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ORIGINAL ARTICLE

Real-world management of patients with complete response under immune-checkpoint inhibition for advanced melanoma

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Summary

Background: Up to now, the optimal duration of immune checkpoint inhibitors (ICI) has not been evaluated in prospective studies. However, current clinical practice requires decisions to be made regarding the duration of ICI in complete responders.

Material and Methods: A survey was sent to 80 DeCOG skin cancer centers to assess how decisions are made on treatment duration of ICI in melanoma after having reached complete response, and staging intervals after ICI discontinuation. All responses received by March 10, 2024 (51 centers) were included.

Results: The duration of ICI after having achieved complete remission varies between centers from three to 36 months. In total, 66% of the DeCOG centers continue treatment for up to 6 months, after having achieved complete remission (CR) with ICI. In the first year after discontinuation of ICI, most centers perform staging intervals (CT/MRI) every 3 months. More than 60% of centers continue staging at least once per year even in the 4th and 5th year after discontinuation.

Lisa Zimmer and Andrea Forschner contributed equally to the present article.

Conclusions: There are significant differences between the centers regarding staging intervals and duration of ICI upon CR. Prospective studies are necessary to determine the optimal time point of ICI discontinuation and follow-up.

KEYWORDS
Advanced Melanoma, follow-up, immune checkpoint inhibitor (ICI), pause, PET/CT, surveillance, treatment discontinuation

INTRODUCTION

Combined immune checkpoint inhibitors (ICI) have led to markedly improved survival rates for patients with metastasized melanoma with 6.5 years overall survival of > 50% in the first-line setting. In most clinical trials, the standard duration of ICI therapy was 2 years.[1,2] In real-world practice, however, ICI are not consistently applied for 2 years. There are several reasons for premature/early discontinuation. Mostly, physicians discuss treatment discontinuation in case of toxicity and, in some cases, because of a complete response (CR).[3–5] Patients may also request treatment discontinuation if they experience "treatment fatigue", especially in the case of CR. Observations that anti-PD-1-based therapy may not necessitate a full two-year duration of treatment after having achieved complete response are currently under investigation in the DANTE trial (ISRCTN15837212). Initial analysis is anticipated in 2025, with long-term results expected in 2028. Additionally, the Safe Stop Trial (NL7293) is ongoing, with results expected in October 2025.[4,6,7]

In daily clinical routine, criteria for a premature discontinuation of ICI after a complete response appear to differ between the centers, and each center seems to have its own criteria on how to proceed, as there are no guidelines with clearly defined criteria. The current German S3 guideline "melanoma" includes no recommendation on how to proceed with patients who experience complete remission with ICI but who have not have completed 24 months of therapy.[8] The Survivorship Committee of the German Dermatologic Cooperative Oncology Group (DeCOG) is in intensive contact with patient representatives. Feedback from patient forums has highlighted a significant uncertainty among patients regarding the procedures after having achieved complete remission with ICI. There is a perception of varying practices across different centers. Consequently, the committee "Survivorship" within the DeCOG has invited all skin cancer centers within the DeCOG to participate in a survey on the specific management of each center with the aim of providing a comprehensive summary report.

Aims

This study aimed to assess the real-world management of premature ICI discontinuation in patients with metastasized melanoma at 51 certified skin cancer centers within the DeCOG, primarily in Germany but also in Austria and Switzerland, through a cross-border survey.

MATERIAL AND METHODS

Study design

Under the auspices of the *Survivorship Committee of the German Dermatologic Cooperative Oncology Group* (DeCOG), a questionnaire was developed and discussed/modified within the committee in September 2023 (online supplementary Table S1). The complete questionnaire consisted of different sections. Firstly, it addressed the reasons and decision-making process regarding discontinuation of ICI in metastasized melanoma. This section included questions concerning the criteria deemed necessary by the individual centers for ICI discontinuation. Additionally, it evaluated the relevance of whole-body positron emission tomography/computed tomography (WB PET/CT) scans in this decision-making process. The second section concentrated on follow-up procedures, in particular on the choice of imaging and frequency of diagnostic tests following discontinuation of ICI. Multiple selections (e.g., choosing both a WB PET-CT and a whole-body computed tomography (WBCT)) were allowed in the survey to reflect a more realistic setting.

The questionnaire was provided to all 80 skin cancer centers within the DeCOG, in Germany (n = 72), Austria (n = 4) and Switzerland (n = 4) on November 22, 2023. Two reminders were sent, on December 11, 2023 and January 17, 2024. All responses received by March 10, 2024 were included in the evaluation.

Statistical analysis

The questionnaire was created in Microsoft® Excel® 2016 MSO (Version 2403) and distributed. Descriptive analysis was performed with IBM® SPSS® Statistics (version 28.0.0.0). Incomplete questionnaires were included with the completed or unanswered questions. If a center specified a "from to" interval in the free text entry, the smallest value was used for the statistical analysis. Graphs were created with GraphPad Prism® (version 10.0.1).

RESULTS

Response-rate to the questionnaire among the contacted skin tumor centers

We received responses from 51 of the 80 certified skin cancer centers, resulting in a response rate of 63.8% (Table 1). Forty-nine responses were sent from Germany, and one response each from Switzerland and Austria. The majority of the participating skin cancer centers (n = 31, 60.8%) were university hospitals.

Factors in the decision-making process to discontinue ICI

To gain insight into the center-specific decision-making process regarding the discontinuation of ICI in case of complete remission of metastatic melanoma, survey participants had three choices to describe initiation of the process of stopping ICI (tumor board recommendation, treatment fatigue, and decision by treating physician). Multiple selections were possible. The option tumor board recommendation (88.2%) and patient-reported treatment fatigue (90.0%) were the most common reasons for discontinuing ICI. The physician's decision alone (28.0%) was not a frequent scenario (Table 1, Figure 1).

An excellent response correlates with earlier discontinuation of ICI

A clear variance was observed in the duration of ICI after CR (ranging from 3 to 36 months), considered by the DeCOG centers as the minimum duration of ICI before a possible termination of therapy is discussed (Table 1, Figure 1). The degree of response correlated with the duration of ICI. After a CR (complete response) under ICI, 66.0% of the centers continue ICI only for a maximum of 6 months. In contrast, only a few centers stop ICI therapy within 6 months after having achieved partial response (PR) or stable disease (SD) (Table 1). For partial responders (41.7%) and patients with SD (51.4%), a duration of 24 months was recommended by most of the centers. Only one skin cancer center

TABLE 1 Summarized survey results of 51 skin cancer centers regarding the discontinuation of ICI.

	n	Percent
Response-rate		
Contacted certified skin cancer centers within the DeCOG	80	100
Skin cancer centers that have responded	51/80	63.8
Initiation of discussion on discontinuing ICI		
Tumor board		
Yes	45/51	88.2
No	6/51	11.8
Not answered	0/51	0.0
Physician's decision		
Yes	14/50	28.0
No	36/50	72.0
Not answered	1	–
Patient (treatment fatigue)		
Yes	45/50	90.0
No	5/50	10.0
Not answered	1	–
Duration of ICI until discontinuation after the event of a CR		
≤ 6 mo.	31/47	66.0
12–18 mo.	11/47	23.4
≥ 24 mo.	5/47	10.6
Not answered	4	–
Duration of ICI until discontinuation after the event of a PR		
≤ 6 mo.	8/36	22.2
12–18 mo.	13/36	36.1
≥ 24 mo.	15/36	41.7
Not answered	15	–
Duration of ICI until discontinuation after the event of a SD		
≤ 6 mo.	5/37	13.5
12–18 mo.	13/37	35.1
≥ 24 mo.	19/37	51.4
Not answered	14	–
WB PET/CT available		
Yes	43/49	87.8
No	6/49	12.2
Not answered	2	–
Required diagnostic for discontinuation		
cMRI	48/51	94.1
cCT	4/51	7.8
WBCT	34/51	66.7
WB PET/CT	44/51	86.3
Biopsies of residual findings	33/51	64.7

Abbr.: cMRI, cranial magnetic resonance imaging; cCT, cranial computed tomography; ICI, immune checkpoint inhibitor; mo., months; US, ultrasound; WBCT, whole-body computed tomography; WB PET/CT, whole-body positron emission tomography/computed tomography

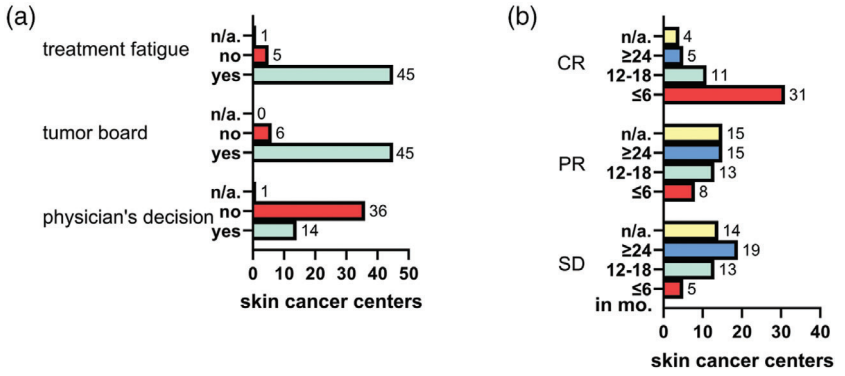

FIGURE 1 Decision-making process for discontinuation ICI in metastatic melanoma after response. Figure 1a presents the results regarding the decision-making process to end ICI (immune checkpoint inhibitors). Figure 1b shows the duration of ICI after reaching a CR, PR, SD in months. *Abbr.*: ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; n/a, not answered.

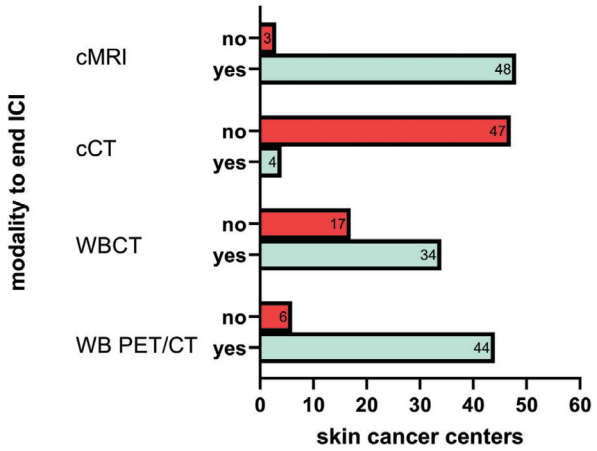

FIGURE 2 Required diagnostic modalities for discontinuation. *Abbr.*: ICI, immune checkpoint inhibitor; cMRI, cranial magnetic resonance imaging; cCT, cerebral computed tomography; WBCT, whole-body computed tomography; WB PET/CT, whole-body positron emission tomography/computed tomography.

reported a treatment duration of ICI of 36 months, whereas the remaining centers discontinued therapy usually after having completed 2 years.

Cranial MRI and whole-body PET/CT are considered the most essential diagnostic tools before deciding on ICI discontinuation

94.1% of the survey respondents indicated cranial magnetic resonance imaging (cMRI) as the most often required cerebral modality before discontinuation of ICI in the metastatic setting. In contrast, cerebral computed tomography (cCT) was chosen by only 7.8% (Table 1, Figure 2). Between the options of WBCT and WB PET/CT, 86.3% opted for WB PET/CT, 66.7% for WBCT. Multiple selections (e.g., choosing both a WB PET-CT and a WBCT) were allowed in the survey to reflect a more realistic setting. It is worth noting that several centers selected both a WB PET-CT and a WBCT. In 6 centers (12.2%) PET/CT is not available for diagnostic purposes. Additionally, 64.7% of the centers consider performing biopsies for further assessment of residual findings before stopping ICI.

Follow-up examinations and intervals in years 1–5 after discontinuation of ICI

A detailed overview of all examination modalities (US, WBCT, cMRI/CT, WB PET/CT, LDH/S100, blood test monitoring) and intervals after discontinuation of ICI over a period of 5 years can be found in online supplementary Figure S1 and Table S2. S100- and LDH-blood tests are conducted comprehensively during the first 3 years by all 51 centers and in years 4–5 by 50 centers. In the categories ultrasound (US) and LDH/S100, the skin centers mostly adhere to the current recommendations in the German S3 guideline regarding the interval for R0-resected stages in lack of a recommendation for the metastasized setting with deep response following ICI is available.[8] However, about 18%–22% of the centers do not perform US in their follow-up care in year 1–5. Regarding imaging (WBCT; cMRI/CT, WB PET/CT), in the first year, more frequent imaging than recommended in the guideline with 3-month intervals is preferred by most skin cancer centers. Only in years 2–3 do most centers choose the 6-month interval. Variation also occurs in years 4–5, where, according to the guideline, imaging by WBCT, cMRI/CT, and WB PET/CT is not recommended. Whereas 84.3% of the centers adhere to this guideline for WB PET/CT, over 60% of centers continue imaging by WBCT and cMRI/CT even in the fourth to fifth year.[8] The guideline does not provide any recommendations regarding the period and monitoring of laboratory parameters after discontinuation of ICI. We therefore asked the centers whether monitoring was carried out, such as complete blood count, electrolytes, transaminases, creatinine, and creatine kinase, and at what intervals.[8] 82.4% of the centers conduct such monitoring in the first year, mostly with 3-month intervals. The number of centers conducting laboratory tests decreases over time. Nineteen centers (37.3%) discontinue monitoring in the second year, 23 centers (45.1%) in the third year, and 26 centers (51.0%) in years 4–5. Additionally, the intervals between blood tests lengthen. Whereas the 3-month interval is still preferred

by the majority of centers in the second year, the 6-month interval is preferred in years 3–5.

DISCUSSION

Due to the limited data available, the optimal duration of ICI treatment for patients with unresectable or metastatic melanoma has yet to be determined by prospective data. The recent Keynote-006 follow-up data provide information from unresectable stage III or IV melanoma patients with pembrolizumab treatment for ≤ 2 years. The OS was particularly favorable in patients who had received ≥ 94 weeks of treatment with an estimated 8-year OS rate from week 94 of 80.8%. Shorter duration of treatment may be sufficient as reported in observational studies.[5,9,10] In a single center study with patients who received anti-PD-1 based therapy with a median treatment duration of 11.1 months and a median follow-up of 20.5 months after treatment discontinuation, 75% of patients remained without disease progression.[5] In another analysis of 237 patients conducted by the *Italian Melanoma Intergroup*, a long-lasting response could be maintained after anti-PD-1-based therapy, even with early discontinuation. Over 70% of recurrences were observed in patients who did not achieve CR at the time of treatment discontinuation.[10] In a third study of 185 advanced melanoma patients from 14 medical centers in Europe and Australia, with a median treatment time of 12 months, the risk of relapse after achieving CR was also low (16%).[9]

Based on this data, patients with CR may be adequately treated with treatment durations of 6–12 months after complete response, while in patients with SD or PR with substantial residual tumor burden, a duration of another 2 years seems to be appropriate.[6,9,11] Neither the optimal time-point for discontinuation of ICI after complete response, nor the procedures concerning follow-up of these patients are clearly defined.[3,6] In a large retrospective study including 1.017 ICI-treated patients with advanced melanoma, the authors compared overall survival between responders that stopped ICI after 6, 12, 18, and 24 months with patients that continued ICI. The results indicate an improved OS for patients that continued ICI for more than 6 months. In patients with a duration of ICI therapy of 12 or 18 months, no difference was seen, whereas in patients with ICI for more than 24 months, OS was worse compared to patients who stopped ICI after 24 months.[12] Another large retrospective study of the EUMelaReg compared OS between 569 melanoma patients with CR under ICI and 630 patients with PR in view of ICI duration. In the CR group, there was no difference between ICI duration of < 6, 6–12 or > 12 months. In the group of partial responders, patients with an ICI duration of > 12 months had the best outcome, while patients with duration of < 6 months had the worst OS.[13] These two studies suggest that ICI can only be safely discontinued if PR/CR persists for at least 6 months with continued ICI. The current melanoma guideline does not contain a recommendation in this regard, and there are obviously differing procedures among the skin cancer centers within the DeCOG. The aim of this evaluation was to assess potential differences and similarities in Germany, Austria and Switzerland, through a cross-border survey.

Tumor-board decisions, along with patient treatment fatigue, appear to be the most common reasons for starting the discussion on whether to discontinue ICI. However, the physician's decision alone is currently a rare reason for ICI discontinuation in most skin cancer centers. Nevertheless, it is still the main reason indicated in 28% of the centers.

We observed a wide variability in the center-specific, required minimum duration of ICI for melanoma in the metastatic setting, ranging from 3 to 36 months. This underscores the relevance of the Stop Safe trial and the DANTE study, the results of which are expected in 2025 and 2028 (long-term results).[4,6,7] As expected, a positive therapy outcome correlates with an earlier discontinuation of ICI. In the event of CR, most centers discontinue ICI already after ≤ 6 months, which is consistent with published recommendations and the discussed observational cohort studies from 2019–2021.[5,6,9,10] However, in view of recent studies, a duration of 6 months seems to be recommendable. On the other hand, the studies did not cover the subgroup of patients with CR and ICI of only 3 months after having achieved CR. In contrast, only a few centers stop ICI therapy after a treatment duration ≤ 6 months if a PR or SD has been achieved as best response only. However, in the CheckMate 067 study, the 6.5-year data show significantly better overall survival (OS) rates in all three arms (nivolumab + ipilimumab, nivolumab, and ipilimumab) for patients with CR and PR compared to those with SD and PD. These data suggest that patients with a PR might eventually be treated more similarly to those with a CR, and that patients with a SD should perhaps be treated for a longer duration, monitored more closely, or have their therapy changed. Nevertheless, it must be noted that some patients in this study discontinued therapy due to side effects, which limits direct comparability.[1] The importance of WB PET/CT in this decision-making process should be noted here, as it reveals that patients who exhibit a PR in WBCT but achieve a complete metabolic response (CMR) in WB PET/CT have outcomes similar to those with a CR in WBCT.[14] This raises the question of whether all patients identified with a PR in WBCT should undergo PET-CT to potentially detect a CMR. Such an approach would not only facilitate accurate diagnostics and treatment but also provide the patient with mental reassurance similar to that experienced by patients with CR.

Regarding the required examinations before deciding on possible discontinuation of ICI, cMRI is clearly preferred by the majority of centers for cerebral imaging. This aligns with the recommendation in the German S3 guideline concerning the diagnostic workup for patients with suspected or confirmed distant metastases.[8] Regarding whole-body imaging, several centers provided both options (WBCT and WB PET-CT). Here, we cannot determine if centers

selected both options (multiple choices possible) because they decide individually for each patient between WB PET-CT and WBCT or if centers that chose PET/CT also reported WB-CT due to its automatic inclusion with this imaging modality.

In general, PET/CT has emerged as a novel imaging modality used for staging, monitoring response, and surveillance of melanoma.[15–17] Nevertheless, nationwide availability and cost coverage of PET/CT scans vary, impacting routine care and raising unanswered questions in clinical practice as already shown in published surveys.[17] In our survey, six centers (12%) reported unavailability of PET/CT for their diagnostic purposes. This corresponds to the 12% that were missing regarding the preferred whole-body imaging diagnostic in our survey, indicating that this may not be a choice but rather a lack of access. Despite the additional information on metabolic activity provided by PET-CT scans, nearly two-thirds of the centers conduct biopsies for further assessment of residual findings before the completion of therapy. This relatively high rate of performed biopsies and the associated risk of complications could be reduced in the future through the findings of the PET-Stop/EA6192-study (NCT04462406). Here, a prospective correlation of PET/CT scans with biopsies is being conducted to find the optimal time for discontinuing ICI therapy in non-resectable stage IIB to IV melanomas.[18] Most recently it was shown that RECIST criteria underestimate the response to neoadjuvant ICI treatment in cases with SD. In contrast, the metabolic response assessment by PET/CT was more accurate, indicating a higher proportion of CR and PR by assessing metabolic response.[14,19]

Regarding the follow-up examinations in the first 5 years, S100 and LDH are conducted comprehensively. In contrast, one-fifth of the centers do not perform US in their follow-up care. With the data available to us, we cannot determine whether this is due to a lack of availability or as a deliberate decision based on the fact that patients are actually in stage IV, and most centers believe that CT staging is sufficient. A different trend is evident regarding imaging (WBCT; cMRI/CT, WB PET/CT), namely a tendency towards shorter intervals and longer imaging: In the first year, a 3-month interval is preferred by most skin cancer centers and more than 60% of the centers still perform imaging using WBCT and cMRI/CT even in the fourth to fifth year. However, the disadvantages of overly frequent surveillance imaging in terms of non-specific findings or false positive findings for metastasis, as well as anxiety while awaiting the scan results, must be discussed.[20–23] The German S3 guideline also does not provide any recommendations regarding the period and monitoring of laboratory parameters after discontinuation.[8] Accordingly, the implementations vary among the centers. Particularly notable is the first year during which some centers perform weekly to monthly blood tests while others do not conduct any blood tests. Based on our questionnaire, which explicitly asks about the centers' intention to act, it remains unclear whether the centers that do not carry out blood tests themselves have them carried out, for example, by the general practitioner and possibly also give a recommendation for action.

The rapid advancements in diagnostics and therapy pose immense challenges for skin cancer centers in adapting and keeping pace with the evolving landscape of melanoma management. However, this dynamic environment demands a structured approach to establish a consistent framework regarding the discontinuation of ICI therapy and follow-up examinations. The data from the 51 centers clearly indicate that certain aspects of the current German S3 guideline need revision in this regard.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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