Original Article

Local therapy in advanced melanoma after immune checkpoint inhibitors aiming to achieve complete response

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ABSTRACT

Background and Objectives: New scenarios for local therapy have arisen after starting immune checkpoint inhibitors (ICIs) to treat advanced melanoma (AM). The aim of this study is to examine the role of local therapies with curative intention for patients with AM that have been on ICI.

Methods: This was a single institution, retrospective analysis of unresectable stage III or IV melanoma patients on treatment with anti-PD1 ± anti-CTLA-4 who underwent local therapy with curative intention with no other remaining sites of disease (NRD).

Results: Of the 170 patients treated with ICI, 19 (11.2%) met the criteria of curative intention. The median time on ICI before local therapy was 16.6 months (range: 0.92–43.2). At the time of the local treatment, the disease was controlled in 16 (84.25%) and progressing in 3 patients (15.75%); 14 patients (73.7%) treated a single lesion and 5 (26.3%) treated 2 to 3 lesions. In a median follow-up of 17 months (range: 1.51–38.2) after the local therapy and 9.8 months after the last ICI cycle (range: 0.56–31), only 2 (10.5%) out of 19 patients relapsed.

Conclusions: Patients with AM on treatment with ICI were able to achieve NRD after local treatment and may benefit from long-term disease control without systemic treatment.

KEY WORDS: Immunotherapy, local therapy, melanoma

INTRODUCTION

The role of surgery in metastatic melanoma before the emergence of effective systemic therapies, which are now capable of producing long-term survival and high response rates, was restricted to treating complications like obstruction, bleeding, pain or perforation, and, in selected cases, resecting metastases with curative intention. The majority of data regarding curative resection in that old era came from small retrospective series, with only a few prospective randomized trials and, many of them, probably influenced by selection bias.[1-14] Prognostic factors deriving from these trials such as the site of disease, number of lesions, recurrence interval, lactic acid dehydrogenase (LDH) values, and resection margins frequently had to be considered before choosing surgery instead of systemic treatment for patients recently diagnosed with metastatic melanoma.[15] As a result, the majority of the patients did not fit into the "optimal surgical candidate" category. Despite that, some patients could achieve long-term recurrence-free survival after curative resections.[16]

The role of curative upfront surgery to treat stage IV disease became more frivolous after the results of BRAF/MEK inhibitors and immune checkpoints inhibitors (ICI) have shown response rates ranging from 40% to 70% and 5-year overall survival of almost 40%.[17,18] Even after the adjuvant trial Checkmate-238, which included patients with resected stage IV melanoma, the choice of surgery as the first step of therapy is still debatable for a large number of patients with metastatic disease, due to adverse prognostic factors usually present in such cases. Starting treatment with systemic therapy may better

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select patients with aggressive disease, thus avoiding unnecessary surgery.[19]

Nonetheless, new clinical scenarios for local therapy have arisen after starting systemic treatment, especially with immunotherapy. Surgery, radiotherapy, ablation therapies, arterial embolization, and combinations of these treatments can be considered at some point to treat remaining or progressive disease, sometimes achieving no evidence of disease activity. The aim of this study is to examine the role of local therapies with curative intention for patients with locally advanced or metastatic disease that have been on therapy with ICI.

MATERIALS AND METHODS

This is a single-institution retrospective cohort study that was approved by the A.C. Camargo Cancer Center review board. The inclusion criteria were unresectable stage III or stage IV melanoma treated with anti-PD-1, with or without anti-CTLA-4, and the adoption of any kind of local therapy aiming to achieve complete response (which was defined as the capability of treating all remaining sites of the disease) after at least 3 months of systemic therapy for patients with advanced melanoma on ICI.

Patients with uveal melanoma, primary resistance to immunotherapy, or who have received local treatment for other reasons were excluded.

A total of 170 patients with advanced cutaneous, mucosal, and unknown primary melanoma treated with anti-PD-1 with or without anti-CTLA-4 were identified between 2015 and 2019. All patients had histologically confirmed disease before initiation of the treatment and were staged with brain magnetic resonance imaging (MRI) and Fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET-CT) or CT scan of chest, abdomen, and pelvis. The eighth edition of the American Joint Committee on Cancer classification was used to classify these cases. Patients with suspected unknown primary tumor underwent complementary investigation based on anamnesis and the existence of symptoms. After excluding patients with a complete response due to exclusive systemic treatment, patients with progressive disease as best response, or missing medical records, 58 patients remained: 29 patients with partial response and 29 with stable disease by RECIST 1.1 criteria. Among them, we searched for patients who underwent local therapy with curative intention, defined by surgery with negative margins or ablative dose irradiation with no other remaining sites of disease. There were no limits on the number of lesions treated and, if necessary, the procedures could be staged, since the intention of total control of disease was clearly stated in the patient's report. When more than one procedure was performed, the time of disease control was calculated from the date of the last local treatment. The final cohort was composed of 19 patients [Figure 1]. Clinical and pathologic factors included age, sex, melanoma histological subtype, stage of the disease, LDH values, BRAF V600 mutational status, line of treatment, ICI in combination or monotherapy, the best response to therapy, type of local therapy, number of lesions treated, and situation of disease at the moment of local therapy: controlled versus in progression. Descriptive analysis was performed to identify frequencies of demographic variables, clinicopathological variables, and recurrence events. Survival curves were estimated with the Kaplan–Meier method. All statistical analyses were conducted using IBM SPSS Statistics version 24 (Armonk, New York) and Stata/IC 13.1 (College Station, TX). All pathologic specimens were evaluated by pathologists at our institution and reported according to the internal protocol. Complete pathological response (pCR) was defined as the complete absence of residual neoplasia in the surgical specimen. All patients underwent standard of care follow-up at AC Camargo Cancer Center, consisting of radiographic assessment every 12 weeks (PET-CT and/or cross-sectional images) and clinical evaluation. The radiological evaluation was defined by RECIST 1.1.

Our main inclusion criterion was the intention to achieve no evidence of active disease. We did not exclude patients based on the presence of active lesions in the brain, disease in progression, number of lesions to be treated, line of treatment, or type of local therapy. We only excluded patients with primary refractory melanoma and uveal melanoma.

RESULTS

A total of 19 patients received local treatment with curative intention after ICI in our hospital from 2015 to 2019. The median age at the time of local therapy was 54 years (22–85); 11 (57.9%) were female. About 16 patients were stage IV (84.21%) and 3 (15.79%) unresectable stage III. From 16 patients stage IV, 4 were M1a (25%), 6 M1b (37.5%), 3 M1c (18.75%), and 3 M1d (18.75%). Cutaneous melanoma was the primary site in 14 patients (73.68%), unknown primary in 3 (15.78%), and mucosal in 2 (10.5%); 9 patients

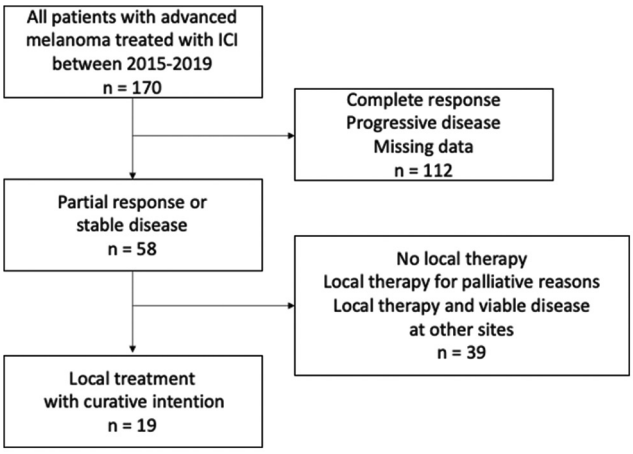

Figure 1: Flow chart of patients

had BRAF V600 mutation (47.3%) and 13 had normal values of LDH (68.4%); 15 patients received ICI treatment with PD1-blockade alone (78.9%) and 4 (21.1%) with PD-1 plus CTLA-4 blockade; 10 patients (52.65%) had ICI treatment as first-line, 7 (36.85%) as second-line, and 2 (10.5%) as third-line or beyond (patient characteristics are described in Table 1). The median time of treatment with ICI before local therapy was 16.6 months (range: 0.92–43.2). The best treatment response was partial response in 14 patients (73.7%) and stable disease in 5 patients (26.3%). However, at the moment of the local treatment, the disease was controlled in 16 (84.25%), progressing in one site of disease (focal progression) in 1 patient (5.25%), and progressing in two or more different sites of disease (oligofocal progression) in 2 patients (10.5%). Of those patients treated during progression, two (66.7%) had disease progression in a previously known metastatic lesion and one (33.3%) in a new one. About 14 patients (73.7%) were treated for a single lesion (single local treatment) and 5 (26.3%) treated for 2 to 3 lesions (multi-local treatment). Regarding the type of local therapy, 14 patients (73.7%) underwent a surgical procedure, 3 (15.8%) radiotherapy, and 2 (10.5%) received both surgery and radiation to control different lesions. Most patients had single local therapy treated lesions in the skin or lymph-nodes (n = 9, metastasectomy or lymphadenectomy), followed by lung (n = 3, metastasectomy in 2 and focal radiotherapy in 1), brain (n = 1, focal radiotherapy), stomach (n = 1, atypical gastrectomy), and rectal mucosa (n = 1, local resection). One patient was treated for 3 lesions in the brain (focal radiotherapy) and three patients underwent combined treatment: (1) surgical resection of a brain metastasis associated with radiotherapy to another lesion in the brain and to a single bone lesion, (2) resection of a single soft tissue lesion associated with brain resection of another lesion, and (3) a left colectomy associated with iliac lymphadenectomy and radiotherapy to a lesion near the pancreatic head. All patients who had any kind of surgery (n = 16) achieved R0 resections or a complete resection (brain lesions) and only one (6.25%) had dehiscence in the axillary wound with cutaneous lymphatic fistula. Patients who received radiotherapy as local treatment achieved complete metabolic response on PET-CT and, in case of brain metastasis, they achieve complete response by RECIST 1.1.

With respect to pathological reports of surgical cases, all three patients with stage III melanoma had pCR and among the 13 stage IV patients, 8 (61.5%) had residual disease, 4 (30.75%) had pCR, and in 1 patient (7.75%) the pathological report revealed Hodgkin's Lymphoma (persistent lymphadenomegaly as residual site of disease after 12 months of ICI for melanoma). Those 13 patients (68.4%) continued to receive anti-PD-1 therapy for an additional period of time after local treatment before ending treatment (median time of treatment after local therapy: 6.46 months). After local therapy, all 19 patients achieved metabolic complete response in subsequent PET-CT exams (treatment characteristics are described in Table 2). In a median follow-up of 17 months (range: 1.51–38.2) after the local therapy and 9.8 months after the last ICI cycle (range: 0.56–31), only 2 out of 19 patients relapsed (both in the brain, one of them as a new lesion) [Figure 2]. These two patients died—one due to continued progression of the disease and the other because of complications of neurosurgery necessary to treat the site of disease progression. There were no more deaths in this cohort until the cut-off date. The median overall survival of the population (time from the first anti-PD1 ± anti-CTAL4 cycle to the last follow-up visit or death) was 27.8 months (range: 3.4–58.1).

Table 1: Patient characteristics

Variable	*n* (%, when applicable)
Age (years)	
Median (range)	54 (22-85)
Gender	
Male	8 (42.1%)
Female	11 (57.9%)
Primary site	
Skin	14 (73.7%)
Mucosa	2 (10.5%)
Unknown primary	3 (15.8%)
BRAF status	
Wild-type	10 (52.7%)
Mutated	9 (47.3%)
Stage	
Unresectable III	3 (15.8%)
Metastatic disease	16 (84.2%)
Stage IV	
M1a	4 (25%)
M1b	6 (37.5%)
M1c	3 (18.7%)
M1d	3 (18.7%)
LDH	
Normal	13 (68.4%)
High	6 (31.6%)
ICI treatment	
PD-1 Blockade	15 (78.9%)
PD-1 + CTLA4 Blockade	4 (21.1%)
Line of treatment	
First-line	10 (52.7%)
Second-line	7 (36.8%)
Third or beyond	2 (10.5%)
Disease status at the moment of local treatment	
Controlled	16 (84.2%)
Progression	3 (15.8%)
Number of lesion (s)	
One	14 (73.7%)
Two	2 (10.5%)
Three or more	3 (15.8%)

DISCUSSION

Immune checkpoint blockade has deeply changed the landscape of advanced melanoma. Long-term follow-up of phase III studies has shown rates of objective response of approximately 40% to 60% (depending on anti-PD-1 as monotherapy or in combination with an anti-CTLA-4 antibody) and median duration of response not yet reached in 5 years of follow-up.[17] Analyzing the quality of the objective responses in these studies, we frequently see rates of complete response of 17% to 22% by RECIST 1.1 criteria.[20] Among the remaining

Table 2: Treatment characteristics

Patient	Stage	Disease status	*n* of lesion (s) treated	Site	Procedure	Resection type	Pathological analysis	PFS (months)
1	M1b	Controlled	1	Colon	Mucosectomy	R0	Melanoma	23, 7
2	M1b	Controlled	1	Lymph node	Lymphadenectomy	R0	Melanoma	4 (death due to complications)
3	III	Controlled	1	Skin and soft-tissue	Cutaneous Metastasectomy	R0	NED	13, 9
4	M1b	Controlled	1	Lymph node	Lymphadenectomy	R0	NED	9, 79
5	III	Controlled	1	Skin and soft-tissue	Cutaneous Metastasectomy	R0	NED	1, 51
6	M1d	Controlled	1	Lung	Lung SBRT	NA	NA	21, 13
7	M1c	Controlled	1	Stomach	Atypical gastrectomy	R0	Melanoma	24, 94
8	M1d	Controlled	1	Multiple sites	Lymphadenectomy	R0	NED	3, 02
9	III	Controlled	1	Lymph node	Lymphadenectomy	R0	NED	14, 26
10	M1a	Controlled	1	Lymph node	Lymphadenectomy	R0	NED	17
11	M1d	Controlled	3	Multiple sites	Brain metastasectomy+ Radiosurgery to one brain lesion + radiotherapy to a bone lesion	Gross resection+ NA + NA	Melanoma	38, 2
12	M1b	Controlled	2	Multiple sites	Brain+soft-tissue metastasectomy	Gross resection + R0	Melanoma	37, 4
13	M1a	Controlled	1	Skin and soft-tissue	Cutaneous Metastasectomy	R0	NED	30, 7
14	M1c	Controlled	3	Multiple sites	Colectomy + lymphadenectomy + pancreatic head radiotherapy	R0 + R0 + NA	Melanoma	24, 8
15	M1b	Controlled	1	Lung	Lung metastasectomy	R0	Melanoma	23
16	M1a	Controlled	1	Lymph node	Lymphadenectomy	R0	Hodgkin's Lymphoma	32
17	M1d	Oligo progression (same lesions)	3	CNS	Radiosurgery	NA	NA	15
18	M1c	Oligo progression (same lesions)	2	Lung	Lung metastasectomy	R0	Melanoma	2, 46
19	M1a	Focal progression (new lesion)	1	CNS	Radiosurgery	NA	NA	12, 9 (death due to melanoma)

NA=Not applicable, NED=No evidence of disease, CNS=Central Nervous system, R0=microscopic negative margins, PFS=progression-free survival from the data of the last local treatment

20% to 40% with partial responses, possibly, a great part of them are patients with a huge reduction in their tumor burden but not enough to be classified as complete response by RECIST 1.1, although the vast majority of them have a negative 18F-FDG PETCT.[21]

As a result of these highly active systemic treatments, the role of upfront surgery for resectable metastatic disease has been revisited. Such cases should be discussed on tumor boards to prevent unhelpful surgeries for biologically aggressive melanomas. In daily practice, the majority of patients with resectable disease at presentation will also have significant adverse prognostic factors, indicating systemic therapy first as a better choice for them. However, carefully selected metastatic patients may benefit from surgery as first step in this modern era of systemic therapy, as suggested by the phase III study Checkmate-238, which has shown significant benefit in terms of relapse-free survival favoring nivolumab over high-dose ipilimumab in the adjuvant setting. It is important to note that only 20% of patients had resected stage IV disease in this study and this subgroup was basically composed of M1a and M1b disease with normal LDH, which means a

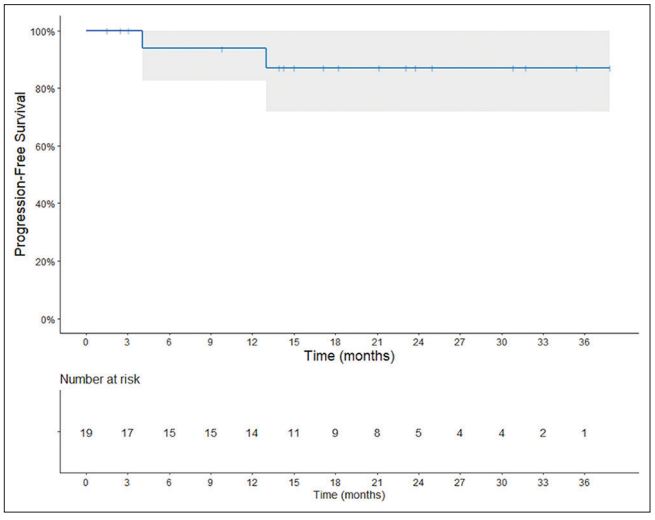

Figure 2: Progression-free survival from the last local treatment

more favorable prognosis. Another point is that patients who progressed during the period before randomization (rapidly progressing disease) were excluded from the analysis, making the stage IV population of this study even more selected.[19] As a consequence, only a minority of patients with recently diagnosed advanced melanoma will start treatment with surgery nowadays.

On the other hand, there is an important rate of secondary resistance in patients with initially controlled disease with ICI and patients who are not able to achieve resolution of their disease only with systemic therapy, carrying the reminiscent disease during the treatment. Interestingly, these patients with residual disease who completed 2 years of treatment and subsequently progress (up to 60% in 2 years of follow-up for patients with stable disease at the end) tend to present regrowth in the residual lesions in approximately 50% of cases and their response may not be as good as they were at first course of treatment.[22,23] Therefore, paradoxically, a more efficient systemic therapy has raised other opportunities for local therapy, such as consolidation therapy for residual disease or salvage therapy for disease in progression.

In our study, we described a single institutional experience of a reference cancer center. Our main objective was to use of local therapy to reach the status of no evidence of active disease. We did not exclude patients based on the presence of brain lesions, disease in progression (patients had to have at least 3 months of prior controlled disease), number of lesions to be treated, line of treatment, or type of local therapy. We only excluded patients with primary refractory melanoma and uveal melanoma. Based on these criteria, 19 out of 170 (11.2%) patients with advanced melanoma treated with ICI received local treatment with curative intent. The vast majority of them underwent local therapy to treat a residual single non-progressing lesion (n = 14) with 93% of relapse-free survival in 17 months of median follow-up after local therapy. Despite a relatively short follow-up, this good result probably reflects the "curative intention" inclusion criteria.

In one of the largest retrospective series of metastasectomy in patients with melanoma treated with ICI, the impact of surgery was categorized based on response to systemic treatment in three groups: (1) single residual lesion in patients with overall response to immunotherapy (n = 12), (2) single site of progressing disease, while the other systemic disease had responded or was stable (n = 106), and (3) multifocal progression (n = 119). There was a clear difference in survival among the groups with an estimated 5-year overall survival of 90%, 60%, and 6%, respectively. Interestingly, 71 patients in group 2 who achieved complete response (patients with single lesions in progression) had an estimated 5-year survival of 75% compared with 30% in patients who treated an isolated lesion in progression but had other remaining sites of disease left, drawing attention to the fact that the possibility of eradication of disease can help to select patients with better prognosis even among progressors.[24] In contrast, in another retrospective study, the results of local therapy (surgery, SBRT, or ablation) for treatment of disease in progression in 52 patients on ICI showed different results. In this study, they allowed up to three sites of progression but excluded patients with brain metastasis. There was no statistical difference in median progression-free survival between patients who achieve no evidence of disease versus residual disease despite the large difference in the numbers (15 vs 8 months, $P = 0.12$). However, it is important to note that the authors used very strict selection criteria like the absence of progression during the first 6 months of ICI therapy and at least two serial imaging evaluations showing stable disease or regression in the remaining disease after local therapy where the complete eradication would not be possible. Therefore, the absence of difference in patients with complete response and non-complete response may be in part due to the selection of favorable tumor biology and the small number of patients. Also, probably for the same reason, no difference between patients with 1 or 2 to 3 lesions treated was found (16 vs 4 months, $P = 0.11$).[25] The importance of the number of sites in progression was reinforced by the results of a retrospective multicenter analysis of 300 patients in another study, where non-solitary progressions compared with solitary ones had worse survival: 2-year overall survival of 55% versus 69%, respectively ($P < 0.001$).[26] Unfortunately, no information about the status of residual disease after local treatment was provided.

In addition, the pattern of failure after immunotherapy has been arising as an important predictive factor of progression-free survival after local therapy.[27] Progression in new lesions instead of existing ones is related to worse control of the disease. In one analysis, patients with progression in established tumors had 3-year progression-free survival of 70%, while those with new metastases had 3-year progression-free survival of 6% ($P = 0.001$).[25] In our study, among the three patients treated for lesions in progression, two lost control of existing lesions. Due to these small numbers, we did not look for possible differences regarding the duration of control based on the pattern of failure; however, one of the two patients in our study who relapsed had been treated for a new lesion.

Treating single residual non-progressive disease seems to represent the best situation for metastasectomy after ICI. Nonetheless, all patients with 2 to 3 sites of controlled disease in our study (n = 4) have been disease-free since the last local treatment (range: 15–38.2 months). More data about the limit in the number of local treatments for multiple sites of controlled disease will be necessary to establish the frontier between benefit and futility in this scenario. Another important point, besides the number of lesions to be treated, is when to deliver the local treatment for controlled disease. In published series, the median time on treatment before local therapy varies between 2 and 3 years.[25,25,28] Considering that the majority of objective responses will take place during the first 6 months of treatment and the median time to acquired resistance seems to be 12 months,[26] it would be reasonable to plan local therapies

Table 3: Scenarios for local treatment in patients on immune checkpoint blockade

Ideal scenario	Intermediate scenario	Worst scenario
Single progression	Limited progression	Multiple progression
Single lesion in progression	Progression in a few existing lesions (up to 3?) and predictable NED after local therapy	2 or more new and/or multiple existing lesions in progression
Existing (preferable) or new lesion	Progression in one existing site and it will leave controlled disease	Any situation in which other sites of progressive disease persist after treatment
Predictable NED after local therapy	No primary resistance	Primary resistance
No primary resistance	Doubling time (High) and LDH values (normal)	Doubling time (low) and LDH values (elevated)
Doubling time (High) and LDH values (normal)	Limited residual disease	Multiple residual disease
Single residual disease	2-3 residual lesions	Not capable of achieving complete response**
Single residual lesion	Predictable NED after local therapy	Multiple residual sites
Predictable NED after local therapy	Ideal time: 6-12 months of treatment*	Ideal time: maybe consider surgery on demand for lesion that starts to progress
Ideal time: 6-12 months of treatment*		

*Patients who have lesions in continuing regression can wait longer; **Sometimes 18F-FDG PET-CT can help to define which lesion (s) should be targeted
NED: no evidence of disease; LDH: lactic acid dehydrogenase

between 6 and 12 months of ICI treatment for patients who are not presenting downsizing of their lesions anymore. This strategy could favorably impact not only in toxicity due to a less prolonged systemic treatment but also financial costs. We found that some of our cases had pathological complete response and one had Hodgkin's lymphoma after surgery. Without surgery or at least a confirmatory biopsy, they would have been maintained on ICI for a longer period. The median time on treatment with ICI before local therapy was 16.6 months (range: 0.9–43.2) in our study.

Finally, there is scarce information in the literature regarding differences in types of local treatment and special sites of disease, as the central nervous system. In our study, three out of four patients with treated brain metastasis are disease-free after local therapy (range: 15–38.2 months). This is a small and retrospective study, but despite it, we believe that we contributed with important hypotheses and insights into this new age of treatments combination for advanced melanoma. A suggestion of approach to this scenario based on the currently available data is illustrated in Table 3.

CONCLUSIONS

In this retrospective cohort of patients with advanced non-uveal melanoma on treatment with ICI, with no primary refractory disease, and able to achieve NRD after local treatment benefited from long-term disease control after stopping systemic therapy, even in selected patients with progressive disease before local therapy.

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Conflicts of interest
There are no conflicts of interest.

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