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Durability of response to immune checkpoint blockade following treatment discontinuation and efficacy of rechallenge in advanced Merkel cell carcinoma

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ABSTRACT

Background Advanced Merkel cell carcinoma (MCC) has a high response rate to immune checkpoint blockade (ICB) therapy, but the durability of responses once treatment is discontinued remains unclear. We therefore reviewed the long-term outcomes of advanced patients with MCC who discontinued ICB treatment after achieving favorable initial response.

Methods We performed a retrospective review of advanced patients with MCC treated at a single high-volume referral center, including all patients who received at least one dose of anti-programmed death receptor 1 (ligand) monotherapy for unresectable or metastatic disease, achieved stable disease (SD) or better, and discontinued treatment for a reason other than disease progression.

Results Of 195 advanced patients with MCC treated with ICB, we identified 45 who met the study criteria. Of these, 21 (46.6%) had a complete response (CR) to initial ICB treatment, 23 (51.1%) a partial response and 1 (2.2%) SD. 25 (55.6%) patients discontinued ICB electively and 20 (44.4%) discontinued due to toxicity. In total, 21 of the 45 patients (46.6%) experienced disease progression at a median of 11.3 months (range 2.1–22.7 months) from ICB cessation. There was a lower rate of progression in patients who achieved CR versus non-CR (23.8% vs 66.7%, p=0.006) and a trend towards a lower rate in those who discontinued electively versus due to toxicity (36.0% vs 60.0%, p=0.14). There was a higher risk for progression in patients with viral positive MCC compared with viral negative MCC (75.0 vs 30.8%, p=0.02). 16 of the 21 patients who experienced progression were retreated subsequently with ICB therapy, including both single-agent rechallenge (12) and escalation to combination ICB (4). 11 of 15 evaluable ICB-retreated patients (73.3%) achieved an objective response.

Conclusions Patients with advanced MCC have a substantial risk of disease progression following treatment discontinuation despite initial favorable ICB response, particularly in those that achieve less than a CR. Most of these patients maintain sensitivity to retreatment with the same drug class. Virus-positive MCC may be a risk factor for post-discontinuation relapse, which should be validated in future studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior studies have observed that patients with advanced Merkel cell carcinoma (MCC) who discontinue checkpoint blockade therapy despite having maintained good response on therapy have a risk for progression after treatment discontinuation. Risk estimates from prior work range from 35–60% to as low as 8% depending on the cohort definition.

WHAT THIS STUDY ADDS

⇒ Our study confirms a high risk for progression following treatment discontinuation with nearly half of patients in our cohort experiencing progression. We identify that the risk of post-treatment discontinuation progression differs by both depth of response as well as molecular subtype, with the viral-positive subtype of MCC at higher risk than the ultraviolet (UV)-mutagenesis subtype.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study has immediate clinical implications and may influence the strategy for the duration of therapy and therapy discontinuation in advanced patients with MCC that experience favorable initial response to therapy. The observed difference in response durability between viral-driven and UV-mutagenesis-driven molecular subtypes of MCC raises important questions regarding antigen type and mechanisms for immune checkpoint blockade resistance versus durability.

BACKGROUND

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer

associated with two distinct etiologic factors: Merkel cell polyomavirus (MCPyV) and ultraviolet (UV) radiation exposure.[1 2] For advanced disease, immune checkpoint blockade (ICB) therapy targeting programmed death receptor 1 (PD-1) or its ligand (PD-L1) has become the standard first-line treatment approach. Reported response rates for anti-PD-(L)1 monotherapy in treatment-naïve advanced MCC are approximately 40–60%, with the majority of these responses durable—at least while patients remain on therapy.[3–5]

The optimal duration of ICB therapy for patients with MCC achieving a favorable response is currently unknown, though 2 years is often considered the "standard" duration based on the design of initial trials. An emerging concern has been raised that a subset of patients with MCC who achieve and maintain response while on active ICB therapy may be at risk for disease progression following treatment discontinuation.[6] In one multicenter retrospective study that followed 40 such patients, 35% experienced disease progression with a median time of 12.3 months of follow-up since treatment discontinuation.[6] In contrast, another study suggested that ICB therapy could be safely stopped after just 1 year of therapy providing that a complete response (CR) is obtained and confirmed by positron emission tomography (PET)/CT.[7] In this study, only 2 of 25 patients (8%) with PET/CT-confirmed CR experienced recurrence following ICB discontinuation, with a median follow-up of over 2 years.[7] Additional study is needed to better characterize the risk of post-ICB relapse in this disease, assess for potential predictive factors to better risk-stratify patients, and as well to report outcomes for patients that do relapse. We therefore performed a retrospective analysis of patients treated with ICB monotherapy in the first-line setting for advanced MCC.

METHODS

We performed a retrospective review of advanced patients with MCC who were treated at a single high-volume referral center. The study was approved by the local institutional review board (Chesapeake IRB, protocol MCC19191) and conducted in accordance with national and local ethics guidelines. Criteria for inclusion in this analysis included patients who were treated for advanced MCC with ICB monotherapy, achieved a response of stable disease (SD), partial response (PR) or CR, and discontinued therapy for a reason other than disease progression or death. We considered advanced MCC to be patients with stage IV or unresectable stage III disease, therefore excluding patients who received neoadjuvant or adjuvant therapy from this analysis. A comprehensive review of medical records for the selected patients was conducted to retrieve data regarding patient demographics, staging data, adverse events (AEs), and other relevant information regarding treatment response, retreatment response, and response duration. MCPyV status of the cancer was collected where available. We considered a tumor viral positive if a biopsy sample had positive immunohistochemistry (IHC) for MCPyV and/or if next-generation sequencing performed on the tumor showed a low mutational burden. We considered a tumor viral negative if next-generation sequencing was performed on the tumor and showed a high mutational burden with UV-mutational signature; a negative IHC for MCPyV alone was not considered sufficient to confirm viral-negative status. The American Joint Committee on Cancer eighth edition was used for staging. Treatment response was assessed by the treating physician and followed Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 guidelines when a CT scan was used for a response. When PET/CT imaging was used for response, we used a modified response criteria that also followed RECIST V.1.1 with the exception that we also required resolution of PET avidity in known disease sites to confirm a CR. Reasons for ICB discontinuation were grouped into two categories based on the primary reason for discontinuation in the judgment of the treating physician: Elective or due to an AE. Note that "elective discontinuation" could include discontinuation for any non-progression reason other than toxicity (eg, convenience, unrelated health issues, treatment plateau) and did not require a prespecified treatment duration. Disease-specific progression-free survival (PFS) was calculated as the time from ICB discontinuation to disease progression, disease-related death, or last follow-up. Where indicated, a modified disease-specific PFS was calculated as the time from ICB initiation to disease progression, disease-related death, or last follow-up. Kaplan-Meier method was used to analyze disease-specific PFS and modified disease-specific PFS. Figures and data analysis were generated using Microsoft Excel and/or SAS.

RESULTS

Baseline characteristics

We identified 195 patients with MCC treated with ICB at our center, of whom 45 met the study criteria. The median age of the patients included in this study was 80 years (range 59–98). Most patients were male (n=35, 77.8%), had stage IV disease (n=30, 66.7%), were treated with pembrolizumab (n=34, 75.6%), and received no prior systemic therapy for MCC (n=37, 82.2%). 2 (4.4%) patients were immunosuppressed at the start of ICB treatment, both due to a concurrent diagnosis of chronic lymphocytic leukemia. Additional baseline clinical details are summarized in table 1.

Response to ICB and outcomes after discontinuation

As per the study inclusion criteria, all 45 patients achieved a favorable response to ICB therapy and discontinued for a non-progression reason. At the time of ICB discontinuation, 21 (44.7%) patients had achieved CR, 23 (51.1%) had a PR, and 1 (2.2%) had SD as the best response. Response determination used PET/CT imaging in 30 patients (66.7%) and conventional CT imaging in

Table 1 Cohort description

Baseline data		
Age (years)		
Median	80 (59–98)	
Gender		
Female	10	22.2%
Male	35	77.8%
Stage at treatment		
III	15	33.3%
IV	30	66.7%
ICB		
Pembrolizumab	34	75.6%
Avelumab	10	22.2%
Nivolumab	1	2.2%
Primary site		
Unknown	10	22.2%
Head and neck	17	37.8%
Upper and arm	8	17.8%
Trunk	2	4.4%
Lower	8	17.8%
Immunosupression status		
Immunosupressed	2	4.4%
Chronic lymphocytic leukemia	2	
Prior therapies		
Chemotherapy	8	17.8%
Adjuvant	3	6.7%
Metastatic	5	11.1%
Radiation	31	68.9%
Lactate dehydrogenase (LDH)		
LDH>ULN	8	17.8%
LDH≤ULN	13	28.9%
Unknown	23	51.1%
Neutrophil to lymphocyte ratio (NLR)		
NLR≥4	13	28.9%
NLR<4	29	64.4%
Unknown	3	6.7%
MCPyV status		
Positive	17	37.8%
Negative	13	28.9%
Unknown	15	33.3%

ICB, immune checkpoint blockade; MCPyV, Merkel cell polyomavirus; ULN, upper limit of normal.

15 (33.3%). The median time to best response was 3.3 months (range 0.7–19.4). 25 (55.6%) patients discontinued treatment electively and 20 (44.4%) discontinued due to an AE. The most common AEs that led to treatment cessation were arthritis (n=4), pneumonitis (n=4), colitis (n=2), and cytopenias (n=2). The median duration of ICB treatment was 11.5 months (range 0.7–35.0 months) for all patients, 12.0 months for patients who electively discontinued treatment, and 9.4 months for patients who discontinued due to an AE. Elective discontinuation was more frequent among patients who achieved a CR (17 of 21, 81.0%), whereas discontinuation due to AE was more frequent among patients who achieved PR/SD (15 of 24, 62.5%).

Of the 45 patients, 21 (46.7%) have experienced MCC progression following therapy discontinuation. Among these patients, progression occurred at a median of 11.3 months (range 2.1–22.7 months) from ICB treatment cessation. The median follow-up of patients in our cohort who have not experienced disease progression was 24.9 months (range 5.8–82.0 months). There was a lower rate of progression in patients who discontinued therapy in radiographic CR versus non-CR (23.8% vs 66.7%, p=0.006) and a trend towards a lower rate in those who discontinued electively versus due to toxicity (36.0% vs 60.0%, p=0.14) and in those that had normal serum lactate dehydrogenase (LDH) at pretreatment baseline versus those with an elevated LDH level (38.4% vs 77.8%, p=0.10). There was no difference in the rate of progression in patients with a pretreatment elevated neutrophil to lymphocyte ratio (NLR ≥4) versus those without (46.2% vs 44.8%, p=0.92). For patients in whom the molecular subtype was known, there was a higher risk of progression in patients with MCPyV-associated MCC (12 of 17, 75.0%) compared with UV-associated (viral negative) MCC (4 of 13, 30.8%, p=0.02). In the remaining cases that were viral indeterminant, the risk of progression was 5 of 15, or 33.3%, which includes 9 cases with negative viral status by IHC alone that was not confirmed by additional testing. The percentage of patients who achieved CR was similar between viral positive and viral negative cases (56.3% vs 38.4%, respectively, p=0.46). The median disease-specific PFS was 20.7 months from the time of ICB therapy discontinuation and was longer in patients who achieved a CR compared with PR/SD (Not Reached [NR] vs 12.8 months, p=0.0015), and in patients with UV-associated MCC compared with viral-associated (NR vs 12.2 months, p=0.038) (figure 1). The timing of disease progression was similar in patients who discontinued due to AE versus those who discontinued electively if considered from the time of ICB discontinuation (median 11.8 months, range 2.1–22.7 and median 11.2 months, range 3.1–19.8, respectively), but was shifted longer in those that discontinued electively if considered from the time of ICB initiation, reflecting longer ICB treatment durations in the latter group (online supplemental figure 1).

Interestingly, we identified four patients in which the disease response was downgraded from CR to PR due to residual PET-avidity in a known disease site that had "normalized" on conventional imaging (three in which responding lymph node(s) decreased to <1.0 cm but maintained PET-avidity and one in which there remained residual PET-avidity and "stranding" in an area of a

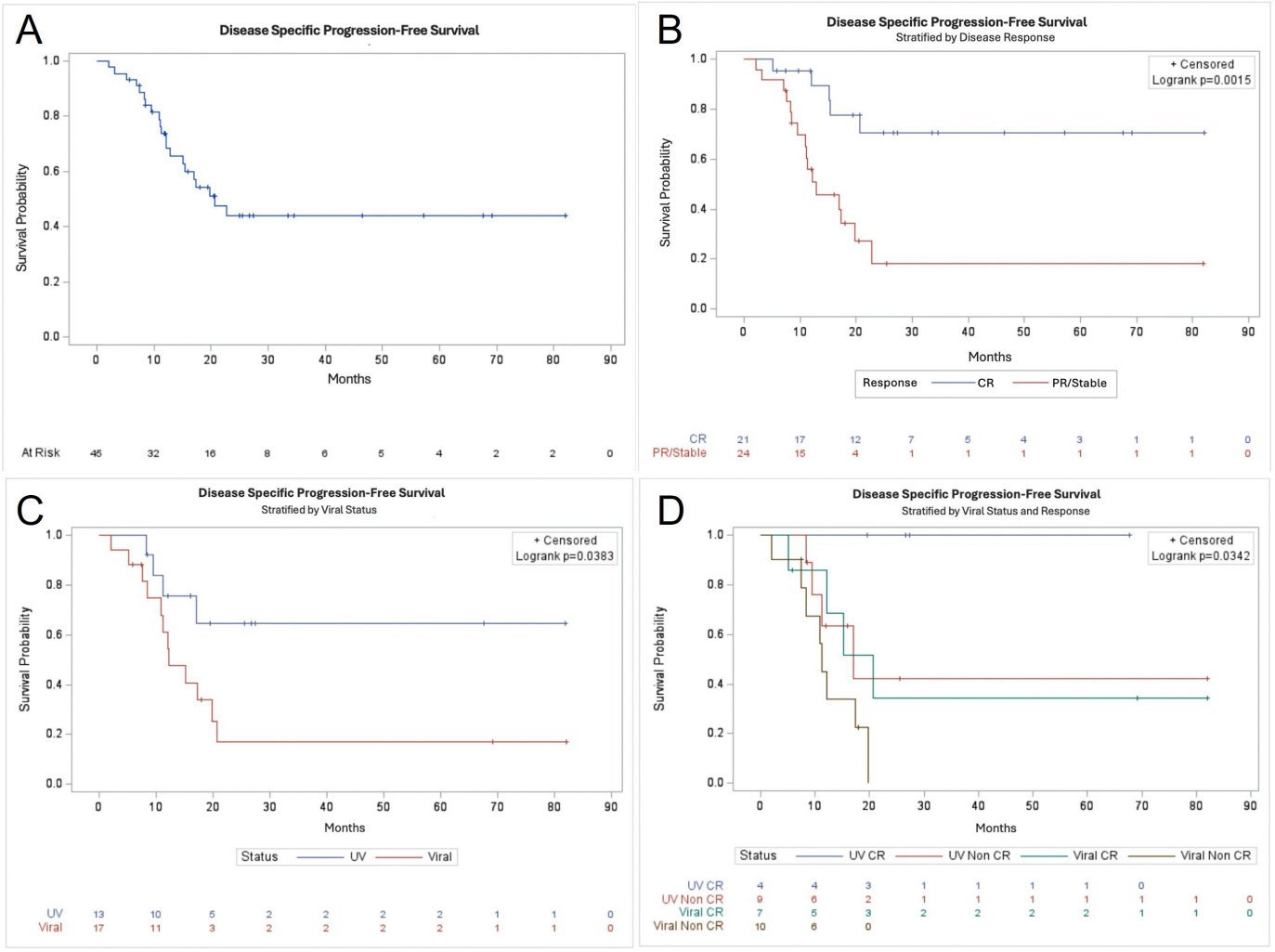

Figure 1 Kaplan-Meier estimates of disease-specific progression-free survival from the time of therapy discontinuation in the entire study cohort (A) and stratified by disease response at the time of therapy discontinuation (B), viral status (C), or both (D). CR, complete response; PR, partial response; UV, ultraviolet.

previous soft tissue nodule). All four of these patients that would have otherwise been characterized as CR by RECIST V.1.1 had conventional CT imaging alone been used experienced disease progression after therapy discontinuation (all at the site of residual PET-avidity). For the 21 patients in our cohort that were determined as having CR at the time of therapy discontinuation, there was a numerically lower likelihood of postdiscontinuation disease progression if that determination was made by PET/CT (3 of 16, 18.8%) as compared with those in which the CR determination was made by conventional CT alone (2 of 5, 40.0%), though these numbers were too small for meaningful statistical comparison.

ICB rechallenge and other post-progression treatment

Of the 21 patients who progressed post-therapy discontinuation, 12 (57.1%) were rechallenged with single-agent ICB therapy as the first post-progression therapy, 4 (19.0%) were treated with combination ICB therapy, 3 (14.3%) with radiation therapy or surgery alone, 1 (4.8%) with chemotherapy, and 1 (4.8%) received no further therapy. Of the 12 patients who were rechallenged with single-agent ICB, 10 (83.3%) received the same agent used previously and two switched to a different anti-PD-(L)1 agent. All four patients treated with combination ICB therapy received ipilimumab+nivolumab using the 1 mg/kg every 6 weeks dosing regimen of ipilimumab.[8] As expected, treatment with a single agent or combination ICB was more commonly used in patients who previously discontinued electively (9 of 9, 100%) as compared with those who discontinued due to AE (7 of 12, 58.3%). 11 of 15 (73.3%) evaluable patients who received ICB therapy in this setting achieved an objective response, 6 patients with CR and 5 patients with PR, including all 3 evaluable patients treated with combination ipilimumab+nivolumab and 8 of 12 (66.7%) patients that were rechallenged with single-agent ICB. One additional patient rechallenged with single-agent ICB achieved sustained durable SD of 24 months duration while on active therapy, but again experienced progression 9 months after treatment discontinuation and declined further therapy due to overall health decline (congestive heart failure, dementia). One patient treated

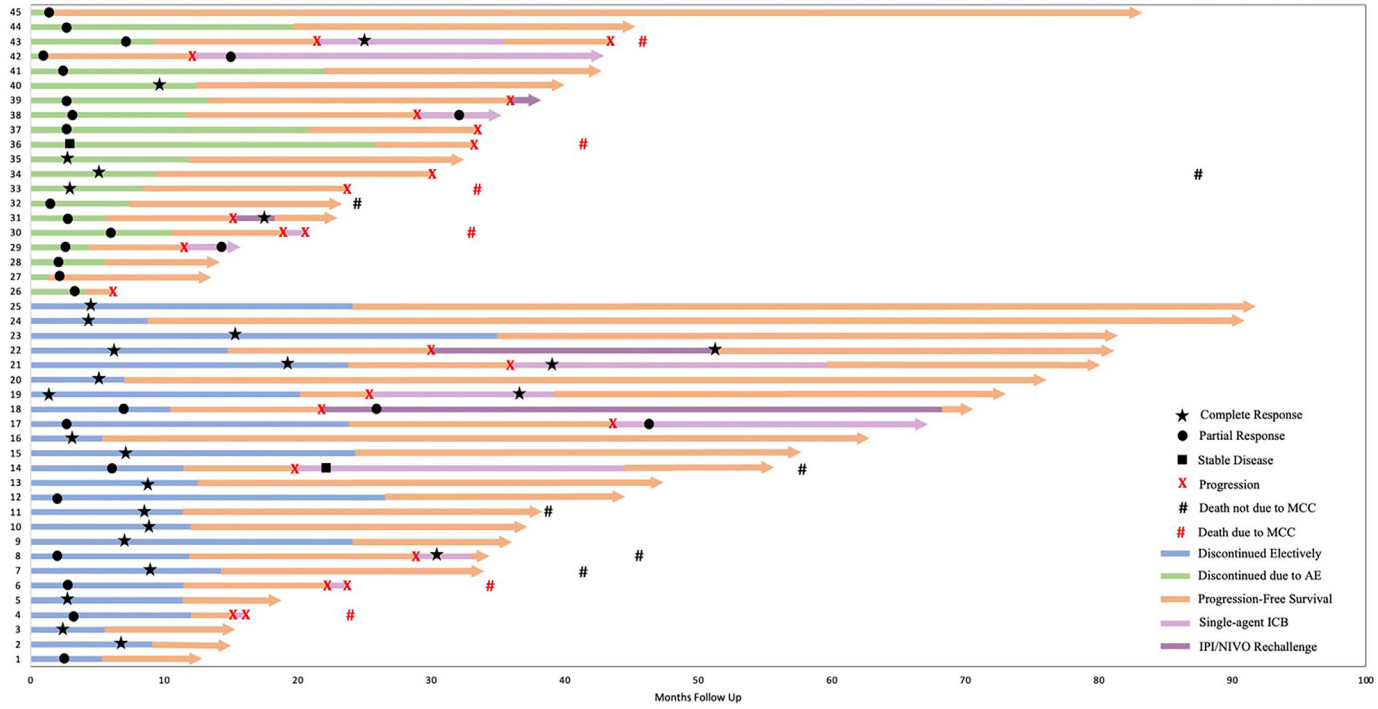

Figure 2 Swimmer's plot depicting durability of response to immune checkpoint blockade and results of therapy rechallenge in patients with Merkel cell carcinoma who initially discontinued treatment for a reason other than disease progression. AE, adverse event; ICB, immune checkpoint blockade; IPI, ipilimumab; MCC, Merkel cell carcinoma; NIVO, nivolumab.

with combination ICB was deemed not evaluable as radiation therapy was also delivered to the only measurable site of disease. The remaining 3 of 12 (25.0%) patients experienced disease progression as the best response to single-agent ICB rechallenge. The median duration of treatment for all patients undergoing ICB treatment in this setting was 6.3 months (range <1–30.3 months) and was ongoing in five patients at the time of analysis. Of the 11 patients who achieved an objective response to ICB treatment, 3 have had subsequent disease progression, 2 occurring after discontinuing therapy for a second time due to toxicity and 1 in a patient who progressed while on active therapy. One patient who achieved a CR to ICB rechallenge died of progressive chronic health issues 8 months after the start of the rechallenge and was without evidence of disease on the latest available imaging. The remaining seven patients remain alive and without a second disease progression following ICB treatment with a median of 8.0 months (range 5.0–51.0 months) of follow-up since the start of their second course of ICB therapy. Patient-level details of ICB treatment outcomes to both initial and subsequent ICB treatment are summarized in figure 2.

Survival

12 of 45 patients died during the study follow-up period, 6 due to progressive MCC and 6 whose deaths were known or strongly suspected to be due to non-MCC causes. Four of the six patients who died of progressive MCC did so after ICB rechallenge, with the remaining two declining further ICB therapy due to rapid clinical decline and/or concern over prior ICB toxicity. The six patients who died of other causes all were free of MCC progression on their latest imaging and reasons for death included other malignancies (two), progressive congestive heart failure (two) and unknown/sudden cardiac death in frail homebound patients (two).

DISCUSSION

The use of checkpoint blockade therapy has radically changed the treatment landscape for patients with advanced MCC, but the optimal duration of treatment, risk of relapse following treatment discontinuation, and success of rechallenge are not well defined. In immunooncology more broadly, the durability of checkpoint blockade response has varied widely between different diseases, with high rates of prolonged response in melanoma for example compared with more modest long-term durability of response in non-small cell lung cancer.[9 10] Between diseases and even within the same disease, studies on rechallenge with ICB following prior discontinuation have produced highly variable results, reflecting differences in patient selection and the inherent challenge of defining true therapy resistance versus waning effects of therapy withdrawal.[11] In addition to providing an essential understanding for current clinical management, the study of this topic in MCC, with its rapid disease pace and high responsiveness to checkpoint blockade, may help further our understanding of the phenomenon of

checkpoint blockade response waning and its associated kinetics.

We report on 45 patients treated with ICB who discontinued treatment for a reason other than progression and have a median follow-up time of over 2 years. In our cohort, nearly half of patients have experienced disease progression following discontinuation, which is somewhat higher than the 35% risk reported in a prior report of 40 patients[6] and similar to the 60% risk reported in a cohort of 20 patients.[12] Of note, both prior reports had shorter median follow-up times of 10.1 and 12.3 months, near the median time to progression that we observed in our cohort, suggesting that a higher percentage of patients are likely to relapse with longer follow-up in these previous studies. Additionally, the percentage of patients in CR on therapy discontinuation varies widely between studies and this clinical feature was strongly associated with risk of progression in all studies.

The reported risk of disease progression specifically in patients who discontinue ICB after achieving a CR varies between studies from only 8% in one 25-patient study[7] as compared with 24% of 21 CR patients in the current cohort and 26% of 31 CR patients in one of the other previous reports.[6] Notably, in the study with the lowest progression rate, a CR required confirmation by PET/CT. We observed four instances of patients in our cohort in which a "CR" by conventional CT imaging using RECIST V.1.1 criteria was downgraded to a PR (and considered as non-CR for our analysis) due to residual increased PET-avidity above background at known disease sites. Though anecdotal, in all four of these instances, the patients with residual PET activity progressed after therapy discontinuation. Taken in whole, PET/CT imaging is likely to be a useful predictive tool to help delineate CR from PR when determining the risk of disease progression post-treatment discontinuation, though this should be further validated.

Outside of depth of response, predictive factors for progression following ICB discontinuation in MCC have not been well elucidated. We observed a higher risk of progression (75% vs 31%) in patients whose tumors were classified as viral positive versus viral negative despite having a similar and numerically higher rate of CR in the viral positive group in our cohort. We used strict criteria for designation of "viral negative" to include only those tumors confirmed high tumor mutation burden (TMB) with a UV mutational signature by next-generation sequencing as viral testing by IHC alone is prone to false negative results and therefore may dilute a true biological effect if included. On the other hand, the risk of progression in "viral indeterminant" cases, which included nine cases that were viral negative by IHC alone, was at 33% nearly identical to that of the viral negative group. To our knowledge, viral status as a potential predictive factor for progression post-ICB discontinuation has not been evaluated in prior studies. If confirmed in future work, it would be of high scientific interest to study the mechanism of ICB durability or failure in these two molecularly distinct subgroups.

In contrast to a prior report,[6] the reason for ICB discontinuation as elective versus toxicity was not predictive of ICB response durability in our cohort, particularly when assessing from the time of ICB discontinuation rather than ICB initiation. Notably, elective discontinuation is more likely to occur for a disease status of CR and after a longer treatment duration as compared with toxicity-related discontinuation, and therefore elective discontinuation may be a surrogate predictive factor for these reasons. Interestingly, the timing of disease relapse relative to the timing of ICB discontinuation is nearly identical in both our and the prior study[6] regardless of he reason for discontinuation and therefore likely is reflective of the intrinsic biological kinetics of this agent class.

The optimal management of patients with MCC who experience progression after ICB discontinuation is largely unknown. We observe that most patients maintain sensitivity to ICB treatment, with only 3 of 12 (25%) patients in our cohort experiencing primary progression on single-agent ICB rechallenge and most of these patients experiencing response durability. This result is in line with a prior report of a 75% response rate in a series of eight ICB retreated patients.[6] Therefore, elective discontinuation of initial ICB treatment with a plan to rechallenge if later progressive is a reasonable treatment strategy in this population. Alternative strategies such as prolonged extended-interval therapy,[13] escalation of ICB therapy to combination therapy,[8] and consolidation of a non-CR with ablative radiation to residual disease site(s) should be further explored and compared with the benchmark established by this retreatment paradigm. For patients that are not candidates for ICB rechallenge due to severe toxicities, this remains an area of high unmet clinical need and should be a focus of continued study.

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