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Ipilimumab plus nivolumab in avelumab-refractory Merkel cell carcinoma: a multicenter study of the prospective skin cancer registry ADOREG

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ABSTRACT

Merkel cell carcinoma is a rare, highly aggressive skin cancer with neuroendocrine differentiation. Immune checkpoint inhibition has significantly improved treatment outcomes in metastatic disease with response rates to programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) inhibition of up to 62%. However, primary and secondary resistance to PD-1/PD-L1 inhibition remains a so far unsolved clinical challenge since effective and safe treatment options for these patients are lacking.

Fourteen patients with advanced (non-resectable stage III or stage IV, Union international contre le cancer 2017) Merkel cell carcinoma with primary resistance to the PD-L1 inhibitor avelumab receiving subsequent therapy (second or later line) with ipilimumab plus nivolumab (IPI/NIVO) were identified in the prospective multicenter skin cancer registry ADOREG. Five of these 14 patients were reported previously and were included in this analysis with additional follow-up. Overall response rate, progression-free survival (PFS), overall survival (OS) and adverse events were analyzed.

All 14 patients received avelumab as first-line treatment. Thereof, 12 patients had shown primary resistance with progressive disease in the first tumor assessment, while two patients had initially experienced a short-lived stabilization (stable disease). Six patients had at least one systemic treatment in between avelumab and IPI/NIVO. In total, 7 patients responded to IPI/NIVO (overall response rate 50%), and response was ongoing in 4 responders at last follow-up. After a median follow-up of 18.85 months, median PFS was 5.07 months (95% CI 2.43—not available (NA)), and median OS was not reached. PFS rates at 12 months and 24 months were 42.9% and 26.8 %, respectively. The OS rate at 36 months was 64.3%. Only 3 (21%) patients did not receive all 4 cycles of IPI/NIVO due to immune-related adverse events.

In this multicenter evaluation, we observed high response rates, a durable benefit and promising OS rates after treatment with later-line combined IPI/NIVO. In conclusion, our patient cohort supports our prior findings with an encouraging activity of second-line or later-line IPI/NIVO in patients with anti-PD-L1-refractory Merkel cell carcinoma.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, highly aggressive skin cancer with neuroendocrine differentiation which occurs predominantly in chronically ultraviolet (UV)-exposed skin sites of elderly.[1 2] Etiological factors promoting the development of this cutaneous neoplasia include the Merkel cell polyomavirus (MCPyV) and UV irradiation.[1] For unresectable and metastatic disease immune checkpoint inhibition (ICI) has transformed treatment outcomes in a subset of patients. First-line programmed cell death protein 1 (PD-1) blockade with pembrolizumab and programmed cell death 1 ligand 1 (PD-L1) blockade with avelumab have shown high objective response rates (ORR) of 56% and 62%.[3–5] Hence, the approval of PD-L1 inhibition with avelumab for advanced and metastatic MCC has replaced chemotherapy as first-line systemic therapy.[5] However, a substantial number of patients show primary or acquired resistance to PD-L1 monotherapy. Unfortunately, homogenous data on subsequent treatment options for PD-L1/PD-1 refractory patients are still lacking. We recently reported a retrospective multicenter cohort of five patients with metastatic MCC showing primary resistance to avelumab being treated with subsequent ipilimumab plus nivolumab (IPI/NIVO).[6] In our analysis, later-line treatment with combined immunotherapy resulted in a promising ORR of 60%. With approved systemic treatment options for these patients being limited to chemotherapy regimes showing mostly short-lived responses, we now conducted an extended analysis using the prospective multicenter skin cancer registry ADOREG.

MATERIALS AND METHODS

Patient cohort and data acquisition

The database of the prospective multicenter skin cancer registry ADOREG was queried for patients with unresectable stage III or stage IV MCC with primary resistance (best overall response (BOR) progressive disease (PD) or stable disease (SD) for less than 6 months according to Response Evaluation Criteria In Solid Tumors (RECIST) V.1.1) to first-line therapy with the PD-L1 inhibitor avelumab who received combined IPI/NIVO as any later treatment line. First-line treatment with avelumab for unresectable or metastatic disease was initiated between January 2017 and April 2021. Treatment with IPI/NIVO was initiated between January 2019 and September 2021 (data-cut off May 3, 2022). Tissue used for molecular analyses was collected during routine care for diagnostic or therapeutic reasons.

Exclusion criteria comprised prior adjuvant treatment with a PD-1 or PD-L1 inhibitor. Patients who had received adjuvant radiotherapy or had additive radiotherapy during ICI with avelumab or IPI/NIVO were eligible. Demographic and clinicopathological data including treatment specific outcomes were extracted from the ADOREG registry and hospital records by chart review.

ADOREG is a multicentric registry of the German Dermatologic Oncology Group (DeCOG) prospectively collecting real-world data of patients with skin cancer treated at skin cancer centers. On August 1, 2022, 67 centers were actively recruiting patients into ADOREG, and 794 patients with MCC had been enrolled. Details are provided at https://www.hautkrebsregister.de/en. The participating institutions were queried for endpoint data.

Five of the 14 patients were reported previously and included in this analysis with additional follow-up.[6] For these patients, informed consent had been waived by the Ethics Committee of the University of Würzburg due to the retrospective nature of the study.

Definition of end-points and statistical analysis

Endpoints were ORR, progression-free survival (PFS), overall survival (OS) and safety (irAE). Radiological tumor assessment and response was performed according to the RECIST V.1.1.[7] Radiological response to tumor therapy was defined as follows: complete response (CR), partial remission (PR) or stable disease (SD) for more than 6 months. Best changes in the sum of diameters were calculated with Microsoft Excel and depicted in a waterfall plot as % change from baseline. PFS and OS were calculated from the first cycle of IPI/NIVO to the last tumor assessment, respectively, the last consultation or date of death using the Kaplan-Meier method. The analyses were performed using R V.4.1.1 (R packages *survival, swimplot*). IrAE were documented and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

RESULTS

Patient demographics

Fourteen patients, 64.3% (9/14) being male, with unresectable stage III (21.4%) or stage IV (78.6%) MCC according to UICC 2017 with a median follow-up of 18.85 months (IQR 17.63–22.40) were included in our analysis. Median age at first MCC diagnosis was 64 years (range 53–83). MCPyV status was determined in 10 patients. For the remaining patients, tissue for analysis was unavailable. Congruent to the literature, 80% were MCPyV positive. The PD-L1 status was determined in seven patients. Patient demographics are summarized in table 1.

First-line avelumab and subsequent therapies

All patients received first-line avelumab treatment for unresectable or metastatic disease. Median number of cycles was 5 (range 2–12). Twelve patients showed PD in the first tumor assessment and two patients experienced a short-lived stabilization (SD) followed by disease progression. Four patients received chemotherapy (carboplatin plus etoposide or cisplatin plus etoposide) as second-line treatment. Two of these 4 patients showed partial remission under chemotherapy and were re-exposed to avelumab after tumor progression. One of these 4 patients received third-line therapy with the PD-1 inhibitor nivolumab. All 3 patients showed PD to third-line PD-L1 or PD-1 inhibition, respectively. One patient was treated with nivolumab and another patient with a Mdm2 inhibitor as second-line treatment. The remaining 8 patients did not receive a systemic therapy in between avelumab and IPI/NIVO.

Therapy outcome IPI/NIVO

All 14 patients received combined IPI/NIVO (10 patients with IPI 3 mg/kg plus NIVO 1 mg/kg; 4 patients with IPI 1 mg/kg plus NIVO 3 mg/kg) as subsequent later-line therapy. Three out of 4 patients responded to the flipped-dose (IPI 1 mg/kg plus NIVO 3 mg/kg). Seven (7/ 14; 50%) patients had normal lactate dehydrogenase levels and Eastern Cooperative Oncology Group Performance Score was ≤1 in 78.6% (11/14) of the patients prior to IPI/NIVO. A median number of 4 cycles (range 1–4) IPI/NIVO was administered. Only 1 patient (1/14; 7.1%) received additive radiotherapy accompanying IPI/NIVO and showed PD as BOR.

Seven out of 14 patients (1 × CR; 6 × PR) responded to combined IPI/NIVO according to RECIST V.1.1 resulting in an ORR of 50%. A waterfall plot showing the best change in target lesion diameters can be found in online supplemental figures 1A. The median PFS (mPFS) on IPI/NIVO was 5.07 (95% CI 2.43 to not available (NA)) months (figure 1A). The PFS rates were 42.9% at 12 months and 26.8% at 24 months (figure 1A). The median OS (mOS) from start of IPI/NIVO has not been reached after a median follow-up of 18.85 months (figure 1B). The OS rate at the landmarks 12 months, 24 months and 36 months is 64.3% (figure 1B). Detailed outcome data can be found in table 2.

Table 1 Patient characteristics

	Patients % (n)
Age, median (range), years	64 (53–83)
Sex	
Female	35.7 (5/14)
Male	64.3 (9/14)
Stage (UICC 2017)	
III	21.4 (3/14)
IV	78.6 (11/14)
MCPyV	
Positive	57.1 (8/14)
Negative	14.3 (2/14)
Unknown	28.6 (4/14)
PD-L1	
Positive	0 (0/14)
Negative	50.0 (7/14)
Unknown	50.0 (7/14)
Avelumab	
Median number of cycles (range)	5 (2–12)
BOR	
PD	85.7 (12/14)
SD	14.3 (2/14)
Subsequent therapy	
None	57.1 (8/14)
Chemotherapy*	28.6 (4/14)
PD-1 monotherapy	7.1 (1/14)
Other	7.1 (1/14)
Two subsequent therapies	21.4 (3/14)
IPI/NIVO	
LDH	
Normal	50.0 (7/14)
Elevated	42.9 (6/14)
Unknown	7.1 (1/14)
ECOG	
0	50.0 (7/14)
1	28.6 (4/14)
2	21.4 (3/14)
Dosing	
IPI3/NIVO1	71.4 (10/14)
IPI1/NIVO3	28.6 (4/14)
Median number of cycles (range)	4 (1–4)

*Cisplatin+etoposid or carboplatin+etoposid.
BOR, best overall response; IPI1/NIVO3, ipilimumab 1 mg per kg+nivolumab 3 mg per kg; IPI3/NIVO1, ipilimumab 3 mg per kg+nivolumab 1 mg per kg; IPI/NIVO, ipilimumab plus nivolumab; LDH, Lactate dehydrogenase; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; PD-1, programmed cell death protein 1; PD, progressive disease; PD-L1, programmed cell death 1 ligand 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; SD, stable disease; UICC, Union international contre le cancer.

Adverse events and safety

In our analysis, 57.1% (8/14) of the patients experienced an irAE of any grade according to CTCAE V.5, with 50% (4/8) graded mild to moderate (grade 1–2) and 50% (4/8) graded severe (≥ grade 3). Involved organ systems were, as previously described, the gastrointestinal (colitis), respiratory (pneumonitis) and endocrine system (adrenal insufficiency). In 1 patient cycles 3 and 4 of IPI/NIVO were delayed and 3 patients received less than 4 cycles of IPI/NIVO due to an irAE. Two of the 3 patients who did not receive 4 cycles of IPI/NIVO due to an irAE showed PD in the first tumor assessment while the remaining patient showed PR and is receiving nivolumab as maintenance therapy despite the former toxicity. Detailed information is shown in table 3.

Follow-up

At a median follow-up of 18.85 months (IQR 17.63–22.40), 64.3% (9/14) of the included patients were still alive. Of these 9 patients, 44.4% (4/9) have not progressed so far. Of these 4 patients showing ongoing responses, two are receiving maintenance therapy with nivolumab. Five patients (5/14, 35.7%) died due to tumor progression (online supplemental figures 1B).

Of note, 1 patient showed a CR after 4 cycles of IPI/NIVO. Unfortunately, he relapsed twice after combined ICI. He was treated with surgery (PFS 12.2 months) and re-exposed to IPI/NIVO following relapse after surgery. Ten months after re-exposition to IPI/NIVO tumor assessment showed a CR again (re-exposure PFS 10.6 months).

DISCUSSION

In this multicenter analysis, later-line combined ICI showed a meaningful response rate and durable responses in patients with avelumab-refractory MCC. For these patients, data on subsequent systemic therapies have so far been reported in rather heterogenous and small patient cohorts. LoPiccolo *et al* reported a heterogenous case series with in total 13 patients of which only 2 patients received palliative avelumab monotherapy and subsequent combined ICI with IPI/NIVO.[8] While one patient was primary resistant to avelumab, the other patient showed an initial PR. Both patients did not respond to subsequent IPI/NIVO. Shalhout *et al* recently published a retrospective study of 13 patients with anti-PD-L1 or -PD-1-refractory MCC receiving subsequent IPI/NIVO.[9] In their analysis, 9/13 (69%) received PD-1 blockade with either pembrolizumab or nivolumab and only 4/13 (31%) PD-L1 blockade with avelumab as first-line therapy. Fifty-four percent were primary refractory to their first-line treatment and no patient responded to subsequent IPI/NIVO in terms of a CR or PR. Median PFS was 1.3 months and mOS was 4.7 months. These findings indicate that prior PD-L1 vs PD-1 blockade as well as primary versus acquired resistance to PD-L1/PD-1 blockade might influence outcome of later-line IPI/NIVO. Our extended analysis still shows a high ORR of 50% to subsequent IPI/NIVO in patients being primary resistant to avelumab while Shalhout *et al* reported an ORR of 0% (no CR or PR).[9] Apart, survival outcome in our analysis fundamentally differs with median OS not being reached after 36 months. For first-line avelumab, the JAVELIN Merkel 200

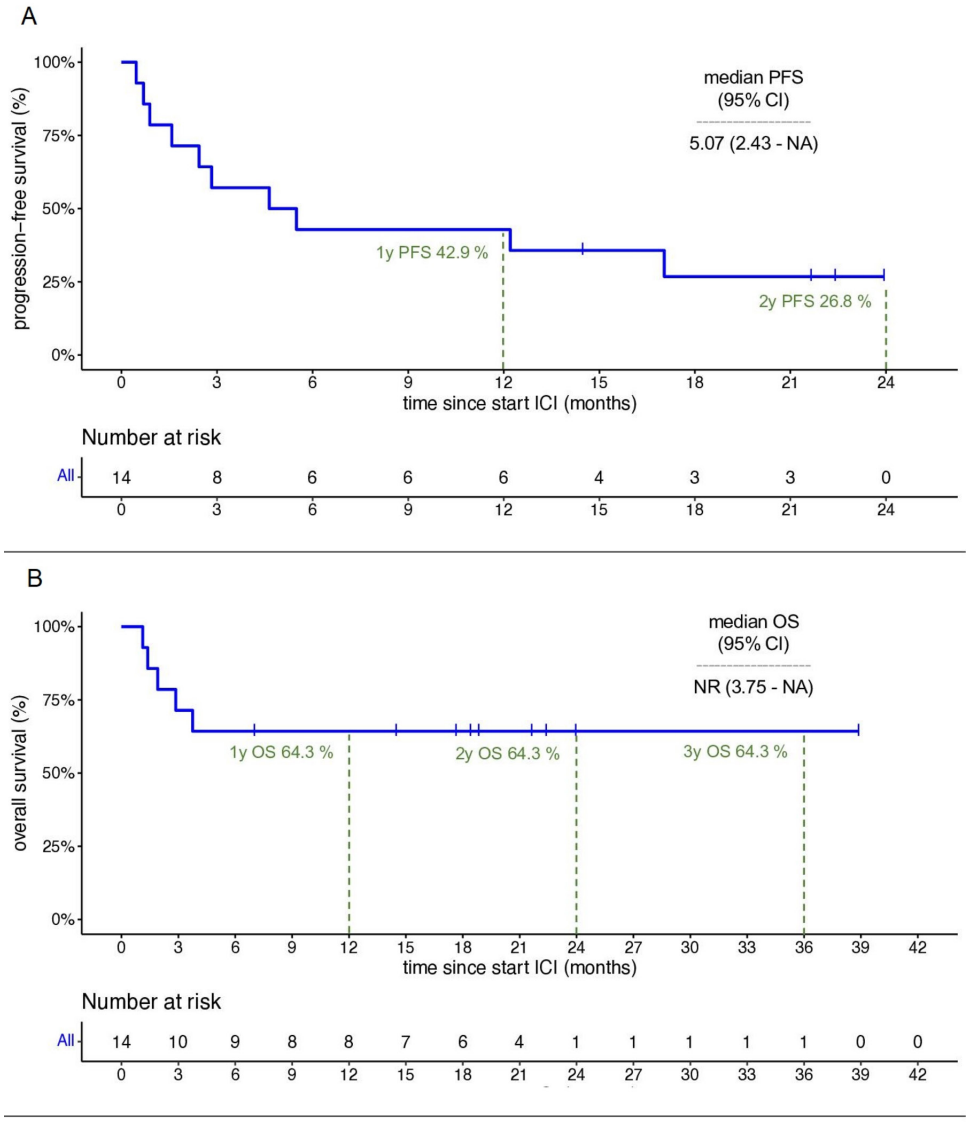

Figure 1 Kaplan-Meier analyses. (A) Progression-free survival (PFS) for all patients (n=14). (B) Overall survival (OS) for all patients (n=14). Dashed lines indicate 1-year (1y), 2-year (2y) and 3-year (3y) landmarks. ICI, immune checkpoint inhibition; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached.

trial resulted in a median OS of 20.3 months in the total cohort.[10] Survival data for the subgroup with PD (41.1%), indicating primary resistance to first-line avelumab, have not been published so far and is NA for indirect comparison.[10] Similarly, the recently published real-world data analysis on avelumab in metastatic MCC does not provide accurate conclusions on OS of the subgroup with primary resistance to avelumab.[11] When comparing our data to those by Shalhout *et al*, primary (not acquired) resistance to PD-L1 (not PD-1) blockade seems to be the crucial factor for response to subsequent CTLA-4- and PD-1-blockade in our cohort, possibly explaining the huge differences in ORR and OS. Since activity of combined IPI/NIVO has also been observed in patients with PD-1-refractory advanced melanoma,[12] our data now suggest that IPI/NIVO is a rational option for second-line or later-line systemic treatment in those cutaneous malignancies causing the majority skin cancer related deaths. However, the just published randomized, open-label, phase 2 trial on first-line IPI/NIVO±stereotactic body radiation with an impressive ORR of 100% in ICI-naïve patients now gives justified reason to possibly even prefer IPI/NIVO as first-line therapy over PD-L1 or PD-1 monotherapy.[13]

Clinical characteristics and other biomarkers might predict response to immunotherapies. MCC shows a particular biology with MCPyV being integrated into ~70% of the tumor genomes, while the remaining 30% presumably are linked to UV irradiation showing a strikingly high tumor mutational burden (TMB).[14–16] Both factors provide a promising rationale for response to ICI.[4 17] In our cohort, MCPyV status was analyzed in 10 patients with response to subsequent IPI/NIVO in 62.5% (5/8) of the MCPyV positive and 50% (1/2) of the MCPyV negative tumors. These results are congruent to the so far published data showing response to first-line pembrolizumab, second-line avelumab or neoadjuvant

Table 2 Outcome associated with later-line IPI/NIVO

	Patients % (n)
IPI/NIVO	
BOR	
CR	7.1 (1/14)
PR	42.9 (6/14)
SD	0 (0/14)
PD	50.0 (7/14)
Maintenance therapy (NIVO)	
Yes	35.7 (5/14)
No	64.3 (9/14)
PFS	
Median (range)	5.07 (2.43–NA)
1-year rate (%) (95% CI)	42.9 (23.4 to 78.5)
2-year rate (%) (95% CI)	26.8 (10.9 to 66.0)
OS	
Median (range)	NR (3.75–NA)
1-year rate (%) (95% CI)	64.3 (43.5 to 95.0)
2-year rate (%) (95% CI)	64.3 (43.5 to 95.0)
3-year rate (%) (95% CI)	64.3 (43.5 to 95.0)
Median follow-up (months) (IQR)	18.85 (17.63–22.40)

BOR, best overall response; CR, complete response; IPI/NIVO, ipilimumab plus nivolumab; NA, not available; NIVO, nivolumab; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; SD, stable disease.

nivolumab in both, patients with MCPyV-positive and MCPyV-negative MCC.[18–20] Thus, negative MCPyV status does not seem to be associated with resistance to ICI.

Table 3 Immune-related adverse events associated with later-line therapy with IPI/NIVO

	Patients % (n)
irAE related to IPI/NIVO	
Any grade	57.1 (8/14)
Grade 1–2	28.6 (4/14)
≥ Grade 3	28.6 (4/14)
Organ system affected	
Gastrointestinal	14.3 (2/14)
Respiratory	14.3 (2/14)
Endocrine	7.1 (1/14)
Hematological	7.1 (1/14)
Other (Fatigue)	14.3 (2/14)
Dose delay or end of therapy due to irAE	
Delay	7.1 (1/14)
End (less than 4 cycles due to irAE)	21.4 (3/14)

IPI/NIVO, ipilimumab plus nivolumab; irAE, immune-related adverse event.

Although a high TMB is known as a marker for response to ICI in other entities,[17] only a weak association with PFS and OS could be shown for second-line avelumab in metastatic MCC.[19] Hence, the significance of this surrogate marker in MCC remains unclear and therefore was not analyzed in our cohort. Taken together, the presence of MCPyV and high TMB indicate immunogenicity of this entity rather than providing a predictive value for clinical decision making or predicting response to ICI.

The JAVELIN Merkel 200 trial revealed better response and survival data in the subgroup with positive PD-L1 status for patients with previously treated metastatic MCC receiving subsequent avelumab (mOS 12.9 vs 7.3 months) and for patients receiving first-line avelumab (ORR 61.9% vs 33.3%, mOS not reached vs 15.9 months).[10 21] Unfortunately, PD-L1 status could be evaluated in only 50% (7/14) of our patients. All analyzed tumors were negative for PD-L1 which could be a possible surrogate marker associated with primary resistance to PD-L1 monotherapy in these patients.[10] However, there are also data showing that PD-L1 expression by tumor cells is not associated with response to both PD-1 or PD-L1 blockade in MCC patients.[22] The data from Spassova *et al* also show a better probability of disease control to PD-1 blockade compared with PD-L1 blockade which could in part explain response to IPI/NIVO in PD-L1 resistant patients. Despite these controversial data and on the basis of our results as well as the data from the JAVELIN Merkel 200 trial, we hypothesize that patients with metastatic MCC with negative PD-L1 status could be more likely to benefit from dual agent CTLA-4- and PD-1 targeting ICI similar to data from the Checkmate-067 trial in patients with metastatic melanoma.[23 24] To validate this hypothesis which at the moment is based on few and heterogenous data, a prospective clinical trial with PD-L1 status as stratification criterium is needed.

IPI/NIVO is known for a high rate of severe irAE.[23] In our cohort, 57% of patients experienced an irAE of any grade while only 29% showed a severe irAE. Moreover, only 3 (21.4%, 3/14) patients did not receive all 4 cycles of IPI/NIVO due to an irAE. In this context, it must be noted that 3 (21.4%, 3/14) patients did not receive all 4 cycles of IPI/NIVO due to rapid tumor progression. In these patients, no irAE were documented which might bias our data. Still the rate of severe irAE is rather low in our cohort indicating a surprisingly good tolerability in these elderly patients. Since the toxicity of combined ICI seems to depend on the dosing of IPI,[25] the dosing with IPI 1 mg/kg and NIVO 3 mg/kg (dosing chosen according to the ongoing CheckMate-358 study) in 4 patients might, at least in part, explain the rather low percentage of high grade AE in our cohort.

Our study has several limitations. The main limitations are the small number of patients as well as the registry-based data collection. In addition, adverse events might be under-reported in this registry which could be an additional explanation for the rather low rate of severe irAE in this cohort.

In conclusion, this multicenter ADOREG analysis showed promising OS and ORR to later-line combined ICI with IPI/NIVO in patients with advanced or metastatic MCC with primary resistance to first-line avelumab. To further investigate the efficacy of IPI/NIVO in avelumab-refractory patients as well as to identify biomarkers of response prospective, randomized clinical trials are needed.

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