Treatment Outcomes for Metastatic Melanoma of Unknown Primary in the New Era: A Single-Institution Study and Review of the Literature

Kierstin Utter^{a, b} Chloe Goldman^{a, b} Sarah A. Weiss^{b, c} Richard L. Shapiro^{b, d}
Russell S. Berman^{b, d} Melissa Ann Wilson^{b, e} Anna C. Pavlick^{b, e} Iman Osman^{a–c}

^aThe Ronald O. Perleman Department of Dermatology, ^bInterdisciplinary Melanoma Cooperative Group,

^cDepartment of Medicine, ^dDivision of Surgical Oncology, Department of Surgery, and ^eDivision of Hematology and Oncology, Perlmutter Cancer Center, Department of Medicine, New York University School of Medicine, New York, NY, USA

Keywords

Melanoma · Unknown primary · Occult primary · Immunotherapy · Targeted therapy

Abstract

Background: Metastatic melanoma of unknown primary (MUP) is uncommon, biologically ill defined, and clinically understudied. MUP outcomes are seldom reported in clinical trials. In this study, we analyze responses of MUP patients treated with systemic therapy in an attempt to inform treatment guidelines for this unique population. **Methods:** New York University (NYU)'s prospective melanoma database was searched for MUP patients treated with systemic therapy. PubMed and Google Scholar were searched for MUP patients treated with immunotherapy or targeted therapy reported in the literature, and their response and survival data were compared to the MUP patient data from NYU. Both groups' response data were compared to those reported for melanoma of known primary (MKP). **Results:** The MUP patients treated at NYU had better outcomes on immunotherapy but worse on targeted therapy than the MUP patients in the literature. The NYU MUP patients and those in the literature had worse outcomes than the majority-MKP populations in 10 clinical trial reports. **Conclusions:** Our study sug-

gests that MUP patients might have poorer outcomes on systemic therapy as compared to MKP patients. Our cohort was small and limited data were available, highlighting the need for increased reporting of MUP outcomes and multi-institutional efforts to understand the mechanism behind the observed differences.

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Introduction

Metastatic melanoma of unknown primary (MUP) is uncommon, biologically ill defined, and clinically understudied. MUP is defined as melanoma detected in a subcutaneous, lymph nodal, or visceral metastatic site without evidence of a primary lesion. In 2017, 2–3% of patients diagnosed with melanoma in 2017 will present with MUP [1, 2]. Clinically, it has been postulated that primary lesions are missed – errantly diagnosed or imperceptible on physical examination – or absent following complete regression due to a robust host immune response [2, 3]. Biologically, it has been suggested that MUP results from malignant transformation of a melanocyte after migration to a lymph node or visceral site [3]. Molecularly, MUP tumors carry high somatic mutation rates consis-

tent with the ultraviolet signature of melanoma of known primary (MKP), as well as comparable rates of BRAF and NRAS mutations [3–5].

Despite the fact that MUP connotes “metastatic” disease, investigators to date have reported largely on the use of localized treatment for MUP (surgery or radiotherapy), while the efficacy of systemic therapy in MUP patients remains unexplored [1, 6–9]. Clinical trials of immunotherapy and targeted therapy in patients with advanced cutaneous melanoma have not explicitly reported response rates specific to MUP patient subgroups due to its low incidence and lack of annotation. The response of MUP to these now FDA-approved therapies could add to the discussion of its elusive biological characteristics, as well as aid in making clinical recommendations.

In this study, we analyze therapeutic responses to systemic therapy and survival times in patients from our institution with MUP. We also perform a systematic literature review to identify published cases of systemically treated MUP. To the best of our knowledge, this is the first study to specifically address the responses and survival of MUP patients receiving systemic therapy.

Methods

NYU Study Population

Melanoma patients who presented to a medical or surgical oncologist at NYU’s Perlmutter Cancer Center between 2002 and 2016 were prospectively enrolled in the Interdisciplinary Melanoma Cooperative Group (IMCG) biorepository and clinicopathological database at NYU. This study was approved by the NYU Institutional Review Board, and informed consent was obtained from all patients at the time of enrollment. Recorded information includes patient demographics, disease and clinicopathological characteristics, details of the systemic therapy course, survival outcomes, and protocol-driven follow-up information.

Patients with MUP in NYU’s melanoma database were identified by searching the field “primary tumor type” and filtering for “unknown primary.” Cases were included if the clinical notes confirmed the existence of MUP after a complete skin examination, and excluded if the pathology reports documented a primary lesion or if there was a history of primary cutaneous, ocular, or mucosal melanoma. We then identified all patients treated with immunotherapy (ipilimumab, pembrolizumab, or nivolumab), targeted therapy (vemurafenib and/or cobimetinib, dabrafenib and/or trametinib), or chemotherapy (temozolomide, thalidomide, dacarbazine, or CarboTaxol) with sufficient radiographic evidence and clinical follow-up to assess therapeutic response and survival. Primary outcomes included tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and survival in months following treatment initiation [10]. Following the RECIST criteria, the patient radiology reports were reviewed, lesion sizes were recorded, and the response was ultimately categorized as progressive disease (PD), stable disease (SD),

partial response (PR), or complete response (CR), as previously defined [6]. These analyses were confirmed by reviewing clinical notes in which the response was often explicitly stated. Survival in months following treatment initiation was determined by reviewing the clinical records.

Systematic Literature Search

A systematic literature search for MUP patients treated with immunotherapy or targeted therapy was conducted to evaluate whether NYU’s MUP cohort was similar to that reported in the literature and to increase the size of the overall MUP systemic therapy cohort. Studies were excluded if none of the therapies of interest were administered and/or no follow-up was available to assess patient survival after treatment initiation (Fig. 1). Papers reporting the use of immunotherapy and targeted therapy were of particular interest, as shown in Figures 2b and 3b. Papers reporting the use of chemotherapy for MUP were secondarily assessed, as outlined in Figure 1 and discussed briefly in Results.

PubMed and Google Scholar were searched for all potential studies, including case reports, meta-analyses, and clinical trials, using the following keywords: melanoma, melanoma unknown primary, and melanoma occult primary. The titles and abstracts of articles yielded through this search were evaluated against the inclusion criteria. The manuscripts of eligible articles were obtained and reviewed in full. The bibliographies of the included articles were browsed to supplement the original search. Two investigators performed this search independently to ensure an exhaustive literature review.

The primary outcomes were survival in months following treatment initiation and response to therapy. The survival of the patients was either noted in the manuscript or calculated from Kaplan-Meier curves. Of note, follow-up was not available after publication. The response to therapy was either explicitly stated in the manuscript or inferred based on the clinical context and agreed upon by two independent investigators. The disease control rate (DCR; the proportion of patients with a PR, CR, or SD), median overall survival (mOS) following treatment initiation, and percent of patients alive 1 year following treatment initiation were calculated for each of the cohorts.

Results

The Metastatic MUP Patients at NYU Receiving Immunotherapy Had Better Outcomes than the MUP Patients Reported in the Literature

The NYU database includes 2,930 patients diagnosed with melanoma between 2002 and 2015, 66 (2.3%) of whom were identified as having MUP, similar to the rate reported in the literature [2]. All 66 patients were confirmed to have no prior history of cutaneous, mucosal, or ocular melanoma primary tumors. Patients with suspicious-appearing moles at presentation were evaluated by dermatology to rule out a primary tumor. No patients presented with symptoms of an advanced ocular or mucosal primary (ocular discoloration, vision changes, vagi-

Fig. 1. A systematic review of the literature reveals few papers reporting systemic treatment for melanoma of unknown primary (MUP) that include patient survival data.

nal or anal bleeding or obstruction, oral lesions or pain, or nasal blockage).

The characteristics of the 66 MUP patients are outlined in Table 1. Similar to the general melanoma patient age and gender distribution, the median age at the time of MUP diagnosis was 56 years (range 22–92), and 39 patients (59%) were male. Of note, 11 (17%) presented with stage III disease, while 55 (83%) presented with stage IV disease (6 patients with M1a, 2 with M1b, and 47 with M1c disease). The performance status was known for 53 patients, 38 (72%) of whom had a performance status of 0 or were fully functional. Fifty-two patients (79%) ultimately developed brain metastases, either alone or concurrently with other visceral sites.

Twenty-three NYU MUP patients received immunotherapy. The follow-up time for these patients ranged from 1 to 96 months. Nineteen patients received ipilimumab only, 1 received ipilimumab and nivolumab combination treatment, 2 received pembrolizumab only, and 1 received pembrolizumab followed by ipilimumab. The responses to treatment by the RECIST criteria and the

survival times from treatment initiation of the 23 NYU patients who received immunotherapy are outlined in Figure 2a. The median age at immunotherapy initiation was 57 years (range 33–74) and 18 patients (78%) were male. The majority received local therapies – surgery and/or radiation – before or in addition to immunotherapy, and 15 received another systemic treatment prior to immunotherapy. A minority were noted to have elevated lactate dehydrogenase (LDH) levels at the time of treatment initiation. Seven patients are living at the time of this publication, 6 with an ongoing therapeutic response.

After excluding papers that did not discuss immunotherapy or targeted therapy, or did not report patient survival data, a total of 10 papers were included for analysis, 3 of which discussed immunotherapy in particular. These 3 papers reported on a total of 24 MUP patients treated with immunotherapy for whom response rates and survival were documented, as illustrated in Figure 2b, with a maximum follow-up time of 24 months. None of the papers included in Figure 2b have overlapping patient populations. Of the 24 MUP patients identified, 13 (54%)

Fig. 2. a The MUP patients from NYU treated with immunotherapy showed an overall survival ranging from 1 to 96 months at the time of this publication. **b** The MUP patients from the meta-analyzed publications treated with immunotherapy showed shorter survival than the patients in **a**, but they were lost to follow-up after a maximum of 24 months. MUP, melanoma of unknown primary; NYU, New York University.

Fig. 3. a The MUP patients from NYU treated with targeted therapy showed a survival duration similar to their counterparts treated with immunotherapy, but no patients showed a continued response at the time of publication. **b** In contrast to the patients in **a**, 4 MUP patients from the meta-analyzed publications showed a continued response to targeted therapy at the time of publication, a shorter follow-up period notwithstanding. MUP, melanoma of unknown primary; NYU, New York University.

(labeled as L-I1–L-I13 in Fig. 2b) were enrolled on a phase II clinical trial assessing the efficacy of ipilimumab in pre-treated stage IV patients, 10 patients (42%) (L-I14–L-I23) were enrolled on the ipilimumab expanded access program, and 1 patient (4%) (L-I24) was featured in a case report [11–13]. All patients were treated with ipilimumab 3 mg/kg every 3 weeks for 4 planned cycles. Patients L-I1–L-I13 had a median age of 62 years (range 40–77), were mostly male ($n = 11$; 85%), and mostly had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 ($n = 12$; 92%). Five patients were living at the time of the report, but are lost to ongoing follow-up.

In both the NYU cohort and those reviewed in the literature, the majority of patients ultimately showed PD on

immunotherapy – 74% in the NYU group and 90% in the literature group. About one-third of the patients in both groups survived 1 year or longer after treatment initiation (39% at NYU and 33% in the literature). The mOS following treatment initiation was 9 months for the NYU patients and 8 months for the patients in the literature. The DCR of the NYU group was 26%. The DCR of the literature group was 10%; 1 literature patient showed PR and 1 showed SD, though this is not annotated in Figure 2b. Both of these patients fall within the range of L-I1–L-I13, for whom responses are labeled “N/A.” While this report indicated the numbers of patients with PD, SD, PR, and CR, it did not match these responses to the corresponding patient survival times [11].

The NYU Patients and Patients Reported in the Literature Together Had Worse Outcomes when Compared to the General Melanoma Distribution on Immunotherapy

Pooling the NYU and literature MUP groups treated with immunotherapy, the DCR was 17%, 1-year survival was 38%, and the mOS following treatment initiation was 8 months. In a phase III ipilimumab trial of previously treated metastatic melanoma patients, the ipilimumab treatment arm had a DCR of 29%, an mOS of 10.1 months, and a 1-year survival rate of 46% [14]. In a study of monotherapy ipilimumab in 155 patients, the DCR was 27% and 1-year survival was 47.2% [15]. In an analysis of 12 pooled studies of ipilimumab (1,861 patients), an mOS of 11.4 months was reported [16]. As a pooled group, the MUP patients performed marginally worse in our study when compared to the general melanoma distribution.

The Metastatic MUP Patients at NYU Receiving Targeted Therapy Responded Worse than the MUP Patients Reported in the Literature

Thirty-eight NYU patients had their metastatic tumors tested for BRAF mutations, of which 17 (45%) were positive for mutations (13 V600E, 1 V600K, and 3 unclassified variants). Typing was performed either for clinical purposes including clinical trial enrollment by qPCR (9 patients) or for research by sequencing (8 patients).

Eight NYU MUP patients received targeted therapy and were evaluable for posttreatment survival assessment. Three patients received only vemurafenib, 1 received only dabrafenib, and 1 received vemurafenib and cobimetinib combination treatment. One received dabrafenib and trametinib combination therapy followed by single-agent vemurafenib, 1 received single-agent dabrafenib followed by single-agent vemurafenib, and 1 received vemurafenib and cobimetinib combination therapy followed by dabrafenib and trametinib combination treatment. The follow-up times ranged from 1 to 59 months. The median age at targeted therapy initiation for the NYU patients was 59 years, and 5 patients (63%) were male. The responses to treatment by the RECIST criteria and the survival times from treatment initiation of the 8 NYU patients who received targeted therapy are outlined in Figure 3a. Of note, 5 NYU patients received both immunotherapy and targeted therapy and are represented in both Figure 2a and Figure 3a with different identification numbers (N-I2 = N-T3; N-I8 = N-T5; N-I15 = N-T6; N-I22 = N-T7; N-I14 = N-T8). Four patients received targeted therapy prior to immunotherapy, and 1 patient (N-T7) received immunotherapy prior to targeted therapy.

Table 1. Characteristics of the 66 MUP patients treated at NYU between 2002 and 2015

Age at diagnosis, years	
Mean	55.8
Median	56
Range	22–92
Sex, <i>n</i>	
Female	27
Male	39
Stage at presentation, <i>n</i>	
III	11
IV	55
M1a	6
M1b	2
M1c	47
Site(s) at last follow-up, <i>n</i>	
Nodal only	6
Subcutaneous only	3
Nodal and subcutaneous only	3
Brain only	2
Non-brain visceral	30
Brain and other	22
ECOG performance status at diagnosis, <i>n</i>	
0	38
1	10
2	5
Unknown	13
Serum LDH level at diagnosis, <i>n</i>	
High	13
Normal	8
Unknown	45
Treatment, <i>n</i>	
Adjuvant	12
Chemotherapy	33
Immunotherapy	23
Targeted therapy	8
Other therapy, <i>n</i>	
Surgery	52
Radiation	40
Unknown	3
BRAF status, <i>n</i>	
Wild type	21
Mutant	17
Unknown	28

Many patients received more than one “treatment” or “other therapy.” MUP, melanoma of unknown primary; NYU, New York University; LDH, lactate dehydrogenase.

A review of the literature yielded a total of only 7 MUP patients treated with targeted therapy for whom response and survival rates were documented, as shown in Figure 3b. None of the papers included in Figure 3b have overlapping patient populations. Six patients (L-T1–L-T5 and L-T7) were featured in case reports, and 1 patient (L-T6)

received therapy through a compassionate access program [17–23]. Patients L-T1–L-T7 had a median age of 63 years (range 30–85), and 4 (57%) were male. Two patients (L-T2 and L-T4) had unresectable stage III melanoma, while the remaining 5 patients were stage IV at the time of treatment initiation.

Comparing the NYU and literature cohorts revealed important differences despite the limited number of patients. All patients in the NYU cohort showed PD (DCR = 0%). Figure 3a displays the time points at which these patients developed new sites of metastatic disease (*) or showed increases in size of lesions qualifying as PD as per the RECIST criteria (^). Of the 8 patients, 5 (63%) were alive 1 year following treatment initiation. The mOS from time of treatment initiation was found to be 13 months. In the literature, tumor assessments according to the RECIST criteria were reported to be 2 CR (29%), 3 PR (43%), and 2 PD (29%), equating to a DCR of 71% (Fig. 3b). Five patients showed ongoing response at the time of publication. Not accounting for ongoing responses, the estimated mOS from time of treatment initiation at the time of publication was 10 months, and 2 patients (29%) were reported to be alive at 1 year.

The NYU Patients and the Patients Reported in the Literature Together Had Worse Outcomes when Compared to the General Melanoma Distribution on Targeted Therapy

When the NYU cohort on targeted therapy was pooled with the patients reported in the literature, the DCR was 33%, the 1-year survival rate was 47%, and the mOS following treatment initiation was 12 months. Similar to our observations regarding immunotherapy, these numbers were slightly lower than those for the outcomes reported in large randomized trials. Original phase III studies and follow-up reports of single-agent BRAF inhibitors have shown a DCR of 92%, an mOS of 13.6–18.2 months, and a 56% 1-year survival rate [24–27]. For patients treated with the combination of BRAF and MEK inhibitors, trials have reported more improved outcomes, with a DCR of 90–92% and a 1-year survival rate of 72–74% [28–31].

Chemotherapy Has Negligible Therapeutic Value for MUP Patients

Nineteen of NYU's 66 MUP patients received chemotherapy alone for their disease. All 19 of these patients progressed to expiration. Thirteen papers were found in the literature in which patients with MUP were reported to be treated with chemotherapy. Within these 13 papers, the responses and survival data from 15 individual pa-

tients were reported. One of the 15 showed SD on chemotherapy, and 1 showed a PR at the time of the report. The remaining 13 patients experienced PD [32–36]. Other investigators reported survival data from MUP patients as a group rather than individually on chemotherapy. Santini et al. [37], for example, reported that for 96 patients with melanoma metastatic to cervical and parotid lymph nodes from an unknown primary, “chemotherapy had no therapeutic value.”

Discussion

Our study reveals several important points about MUP in the new era of immunotherapy and targeted therapy. We first observed that in addition to being an uncommon disease, MUP is largely underreported in the literature. Whereas some patient characteristics – demographics, treatment history, and sites of disease – are reported in clinical trials, annotation of MUP versus MKP remains a rarity. Moreover, research emphasis has been placed disproportionately on localized treatment of what is more often a systemic, unresectable disease. In fact, two-thirds of the papers were excluded from our literature search for not discussing systemic therapy. Meanwhile, the large majority (83%) of the MUP patients identified at NYU presented with stage IV disease, and 81% received systemic therapy of some kind.

Despite the lack of relevant literature from which to extract data, we were able to identify a small pool of non-NYU MUP patients to compare to the NYU cohort who had been treated with immunotherapy or targeted therapy. Interestingly, we did observe differences between these two groups regarding both immunotherapy and targeted therapy.

The NYU immunotherapy patients showed a longer mOS following treatment initiation, a higher DCR, and a longer 1-year survival than the patients reported in the literature. There may be multiple explanations for this observed difference. First, 13 patients reported in the literature were treated as part of an expanded access program, suggesting poor prognostic features at baseline. Second, all patients reported in the literature received ipilimumab alone, whereas 4 of the NYU patients received more recently approved PD-1 or combination CTLA-4/PD-1 inhibitors with known higher response rates [38]. The lack of demographic data reported for the patients in the literature makes it difficult to draw firm conclusions about the nature of the differences between the NYU and non-NYU cohorts.

Both the NYU patients and those reported in the literature together had a worse outcome on immunotherapy when compared to the general melanoma distribution treated with immunotherapy in clinical trials. This is interesting considering MUP and MKP are known to have similar mutational loads reportedly associated with the response to immunotherapy (patients with higher mutational loads are shown to respond better) [39]. It is possible that the MUP patients showed a worse response because most had initially been diagnosed prior to 2011 and therefore had not been treated with first-line immunotherapy, whereas clinical trials largely exclude pretreated patients. Our sample size makes it difficult to make a formal statistical comparison, but the trend observed highlights MUP as a unique clinical paradigm and emphasizes the need for more consistent reporting of MUP cases.

The targeted therapy patients reported in the literature showed a much higher DCR than the NYU targeted therapy patients. This may in part be due to the poor prognostic characteristics of the NYU patients at diagnosis. Patient N-T1, a 22-year-old female with diffuse metastatic disease at presentation, expired 1 week after starting treatment with dabrafenib. Patient N-T2 had elevated LDH at the time of treatment initiation, and had had no prior resections to reduce the disease burden. Patient N-T3 presented with disease in the thyroid, cervical lymph nodes, lungs, mediastinum, liver, osseous structures, and soft tissues. N-T4 had elevated LDH at the time of treatment initiation, and a year prior to starting treatment had been diagnosed with aggressive axillary disease requiring two dissections, before developing visceral disease in the adrenal glands. Patient N-T5 had received chemotherapy prior to induction of targeted therapy. N-T6 likewise had received chemotherapy prior to targeted therapy, had elevated LDH at the time of treatment initiation, and presented with brain metastases. Patient N-T7 had had a lung resection, radio-frequency ablation of a liver metastasis, gamma knife surgery of a brain metastasis, and ipilimumab prior to starting combination therapy with vemurafenib and cobimetinib. He then progressed on treatment, with development of multiple small brain metastases, underwent whole-brain radiation and gamma knife surgery for a cerebellar metastasis, and ultimately became disease free. Since then, he has been treated with a combination of dabrafenib and trametinib, during which time he required another resection for new brain metastases. Patient N-T8, who showed the longest survival, had metastases limited to multiple lymph nodes, a normal LDH level at treatment initiation, and no history of brain metastases, which may have contributed to her continued response to vemurafenib for approxi-

mately 3 years. She eventually progressed and received 8 cycles of pembrolizumab, and she remains without evidence of disease off treatment.

The differences in outcome between the MUP patients at NYU and those in the literature may also be due to the vastly different follow-up times of the two groups. The NYU patients were followed up for as long as 57 months, whereas the non-NYU patients had a maximum follow-up time of 24 months. The development of resistance to targeted therapy is a well-known phenomenon and becomes more likely with time, as we see likely reflected in the NYU cohort, where all patients developed PD. Additionally, the superior response seen in the literature cohort on targeted therapy may be related to this population's status as a select group, individually chosen as unique examples of melanoma presentation and treatment response. The literature often reports adverse events, success stories, or treatments used in an unconventional setting. Therefore, the patients on targeted therapy we identified in the literature may be a biased cohort.

Conversely, the NYU patient mOS following treatment initiation was somewhat longer than that of the patients in the literature. However, 5 patients in the literature showed a continued response to treatment at the time of publication. These may in truth have considerably longer survival times than the publication time estimates used for the calculation of mOS following treatment initiation. Additionally, 4 NYU patients received immunotherapy following progression on targeted therapy, allowing the possibility that the longer survival of these patients was due to a response to immunotherapy rather than to targeted therapy.

As was the case for immunotherapy, the NYU patients and those reported in the literature together showed worse DCR, OS, and 1-year survival on targeted therapy when compared to the general melanoma distribution treated with targeted therapy in clinical trials. This could be due to the ongoing responses of the patients in the literature cited previously, which makes it difficult to accurately calculate mOS and 1-year survival. The NYU patients treated with targeted therapy were heavily pretreated, in contrast to the patients typically accrued for clinical trials.

While our observations are limited by the small sample size, the worse outcome of our sample of MUP patients on immunotherapy and targeted therapy when compared to the general melanoma distribution raises questions about the inherent nature of MUP. There is no evidence as yet that MUP is biologically more aggressive than metastatic MKP. In fact, previous publications have found stage III MUP to have a better prognosis than stage III

MKP [1, 7, 8]. Our observations regarding systemic therapy for metastatic disease suggest otherwise, and they require deeper investigation and more vigilant reporting of MUP cases to be fully understood.

Several limitations were taken into consideration when making our observations. Our sample size was small, and those reported as case studies in the literature were often exceptional cases with unusually poor or dramatic outcomes. We cannot conclude that the different outcomes with MUP and MKP we observed were due to the inherent biology of MUP rather than due to other prognostic factors within our patient population. Most of the immunotherapy patients presented in this report received ipilimumab, whereas PD-1 and combination CTLA-4/PD-1 inhibitors are mainly used today. It may be inappropriate to pool the NYU patients, many of whom received commercial drugs, with the patients reported in the literature, the majority of whom received treatment through a clinical trial (as in the case of immunotherapy). The comparison made between pooled MUP groups and the general melanoma distribution in clinical trials relies on the assumption that the compared groups are similar enough to compare on all grounds except MUP status.

Conclusion

We have performed a small, thoroughly observational study of a very specific group of advanced melanoma patients: those with an unknown primary tumor treated

with systemic therapy. While our study is limited by the small sample size, it is a testament to the lack of literature on this subject. To the best of our knowledge, this study is the first attempt to make observations about these particular patients in the post-chemotherapy era. We observe marginally worse outcomes for MUP patients as compared to the melanoma distribution when pooling our NYU MUP cohort with patients reported in the literature. We therefore highlight the need for further investigation of treatment implications for this unique group of patients. We also emphasize the need for increased reporting of this specific type of melanoma, so that these patients may be more carefully and consistently investigated as a population of their own in future studies.

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Disclosure Statement

The authors have no conflicts of interest to disclose in relation to the presented manuscript.

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