HDAC inhibitor (1–3, 38–40). No new toxicities, including irAEs, were seen for either drug. irAEs of interest that were grade ≥3 included colitis ($n = 3$), pneumonitis ($n = 3$), encephalitis ($n = 1$), pancreatitis ($n = 1$), and hyperthyroidism ($n = 1$), none of which were unexpected.

Other anti–PD-(L)1 combinations with immunotherapy in patients already treated with immune checkpoint inhibitors have also shown some activity. In patients with prior immune checkpoint inhibitor therapy, sitravatinib in combination with nivolumab resulted in PRs in 7/25 patients (4 confirmed; ref. 41). Another HDAC inhibitor, vorinostat, has also been examined in combination with pembrolizumab in patients with NSCLC previously treated with immune checkpoint inhibitors, and 3 of 24 patients had PRs (1 confirmed; ref. 40). Similar to the results of this study, outcomes and treatment duration in patients treated with vorinostat plus pembrolizumab were not associated with PD-L1 expression.

Limitations of this phase II study include a small sample size and lack of direct comparison with the standard of care. In addition, the pretreated patient population enrolled in this study may be more susceptible to increased or cumulative toxicities. Another limitation was the lack of prospective incorporation of biomarkers for patient selection.

The treatment landscape of NSCLC is changing quickly, and the advent of immunotherapy has led to increased options for patients. However, patients progressing on, or not responding to, currently

available immune checkpoint therapy–based regimens require novel approaches to overcome resistance. The results of this study in patients with NSCLC relapsed or refractory to prior anti–PD-(L)1 therapy identify no new toxicities, including irAEs, for either drug and suggest that entinostat combined with pembrolizumab provides significant clinical benefit to a subset comprising 9% of patients that may be identified through measurement of circulating baseline classical monocytes.

Authors' Disclosures

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Authors' Contributions

M.D. Hellmann: Conceptualization, data curation, formal analysis, supervision, writing-original draft, writing-review and editing. **P.A. Jänne:** Data curation, formal analysis, writing-review and editing. **M. Opyrchal:** Data curation, formal analysis, writing-review and editing. **N. Hafez:** Data curation, formal analysis, writing-review and editing. **L.E. Raez:** Data curation, formal analysis, writing-review and editing. **D.I. Gabrilovich:** Formal analysis, writing-review and editing. **F. Wang:** Data curation, formal analysis, methodology, project administration, writing-review and editing. **J.B. Trepel:** Data curation, formal analysis, writing-review and editing. **M.-J. Lee:** Data curation, formal analysis, writing-review and editing. **A. Yuno:** Data curation, formal analysis, writing-review and editing. **S. Lee:** Data curation, formal analysis, writing-review and editing. **S. Brouwer:** Data curation, formal analysis, writing-review and editing. **S. Sankoh:** Conceptualization, data curation, formal analysis, methodology, writing-review and editing. **L. Wang:** Data curation, formal analysis, methodology, project administration, writing-review and editing. **D. Tamang:** Data curation, formal analysis, writing-review and editing. **E.V. Schmidt:** Conceptualization, data curation, formal analysis, project administration, writing-review and editing. **M.L. Meyers:** Conceptualization, data curation, formal analysis, supervision, methodology, writing-review and editing. **S.S. Ramalingam:** Conceptualization, data curation, formal analysis, supervision, writing-review and editing. **E. Shum:** Data curation, formal analysis, writing-review and editing. **P. Ordentlich:** Conceptualization, data curation, formal analysis, writing-review and editing.

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Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti–PD-(L)1 Therapy

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