Immunomodulation by Entinostat in Renal Cell Carcinoma Patients Receiving High-Dose Interleukin 2: A Multicenter, Single-Arm, Phase I/II Trial (NCI-CTEP#7870)

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Abstract

Purpose: On the basis of preclinical data suggesting that the class I selective HDAC inhibitor entinostat exerts a synergistic antitumor effect in combination with high-dose IL2 in a renal cell carcinoma model by downregulating Foxp3 expression and function of regulatory T cells (Treg), we conducted a phase I/II clinical study with entinostat and high-dose IL2 in patients with metastatic clear cell renal cell carcinoma (ccRCC).

Experimental Design: Clear cell histology, no prior treatments, and being sufficiently fit to receive high-dose IL2 were the main eligibility criteria. The phase I portion consisted of two dose levels of entinostat (3 and 5 mg, orally every 14 days) and a fixed standard dose of IL2 (600,000 U/kg i.v.). Each cycle was 85 days. The primary endpoint was objective response rate and toxicity. Secondary endpoints included progression-free survival and overall survival.

Results: Forty-seven patients were enrolled. At a median follow-up of 21.9 months, the objective response rate was 37% [95% confidence interval (CI), 22%–53%], the median progression-free survival was 13.8 months (95% CI, 6.0–18.8), and the median overall survival was 65.3 months (95% CI, 52.6–65.3). The most common grade 3/4 toxicities were hypophosphatemia (16%), lymphopenia (15%), and hypocalcemia (7%), and all were transient. Decreased Tregs were observed following treatment with entinostat, and lower numbers were associated with response (P = 0.03).

Conclusions: This trial suggests a promising clinical activity for entinostat in combination with high-dose IL2 in ccRCC patients and provides the first example of an epigenetic agent being rationally combined with immunotherapy. Clin Cancer Res; 23(23); 7199–208. ©2017 AACR.

Introduction

The treatment of metastatic clear cell renal cell carcinoma (ccRCC) is rapidly evolving (1, 2). The use of cytokine therapies such as IL2 and INFα has been progressively replaced by vascular growth factor receptor tyrosine kinase inhibitors (RTKIs) such as sunitinib and pazopanib, in the first-line setting. More recently, the approval of the immune checkpoint inhibitor nivolumab has introduced the use of this novel class of immunotherapy in previously treated RCC patients (3). However, there remains a critical need for improving the current standard treatments for RCC.

High-dose IL2 was approved for the treatment of RCC based on the response rate and duration of responses. A total of 255 patients treated in 7 clinical trials at 21 institutions showed an objective response rate (ORR) of 15% (4). The recent SELECT trial (120 patients) has reported a 25% ORR by WHO criteria, a median duration of response of 20 months, and a median progression-free survival (PFS) of 4.2 months (5). This falls in a similar range with immune checkpoint inhibitor monotherapy in RCC, and until durability of checkpoint inhibitor therapy can be determined, supports a continued role for high dose IL2 (3). Increasing the magnitude of benefit of IL2 therapy remains an important clinical goal.

Histone deacetylase (HDAC) inhibitors are a class of drugs targeting different enzymes that regulate the chromatin structure and the acetylation of lysine residues on the histone tails (6). Different classes of HDAC have been identified, but drug development in oncology has focused on class I (HDAC 1, 2, 3, and 8) and class II (HDAC 4, 5, 6, 7, 9 and 10). Four HDAC inhibitors, one selective class I (romidepsin) and three class I/II (vorinostat, panobinostat, and belinostat) inhibitors, have been approved for the treatment of cutaneous/peripheral T-cell lymphoma, and multiple myeloma. Our group has recently reported the activity...
of vorinostat in combination with bevacizumab in previously treated ccRCC patients (7). Entinostat is a class 1 selective oral HDAC inhibitor with antitumor activity in several preclinical models (8). This agent is currently in clinical development for breast cancer and other solid tumors in combination therapies (9–12). Its long 140-hour half-life allows continuous exposure with either once-weekly or biweekly oral dosing.

There is increasing evidence that epigenetic modulation may have immunostimulatory activity in addition to a direct antitumor effect. Our group reported that the combination of high-dose IL2 and entinostat had a synergistic antitumor effect in an immunocompetent murine model of RCC (13). The biological effect induced by low-dose entinostat was associated with reduction of Foxp3 expression in Tregs and impairment of their immunosuppressive function without affecting T effector cells (14). Thus, based on reported clinical evidence that lower Treg numbers in the peripheral blood are associated with better outcomes in patients receiving high-dose IL2 (15, 16), we generated the hypothesis that the inhibitory effect of the selective class I HDAC inhibitor entinostat on Tregs may increase the response rate and PFS in patients receiving high-dose IL2 (Fig. 1A; refs. 17, 18).

Patients and Methods

Eligibility

This was a phase I/II study conducted at four academic centers in the United States [Roswell Park Cancer Institute (Buffalo, NY), Johns Hopkins University (Baltimore, MD), Ohio State University (Columbus, OH), and University of Southern California (Los Angeles, CA)]. The study was performed after approval by the Institutional Review Board at each participating site and was conducted in accordance with the ethical guidelines included in the Declaration of Helsinki. Eligible patients had pathologic
diagnosis of RCC, clear cell, or predominantly clear cell that was metastatic and progressive. The patients were required to be sufficiently fit to receive high-dose IL2. Main exclusion criteria included any prior systemic therapy for metastatic ccRCC, ongoing immunosuppressive therapy, and the presence of untreated brain metastases. The study was registered at ClinicalTrials.gov identifier NCT01038778. All patients provided written informed consent.

Endpoints
The primary objective of the phase I portion of this study was to evaluate the safety and establish the recommended phase II dose of entinostat in combination with high-dose IL2. The primary objective of the phase II portion was to evaluate the efficacy of this regimen. The primary endpoint was ORR. Secondary endpoints included PFS and overall survival (OS), and parameters measuring immune response.

Treatment schema
Patients were admitted to hospital units with appropriate capabilities for the administration of high-dose IL2. One cycle of treatment (85 days) consisted of 2 courses of high-dose IL2 600,000 U/kg administered intravenously every 8 hours on day 1 to 5 and day 15 to 19 (±7 days; maximum 28 doses; ref. 4), and entinostat orally (1–2 hours prior to IL2 infusion) given once every 2 weeks starting on day 14, administered before IL2 infusion on day 1, 15, and then continuously (Fig. 1B). Entinostat was provided by CTEP through a CRADA with Syndax Pharmaceuticals, Inc. Tumor response assessments were performed on week 7 (±7 days) and every 12 weeks thereafter. In the event of clinical benefit (stable disease or tumor shrinkage), patients received a second cycle of therapy. Entinostat treatment continued every 2 weeks (±7 days) dependent on adjustments necessary for IL2 dosing) until documented disease progression or 8 weeks following documented complete response. Patients who tolerated the combination regimen with evidence of tumor shrinkage received up to 3 cycles of high dose IL2. Cycle 2 started on or within 2 weeks following day 85 (or last day of cycle dependent on dosing adjustment) as in cycle 1, while cycle 3 started within 2 weeks after completion of cycle 2. Tumor response assessment was performed uniformly across all patients at all institution before cycle 2 (~day 85). Patients with stable disease by RECIST V.1.1 criteria, but without evidence of tumor shrinkage after two cycles, received only entinostat until disease progression was documented. To assess the effect of entinostat versus the combination on proposed correlative pharmacodynamic parameters, initial treatment was with entinostat monotherapy, followed by combination with high-dose IL2. The phase I starting dose level of entinostat was 3 mg orally every 2 weeks. The first dose level had a minimum of 3 patients treated unless the first 2 patients experienced dose-limiting toxicity(s) (DLT) before the third patient was enrolled. DLTs were defined as extended grade 4 toxicity (duration of one week or more) during the first 45 days of treatment in view of the prolonged side effects induced by single-agent high-dose IL2. Patients were allowed to remain on the therapy provided that they were tolerating the treatment and were progression free. No dose deescalation for IL2 was allowed.

Correlative studies
Relationships between entinostat and IL2 exposure and pharmacodynamic effects were characterized. Four aliquots of 8 mL of peripheral blood were collected for mononuclear cell fraction. Fresh samples were shipped overnight to Roswell Park Cancer Institute, where they were processed and analyzed by the FACS Core facility. For activated antigen-presenting cells (APC), we used the following antibodies (BD): CD86 B515, CD14 PE, Lin Dump FL3 PC5, HLADR PE/Cy7, CD11c APC, CD45 APC-H7, CD80 BV421, and CD123 BV421. For Tregs, we used the following antibodies (BD Biosciences): FOXP3 PE, CD4 PcP, CD3PC7, CD127 APC, CD45 APC-H7, and CD25 BV421. Expression of surface markers and intracellular protein was assessed with FACSAria or LSRII flow cytometer. Data were analyzed using Winlets software. Pre and post-treatment biopsy of accessible tumors was offered to all participating patients but was not mandatory. Formalin-fixed paraffin sections of tumor biopsies were stained for FOXP3 (clone 236A/E7, Abcam; catalog #ab220034) and CD8 staining (clone C8/144B, Dako; catalog# M7103). [18F]fluoro-2-deoxy-D-glucose(FDG)-PET/CT scan was performed at screening and approximately 30 days into therapy, providing nearly simultaneous acquisition of metabolic and anatomic data. FDG PET/CT studies were conducted in 22 patients who were enrolled at Roswell Park and Johns Hopkins but only 11 patients completed the second scan.

Statistical analyses
The reported analyses are based on a September 2, 2016, database lock. The combination treatment would have been considered unsuccessful if the response rate was 20% or less, and it would have been considered active enough to pursue further if the response rate was 40% or greater. To test this hypothesis, the fixed sample size for a single-stage study with a type I error of 10% and a type II error of 10%, based on an exact binomial test, was 36. If 11 or more of the patients experienced a response, the hypothesis that the response rate was ≤20% would be rejected with a target error rate of 0.10. We also planned to determine whether initial levels of specific T lymphocytes (Treg) in the peripheral blood and tumor or changes in the level of specific T lymphocytes from baseline might predict for response to this combination therapy. In this study, Tregs were defined as CD4+CD25hi T cells. The hypothesis was that low baseline levels of Tregs would be associated with an increased probability of response and that Treg decreases from baseline would be associated with an increased probability of response. Responders and nonresponders were compared using exact Wilcoxon rank sum tests. Responders were compared with nonresponders for 5 outcomes: C1D-14, C1D-7, C1D1, C1D-14 to C1D1 (i.e., change from C1D-14 to C1D1), C1D-7 to C1D1 (i.e., change from C1D-7 to C1D1). As this was an exploratory analysis, no adjustments were made for multiple comparisons.

Results
Patient characteristics
Between January 2009 and December 2015, we enrolled 47 patients with ccRCC. All patients had prior nephrectomy and had either favorable or intermediate MSKCC risk factors (Table 1).

Treatment administration and overall safety
The phase I portion consisted of two dose levels of entinostat (3 and 5 mg) and a fixed standard dose of IL2 (600,000 U/kg every 8 hours) and was enrolled according to a 3 + 3 design. Eleven patients were treated during the phase I portion (3 patients at the 3 mg entinostat dose and 8 patients at the 5 mg entinostat dose).
The 5 mg dose level allowed up to 6 evaluable patients to be enrolled and 2 patients were not evaluable. Dose levels 1 and 2 were completed without DLTs during the first 45 days of treatment. The most common expected grade 3/4 toxicities were hypophosphatemia (attributable to entinostat) and thrombocytopenia (6 patients), as well as neutropenia and lymphopenia (2 patients; attributable to both entinostat and IL2). Table 1 shows the adverse events occurring during the combined phase I and phase II portion. Among all 47 patients, the most common grade 3 or 4 treatment-related adverse events were hypophosphatemia (16%), decreased lymphocytes (15%), and hypocalcemia (7%). No unexpected toxicities were noted. One patient presented a rheumatoid arthritis flare. One death was reported during treatment and was deemed unrelated to study drug. The patient developed cardiac tamponade during the first cycle requiring pericardiocentesis, which revealed the presence of adenocarcinoma cells from previously undiagnosed occult primary lung cancer. The median number of IL2 doses administered was 7.5 (3–14), and 23 patients (49%) received ≥ 1 cycle of treatment.

Primary endpoints

Of the 47 enrolled patients, 43 were evaluable for response. Two patients with no measurable but evaluable disease (positive FGD-PET scan only) at baseline were excluded from objective ORR analysis but were included in the PFS and OS analyses. Figure 2A shows the total proportion of ORR for the 41 completers of both phase I and II. Confirmed overall response was achieved by 15 (37%; 90% confidence interval (CI), 24–51; P = 0.010) patients, including 12 partial responses (PR) and three complete responses (CR). In the phase II portion, 32 patients with measurable disease were included and 10 achieved an objective response (OR; 31%; 90% CI, 18–47; P = 0.090). Stable disease for ≥ 6 months was achieved by 18 patients (44%). The waterfall plot shows the depth of the clinical responses, while the spider plot highlights the duration of the responses in addition to the tumor burden reduction from baseline (Fig. 2B and C). Two patients with PR achieved complete resolution of their target lesions but had persistent subcentimeter nontarget lung nodules. Of note, there were two additional patients with no measurable disease but evaluable lesions who achieved resolution of FDG uptake on PET scan. These patients were not counted as ORs. Delayed response has been observed. For example, a patient who had initial progressive disease and discontinued treatment after two cycles has subsequently achieved stable disease and did not require further therapies. After 3 years of follow-up, the patient is now presenting continuous, slow reduction in number and size of the lung nodules in the absence of further treatments.

At the time of data cutoff, median follow-up was 21.9 months (95% CI, 2.1–65.0). At the last follow-up, the 3-year PFS was 19% (95% CI, 6–38), and the median PFS was 13.8 months (95% CI, 6–18.8; Fig. 3A). The 3-year OS was 84% (95% CI, 62–94), and the median OS was 65.3 months (95% CI, 52.6–65.3; Fig. 3B). When we subgrouped the patients between those who achieved an OR and those who did not (not OR), the 3-year PFS was 45% (95% CI, 13–73) in the responders (OR) and 0% (95% CI, 2–31) in the nonresponders (not OR). Similarly, the median PFS was 28.5 months (95% CI, 12.6–NR) in the responders (OR) and 5.7 months (95% CI, 3–10.4) in the nonresponders (not OR; P = 0.003; Fig. 3C). Interestingly, there was no difference between the patients who achieved an OR and those who did not in terms of the median number of IL2 doses administered (7.8 vs. 7.0).

Correlative studies

In a small number of patients, we were able to perform FDG-PET/CT scans at baseline and at approximately day 30. Following treatment with entinostat and high-dose IL2, we observed a greater decrease in FDG uptake in the target lesions in those patients who achieved an OR as compared with those who did not (Fig. 4A and B). In 3 patients with accessible tumors, we were able to perform a biopsy before starting treatment and during the first cycle at approximately day 15. The results suggest that there was a significant increase of tumor-infiltrating CD8 cells in patients with either prolonged stable disease (patient 1; >15 months) or PR (patient 3; Fig. 5A and B). The biopsies also showed either stable or decreased Treg infiltration despite the administration of high-dose IL2, which was expected to increase Tregs, and increased IFN-gamma producing CD8+ T-cells (Supplementary Fig. 1, 2A and B).

We also performed flow cytometry analysis in peripheral blood mononuclear cells collected at different time points. Complete samples were available only from a portion of patients receiving treatment across the participating institutions. Our analysis has focused primarily on the ‘priming phase’ with entinostat (cycle 1 day-14 through cycle 1 day 1) to assess the activity of entinostat alone without the potentially masking effect of high-dose IL2. Following the first dose of entinostat, we observed a statistically
significant decline in peripheral Tregs in 5 patients who achieved an OR as compared with 7 patients who had progressive disease (Fig. 5C). Values for responders were likely to be lower for Tregs at C1D1 (P = 0.0273). Interestingly, we also observed a concomitant, statistically significant increase in circulating activated APCs. Values for responders were likely to be higher for APCs at C1D-7 (P = 0.0095) and APCs at C1D1 (P = 0.0121). Increases in APCs from C1D-14 to C1D1 were also likely to be higher for responders (P = 0.0242).

Discussion

To our knowledge, this study is the first prospective clinical trial to test the immunomodulatory activity of an
Overall, our results, as compared with historical data with single-agent high-dose IL2, suggest that the addition of the selective class I HDAC inhibitor entinostat may increase the clinical efficacy of this cytokine therapy by modulating immunosuppressive cells.

The potential immunomodulatory activity of epigenetic drugs has been postulated since the beginning of their development, in

<table>
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<th>Strata</th>
<th>3-yr PFS rate (95% CI)</th>
<th>5-yr PFS rate (95% CI)</th>
<th>Median PFS (95% CI)</th>
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<tr>
<td>Total</td>
<td>0.19 (0.06–0.38)</td>
<td>0.19 (0.06–0.38)</td>
<td>13.8 (6.0–18.8)</td>
<td>E = 28 C = 15 T = 43</td>
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<tr>
<td>1. OR</td>
<td>0.45 (0.13–0.73)</td>
<td>0.45 (0.13–0.73)</td>
<td>28.5 (12.6–NR)</td>
<td>E = 6 C = 9 T = 15</td>
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<td>2. Not OR</td>
<td>0.00 (0.02–0.31)</td>
<td>5.7 (3.0–10.4)</td>
<td>E = 22 C = 4 T = 26</td>
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**Figure 3.**
Progression-free and overall survival. Kaplan-Meier curves of progression-free survival (A), overall survival (B), and progression-free survival of responders (OR) versus nonresponders (not OR) (C). E, events; C, censored; T, total.
view also of the sporadic tumor responses observed in patients with solid tumors, including melanoma, at doses that likely do not achieve the required micromolar concentrations for a direct antitumor effect. Our group was among the first to report the potential immunomodulatory activity of HDAC inhibitors in a preclinical model of renal cell carcinoma (13). Several preclinical studies now support the hypothesis that HDAC inhibitors may synergize with immunotherapies by modulating the immune response (19–21). For example, HDAC inhibitors have been reported to enhance the effect of vaccine strategies (22). However, this class of agents has been described as a sort of "double-edge sword" (23). On one hand, there have been clinical trials that utilized pan-HDAC inhibitors as adjuvant therapy to reduce GVHD in patients who underwent allogeneic bone marrow transplant by exploiting the "immunosuppressive" properties of these agents (24). On the other hand, preclinical models have shown that HDAC inhibitors have a proimmunomodulatory activity. Intriguingly, there is preclinical evidence that HDAC inhibitors may have opposing effects as shown, for example, in modulating Treg function (14, 25). Several reasons for these conflicting results may be considered. For example, the class of HDACI (I vs. I/II), the dose, and the schedule may be responsible for these "double-edge sword" opposing effects (17). More recently, selective HDAC inhibition focusing on HDAC3 and HDAC11 has been reported to have specific effects on immune response by regulating Tregs and APCs, respectively (26, 27). Ex vivo experiments performed on peripheral mononuclear cells have shown the potential for detrimental effects of class I/II HDAC inhibition on lymphocyte viability and function (28), confirming the challenge that the development of this class of agents presents. Further studies will be needed to elucidate the complex epigenetic regulation of the immune response and to optimally exploit the clinical benefit of HDAC inhibitors in combination with immunotherapies.

The clinical trial was designed on the basis of the results from preclinical studies in which we observed a greater synergy between entinostat and high-dose IL2 when we treated the mice with the HDAC inhibitor first. We hypothesized that this "priming" phase of the immune response with entinostat could suppress Treg function and create a less immunosuppressive tumor

Figure 4. FDG-PET/CT scan response. A, Percentage change in target lesion of standardized uptake value (SUV) of FDG from baseline in patients with either not OR or OR by RECIST 1.1. B, Representative pictures of PET/CT scan in 2 patients with OR.
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Indeed, during the 2-week “lead in” phase with entinostat, we observed a modulation of Tregs. Despite the relatively small number of patients, we observed a statistically significant greater decrease in Tregs in the patients who achieve an OR as compared with patients who had progressive disease. This decrease in Tregs during the priming phase may represent a pharmacodynamic parameter with predictive potential that warrants prospective validation in future clinical trials. This observation is clinically relevant as, to date, we do not have a validated marker to predict

**Figure 5.**
Correlative studies. A, Representative pictures of tumor biopsies pre- and post-treatment with entinostat and high-dose IL2 showing CD8\(^+\) cells tumor infiltration. B, Quantitative analysis of tumor-infiltrating CD8\(^+\) cells and Foxp3\(^+\) cells. C, Quantitative analysis of Treg and activated APCs pre- and post-treatment with entinostat. Color lines, individual patients. *, \(P = 0.003\).
response to high-dose IL2. The SELECT trial attempted to define a predictive signature, but the results were not informative (5). Unfortunately, the collection of peripheral blood immune cells (i.e., Tregs) was not performed in that study. Additional correlative studies on the profile of circulating immune cells and chemokines/cytokines will likely shed some light on the potential predictive values of these markers.

The treatment algorithm for ccRCC includes both anti-VEGF drugs and immunotherapies. Although the use of PD-1/PD-L1 is revolutionizing the therapeutic options for the majority of solid tumors including ccRCC, the only immune checkpoint inhibitor approved to date for ccRCC is nivolumab in the first-line setting; however, the results from two phase III clinical trials involving combinations with PD-1 and PD-L1 inhibitors may lead to the approval of these drugs in the first-line setting. Overall, high-dose IL2 remains an option for selected ccRCC patients who are seeking a durable response and possible cure of their disease. The acute toxicities and the logistics for the administration of this regimen represent undeniable drawbacks, but the side effects are limited in time and are not chronic, unlike those observed with other therapies, including potentially the immune checkpoint inhibitors. Overall, entinostat did not seem to increase the toxicities expected from high-dose IL2.

As several reports regarding the clinical benefit of sequential use of high-dose IL2 and immune checkpoint inhibitors are surfacing, it is intriguing to speculate that these two immunotherapeutic approaches may not necessarily have cross-resistance mechanisms. Our results also support the hypothesis that HDAC inhibitors may have a role in combination with other immunotherapies, including PD-1/PD-L1 inhibitors as suggested by preclinical data generated in our laboratory (unpublished). Interestingly, HDAC inhibition has been shown to increase PD-L1 expression in preclinical models, including in combination with a demethylating agent (29, 30). Furthermore, there is both preclinical and clinical evidence that entinostat may affect myeloid suppressive derived cells (31, 32). Thus, over the next years, several clinical trials will test novel combinations of immunotherapies for ccRCC, including checkpoint inhibitors, vaccines, adoptive T-cell therapy, and T-cell agonists (33), and HDAC inhibitors may provide an additional tool to modulate the immune response more effectively.

Our study has some limitations, including the small sample size, the long time for accrual, the short follow-up, and the non-randomized design, which prevent drawing any more definitive conclusions. The accrual was initially slow because of competing studies at the participating institutions, in particular with the availability of immune checkpoint inhibitors, but it significantly picked up in the past 2 years, homogenously across the four sites. Despite these limitations that could have affected the outcome, the degree of clinical benefit observed with this combination exceeded the prespecified benchmark, providing rationale to design additional studies of epigenetic priming with immunotherapy.

In conclusion, our results suggest that the combination of entinostat plus high-dose IL2 is tolerable with promising clinical activity, including higher response rate and greater median PFS as compared with historical data. These findings represent the first evidence, to our knowledge, of improved benefit through immunotherapy combination with an epigenetic agent in the first-line setting treatment for ccRCC and provide the rationale for a prospective validation of this therapeutic strategy. On the basis of these preliminary results, we are currently planning a multisite, randomized phase II study of high-dose IL2 +/− entinostat in the same patient population.

Disclosure of Potential Conflicts of Interest
H. Hammers is a consultant/advisory board member for Bristol-Myers Squibb. S. George is a consultant/advisory board member for AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis, Janssen, Novartis, and Pfizer. T. Dorff reports receiving speakers bureau honoraria from Exelixis, Pfizer, and Prometheus. No potential conflicts of interest were disclosed by the other authors.

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References

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