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ORIGINAL ARTICLE

Immune checkpoint inhibition and targeted therapy for melanoma: A patient-oriented cross-sectional comparative multicentre study

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Abstract

Background: Choosing the adequate systemic treatment for melanoma is driven by clinical parameters and personal preferences.

Objective: Evaluation of the impact of disease and treatment on the daily life of patients receiving systemic therapy for melanoma.

Methods: A German-wide, cross-sectional comparative study was conducted at 13 specialized skin cancer centres from 08/2020 to 03/2021. A questionnaire was distributed to assess patients' perception of disease and symptoms, the impact of their current treatment on quality of life (QOL) and activities, adverse events (AEs),

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therapeutic visits, as well as believe in and satisfaction with their current systemic melanoma treatment. Patient-reported outcomes (PROs) were rated on a continuous numerical rating scale or selected from a given list.

Results: Four hundred and fourteen patients with systemic melanoma therapy were included. 359 (87%) received immune checkpoint inhibition (ICI) and 55 (13%) targeted therapy (TT). About 1/3 of patients were adjuvantly treated, the remaining because of unresectable/metastatic melanoma. In subgroup analyses, only in the adjuvant setting, TT patients reported a significant decrease in their treatment associated QOL compared to patients with ICI ($p = 0.02$). Patients with TT were 1.9 times more likely to report AEs than patients with ICI, a difference being significant just for the adjuvant setting ($p = 0.01$). ICI treatment intervals differed significantly between adjuvant and unresectable/metastatic setting ($p = 0.04$), though all patients, regardless of their specific ICI drug, evaluated their treatment frequency as adequate. TT patients with dabrafenib/trametinib ($n = 37$) or encorafenib/binimetinib ($n = 15$) did not differ regarding the strain of daily pill intake. Patients older than 63 years rated various PROs better than younger patients.

Conclusions: Patients evaluated their treatment mainly positively. ICI might be preferred over TT regarding QOL and patient-reported AEs in the adjuvant setting. Older melanoma patients appeared to be less impacted by their disease and more satisfied with their treatment.

INTRODUCTION

During the last decade, systemic therapy of advanced melanoma has been revolutionized by the introduction of immune checkpoint inhibition (ICI) and targeted therapy (TT).[1,2] ICI comprises ipilimumab, an antibody directed against the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor, or nivolumab and pembrolizumab, antibodies targeting programmed cell death-1 (PD-1) receptor, or the combination of ipilimumab and nivolumab. TT of melanomas harbouring BRAF V600 mutations consists of the BRAF/MEK inhibitor combinations vemurafenib/cobimetinib, dabrafenib/trametinib, or encorafenib/binimetinib.[3–5] For adjuvant therapy, the anti-PD-1 antibodies nivolumab and pembrolizumab and the combination of dabrafenib/trametinib are approved in the European Union.[3–5]

The individual choice of a drug is often based on efficacy data, which now comprises 5-year follow-up for all agents, or personal preferences.[6–11] However, in the combined use of nivolumab and ipilimumab as well as with the different TTs, adverse events (AEs) are frequent and may be severe or even permanent, thus they need to be considered selecting a certain therapy.[5,7,8]

Immune checkpoint inhibition is administered intravenously in different, drug-specific intervals ranging from 2 to 6 weeks, depending on the administered drug. In the different TT combinations, the number of oral daily tablet intake differs considerably (dabrafenib/trametinib, five pills; vemurafenib/cobimetinib, 11 pills on most days; encorafenib/binimetinib 12 pills). These unequal modes of administration could be perceived differently by patients.[12] Nevertheless, data are lacking, how melanoma patients are bothered by the different intervals or the number of daily pill intake.

Defining the most adequate first-line treatment for the about 50% of patients harbouring a BRAF V600 mutation in the unresectable/metastatic setting is challenging and involves tumour burden, symptoms, and comorbidities.[5,10] It is even more difficult to decide on the first-line treatment in BRAF-mutated patients in the adjuvant setting, since patients usually do not suffer from melanoma-specific symptoms as their metastases have been fully resected and there is no clinically evident tumour.[4,5,10] Thus, this all illustrates the urgent need to analyse, if motives and attitudes towards ICI and TT treatment are different in patients, who receive their therapy either in an unresectable/metastatic or an adjuvant setting.

We conducted a German-wide, multicentre, cross-sectional study, in which we assessed patients' perception of their disease and symptoms, the impact of their current treatment on quality of life (QOL) and activities, AEs, therapeutic visits, as well as believe in and satisfaction with their current systemic melanoma treatment. Our results will contribute to an improved recognition of patient perspectives regarding modern systemic therapy of melanoma.

PATIENTS AND METHODS

Study design and ethics approval

This study was conducted as a cross-sectional multicentre study including 13 Germany skin cancer centres from August 2020 to March 2021 adhering to the principles of the Declaration of Helsinki. It was approved by the institutional review board of the University Medical Center Rostock on

22 June 2020 (approval number A 2020-0147). We closely adhered to the STROBE statement for cross-sectional studies for the reporting of this study.[13]

Survey

As no validated survey tools for the objective of our study existed, the questionnaire was developed de novo in a stepwise process: First, domains of patient-reported perceptions of disease and therapy were identified by unstructured patient interviews, dermatologic expert consulting, and literature review. Those covered disease burden, impact of treatment, AEs and therapeutic visits, intervals between visits, confidence in the current therapy, and important modalities of the actual treatment. Next, a first version of the questionnaire was designed including items on patient-reported outcomes (PROs), sociodemographic information, and current therapy. Subsequently, the questionnaire was pre-tested for clarity and comprehension by independent physicians and revised based on their feedback. Finally, volunteering patients were asked to evaluate the questionnaire regarding understandability, and based on their response, questions were simplified, leading to the final version of the questionnaire (Tables S1 and S2).

Setting and participants

Adult patients (≥18 years) receiving systemic therapy for melanoma were asked to anonymously complete a self-administered 5-page questionnaire (consecutive sampling). If patients had a question of understanding, they were allowed to ask the physicians for advice. All participants gave verbal informed consent before completing the questionnaire. Participation was voluntary. Refusals were not documented, and incentives for study participation were not provided. Each patient was allowed to participate only once in the survey (cross-sectional design).

Patients were questioned about sociodemographic information as well as treatment (ICI vs. TT), setting (adjuvant vs. unresectable/metastatic), current drug, and number of previous therapies. Then they were asked to answer questions regarding perception of disease and symptoms, impact of current treatment on QOL, work, daily activities, or hobbies, treatment-related AEs, treatment visits and the intervals in-between, the bother of daily pill intake, believe in the current treatment and comparison with previous therapies. For the PRO questions, patients were asked to rate the level on a continuous numerical rating scale ranging from 0 to 10 or they could select from a given list.

Data analysis

We calculated an estimated sample size of at least $n = 370$ required for this explorative study by multiplying the number of the questionnaires' items by factor 10.[14]

Statistical analysis was performed using SPSS (IBM SPSS Statistics version 24, IBM Corporation) and GraphPad Prism software (version 5.01, GraphPad Software Inc.). For statistical analysis, data were used from all patients who provided information about their treatment. Missing values were excluded pairwise. Besides, missing data were addressed by indicating the number of participants considered in each analysis. Interval scaled descriptive data included means with standard deviations (SD) and rational scaled descriptive data included medians. Analysis of differences between two normally distributed test groups was performed using the Student's *t*-test or Mann–Whitney *U* test. Welch's correction was applied to Student's *t*-test data sets with significant differences in variance. Comparative analyses of sociodemographic, clinical, or QOL-related data were performed using the Mann–Whitney *U* test, Fisher's exact test or chi-squared test. The comparison of more than two groups was conducted by using the Kruskal–Wallis test and the one-factor analysis of variance (ANOVA). The relationships between parameters were examined with Spearman's correlation. Logistic regression analysis was employed to predict the probability of having AEs. Predictor variables were type of systemic therapy (ICI vs. TT), treatment setting (adjuvant vs. unresectable/metastatic), and median age. Two-tailed *p*-values were calculated. A *p*-value of <0.05 was considered significant with $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

RESULTS

Study population

Out of 542 questionnaires submitted, 414 patients provided information about their treatment and were included in the analysis. Of those, 359 (86.7%) received ICI and 55 (13.3%) were treated with TT. Information on their specific treatment setting was given by 314 (87.5%) patients with ICI and 54 (98.2%) patients with TT. More patients with ICI (63.1%) and TT (68.5%) received their treatment in the unresectable/metastatic setting. Both groups did not significantly differ in treatment setting, age, gender, partnership status, educational level, employment status, social responsibilities, frequency of physical training, or presence of comorbidities (Table 1). However, in the unresectable/metastatic setting, TT patients received their treatment more often in a later line of therapy (Table S3).

Patients' perception of their QOL related to their specific treatment

Reply to the main questions of PROs (questions 1–14, Tables S1 and S2) was satisfactory and ranged between 88.2% and 98.3% of the total cohort of 414 patients (Tables S4 and S5). The comparison with previous therapies (question 17) was not further analysed because it was retrospectively rated as not sufficiently unambiguous.

Notably, TT-treated patients experienced in general a more negative impact on their QOL related to their treatment,

TABLE 1 Comparison of sociodemographic characteristics of all patients treated with immune checkpoint inhibition (ICI) or targeted therapy (TT)

	Total cohort	ICI	TT	
Sociodemographic characteristics	***N* = 414**	***N* = 359**	***N* = 55**	***p* Value**
Treatment setting				
Adjuvant	133 (36.1%)	116 (36.9%)	17 (31.5%)	0.54
Unresectable/metastatic	235 (63.9%)	198 (63.1%)	37 (68.5%)	
Age (years)				
≤29	5 (1.2%)	4 (1.1%)	1 (1.8%)	0.63
30–39	26 (6.3%)	21 (5.8%)	5 (9.1%)	
40–49	29 (7.0%)	27 (7.5%)	2 (3.6%)	
50–59	111 (26.8%)	94 (26.2%)	17 (30.9%)	
≥60	243 (58.7%)	212 (59.2%)	30 (54.5%)	
Gender				
Female	166 (40.1%)	147 (40.9%)	19 (34.6%)	0.46
Male	247 (59.7%)	212 (59.1%)	35 (63.6%)	
Diverse	1 (0.2%)	0 (0.0%)	1 (1.8%)	
Partnership				
Single	95 (23.3%)	81 (22.8%)	14 (26.4%)	0.60
Relationship	313 (76.7%)	274 (77.2%)	39 (73.6%)	
Education				
None	5 (1.2%)	4 (1.1%)	1 (1.8%)	0.97
High school degree	305 (74.4%)	265 (74.4%)	40 (74.1%)	
University degree	100 (24.4%)	87 (24.4%)	13 (24.1%)	
Employment status				
Employment ≥34 h/ weeks	131 (32.8%)	113 (32.8%)	18 (33.3%)	0.92
Retired	197 (49.4%)	169 (49.0%)	28 (51.9%)	
Seeking work	6 (1.5%)	6 (1.7%)	0 (0.0%)	
Not employed	65 (16.3%)	57 (16.5%)	8 (14.8%)	
Social responsibilities				
Caring for minors	39 (10.8%)	32 (10.2%)	7 (14.3%)	0.65
Caring for other family members	19 (5.2%)	18 (5.8%)	1 (2.0%)	
Caring for pets	55 (15.2%)	48 (15.3%)	7 (14.3%)	
Other	17 (4.7%)	16 (5.1%)	1 (2.0%)	
None	232 (64.1%)	199 (63.6%)	33 (67.4%)	
Frequency of physical training				
None	143 (35.0%)	126 (35.5%)	17 (31.5%)	
<1 h/week	84 (20.5%)	77 (21.7%)	7 (13.0%)	0.16
≥1 h/week	182 (44.5%)	152 (42.8%)	30 (55.6%)	
Presence of comorbidities				
Yes	257 (63.5%)	223 (63.7%)	34 (61.8%)	0.88
No	148 (36.5%)	127 (36.3%)	21 (38.2%)	

Note: A *p*-value <0.05 was considered significant.

compared to ICI patients, i.e., TT mean 4.2, ICI mean 4.7 (p = 0.006; 0, strongest decrease of QOL; 5, no change; 10 strongest improvement of QOL) (Figure 1). Looking separately on patients treated in the adjuvant and or in the unresectable/metastatic setting, those adjuvantly treated with TT reported the strongest treatment related QOL decrease (mean 3.9). This was also slightly more than the QOL decrease of TT patients with unresectable/metastatic disease (mean 4.3). In contrast, ICI patients only experienced a minor QOL decrease when adjuvantly treated (mean 4.6), and even less when treated in the unresectable/metastatic setting (mean 4.7). Hence, when considering therapeutic subgroups separately, ICI and TT patients only significantly differed in the adjuvant setting (p = 0.02) (Figure 1).

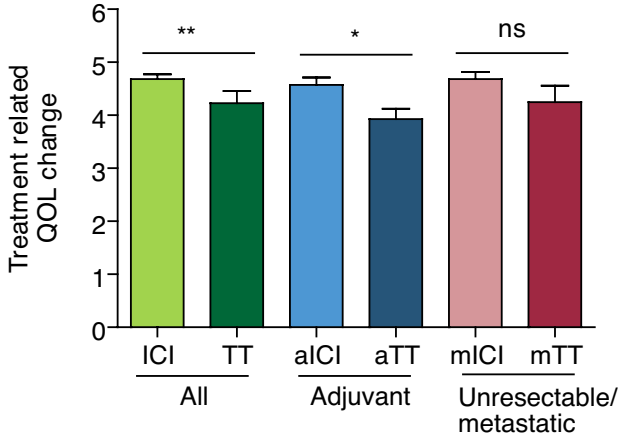

FIGURE 1 Patient-reported treatment related QOL changes. In the whole cohort, ICI mean was 4.7 and TT mean was 4.2. In the separate analysis for both therapeutic subgroups, the difference was only significant in the adjuvant setting. QOL evaluation: 0, very deteriorated; 5, no change; 10, very improved. A, adjuvant; ICI, immune checkpoint inhibition; m, metastatic/unresectable; ns, not significant; QOL, quality of life; TT, targeted therapy. *$p < 0.05$, **$p < 0.01$

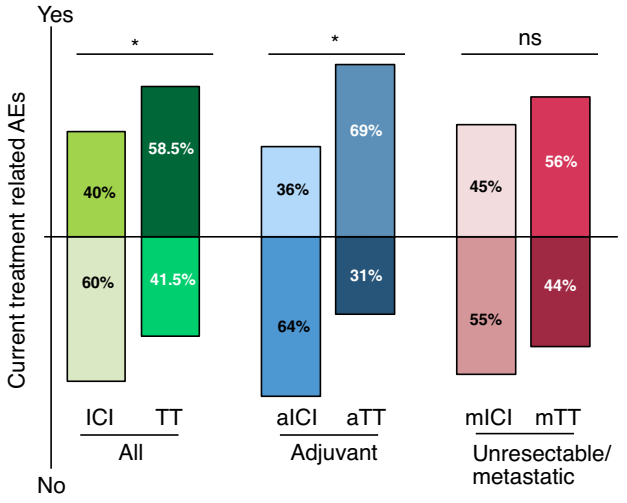

FIGURE 2 Comparison of the occurrence of current treatment-related AEs between patients treated with ICI or TT. 58.5% of all TT versus 40% of all ICI-treated patients reported to currently suffer from AEs. In the adjuvant setting, 69% of TT patients but only 36% of the ICI patients suffered from AEs. Slightly more TT (56%) compared to ICI (45%) patients with unresectable/metastatic melanoma reported current AEs. A, adjuvant; AEs, adverse events; ICI, immune checkpoint inhibition; m, metastatic/unresectable; ns, not significant; TT, targeted therapy. *$p < 0.05$

Comparison of patient-reported AEs under treatment

Regarding the impact of their current treatment on work, daily activities, or hobbies, TT and ICI patients did not significantly differ (Table S4), but more patients with TT (n = 31, 58.5%) experienced AEs than with ICI (n = 135, 40.4%) (p = 0.017; Figure 2). The odds ratio indicated that patients with TT were 1.9 times more likely to experience AEs than patients with ICI. The difference of reported AE was only significant for patients treated in the adjuvant setting (p = 0.01), but not in the unresectable/metastatic setting (p = 0.28) (Figure 2). When patients were asked, how much they were restricted by current AEs, no difference between TT and ICI patients, in the whole cohort or in therapeutic subgroup analysis, was evident (Tables S4 and S5). Neither ICI (mean 3.6) nor TT (mean 4.1) treated patients reported a relevant fear of occurrence or deterioration of AEs (0, not at all; 10, very much; p = 0.95). Accordingly, also in the subgroups of adjuvantly (means, ICI 3.5, TT 4.1, p = 0.56) or in the unresectable/metastatic setting (means, ICI 3.6, TT 4.1, p = 0.31) treated ICI and TT patients, no difference was observed.

Belief in current treatment

The belief in the success of the current treatment (0, no belief; 10, maximum belief) was generally high in all patients; however, patients treated with ICI for unresectable/metastatic disease (mean 7.9) believed even more in the success than patients with TT (mean 7.1) ($p < 0.05$). In contrast, patients treated in an adjuvant indication believed almost equally in the success of their respective treatments (means, ICI 8.2, TT, 7.6; p = 0.61) (Table S5). When considering the means of single drugs or combinations in the adjuvant therapy, belief in the success of the current treatment was the highest for pembrolizumab (mean 8.6), followed by nivolumab (mean 7.8) and dabrafenib/trametinib (mean 7.4) ($p < 0.05$). All other PROs and sociodemographic characteristics were not different between those patients receiving any of these three treatments in an adjuvant indication (data not shown).

Evaluation of specific treatment modalities of TT

Of the 55 patients treated with TT, 37 (67.3%) received dabrafenib and trametinib, of which 37.8% in the adjuvant setting; 15 (27.3%) encorafenib and binimetinib, and only three patients (5.5%) vemurafenib and cobimetinib, who were therefore excluded from further analysis. Perception of disease and PROs of treatment were not different in between patients with dabrafenib and trametinib or encorafenib and binimetinib.

The questionnaire revealed that TT patients were only slightly bothered by their daily pill intake (mean 3.6; 0, no negative impact; 10, maximum negative impact). Since the number of daily tablets differed between TT combinations, we compared how patients rated the burden of their daily pill intake. Unexpectedly, no significant differences between the patients taking dabrafenib/trametinib (mean 3.7) or those with encorafenib/binimetinib (mean 2.8) could be observed (Figure 3).

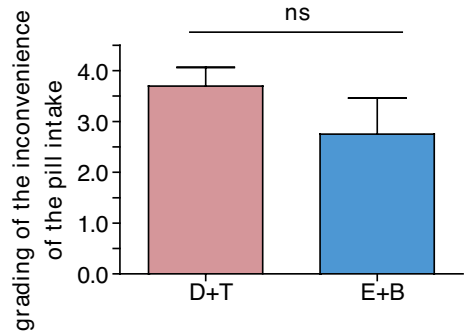

FIGURE 3 Burden of daily TT pill intake. Inconvenience of daily pill intake did not reveal differences between dabrafenib/trametinib (D + T; mean 3.7) and encorafenib and binimetinib (E + B; mean 2.8) despite largely different tablet numbers. Evaluation of inconvenience: 0, not at all; 10, very much. Ns, not significant

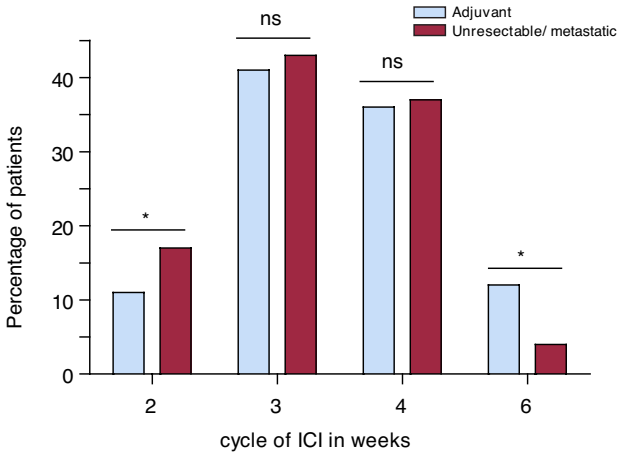

FIGURE 4 Distribution of ICI treatment intervals. In the unresectable/metastatic setting 2-week intervals (17% vs. 11% in the adjuvant setting) were more and 6-week intervals (4% vs. 12% in the adjuvant setting) were less common. ICI, immune checkpoint inhibition; ns, not significant. *$p < 0.05$

Comparison of different immune checkpoint inhibition regimes

Of all 359 patients treated with ICI, 145 (40.4%) received nivolumab, 127 (35.4%) pembrolizumab, 82 (22.8%) the combination of ipilimumab and nivolumab, and five (1.4%) ipilimumab. Most patients (42%) received their drug in a 3-week interval, 36% in a 4-week interval, 17% in a 2-week interval, and only 7% of patients in a 6-week interval. More than half of the patients (50.5%) treated with pembrolizumab versus 36.9% of the patients treated with nivolumab were treated in the adjuvant setting ($p < 0.001$).

Immune checkpoint inhibition treatment intervals significantly differed between adjuvant and unresectable/metastatic patients ($p = 0.042$) (Figure 4). More specifically, unresectable/metastatic patients ($n = 28$, 16.8%) received their therapy more often in a shorter 2-week interval and less often in a 6-week interval than adjuvant patients ($n = 12$, 11%). Four weeks (65.4% of patients) was the most frequent interval of nivolumab infusions, while 3 weeks (77.7% of patients) was the most common interval of pembrolizumab, regardless of treatment setting.

Of note, all patients in each ICI subgroup regarded their treatment frequency as adequate (Figure S1A,B). Neither adjuvant nor unresectable/metastatic patients reported a negative impact by the necessity of a venous access.

No significant differences regarding perception of their disease and specific treatment could be revealed for ICI patients treated with the different substances, with one exception: patients who received pembrolizumab, although their reported frequency of AEs was not different to the other subgroups, reported to be less negatively affected by them ($p = 0.03$, data not shown).

Comparison of younger and older patients

The mean (ICI, 62.7 years; TT, 60.6 years) or median age (ICI, 64 years; TT, 61 years) values were not significantly different between ICI or TT patients. Hence, we used the median of the total cohort with age information to compare 207 patients of 63 years or younger (21–63 years) with 206 patients older than 63 years (64–88 years). The older patients rated various PROs of treatment and disease better than the younger (Figure 5).

DISCUSSION

In recent years, PROs find increasing consideration in clinical practice. Importantly, primarily assessing prevalent patient perspectives and perceptions towards systemic therapy of melanoma is a fundamental basis for clinicians, finally facilitating "shared-decision making".[15]

Patient-reported outcomes represent the patient's report of a health condition and its treatment.[14,16] Studies analysing PROs in melanoma have in common that they rely on a repertoire of validated questionnaires.[17,18] Those mainly evaluate QOL, and general instruments are used because of a better comparability with each other.[18,19] However, certain patient-centred motives and expectations are not captured well. Especially, individual attitudes towards different therapeutic approaches are often not represented. Particularly, it has not yet been investigated how melanoma patients perceive ICI compared to TT, depending on the respective treatment setting.[20–23] Therefore, we designed a de novo questionnaire evaluating different patient perspectives regarding modern systemic therapy of melanoma.

In our study, ICI was less likely to reduce QOL compared to TT, but the difference was only significant in the adjuvant setting. In contrast, in the adjuvant COMBI AD study, dabrafenib and trametinib did not affect QOL during or after treatment compared to placebo, even though there was a non-significant decrease after 3 months in the verum group.[24] Accordingly, in clinical trials using standardized questionnaires, health-related QOL was maintained in

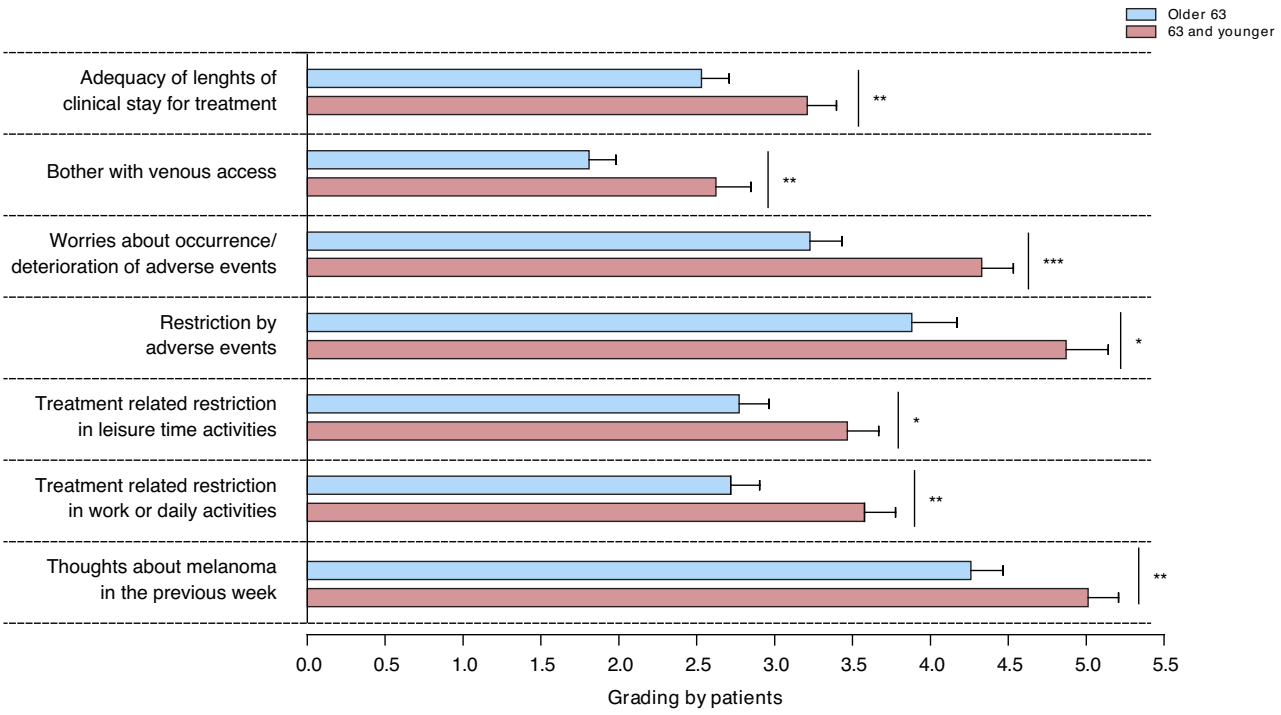

FIGURE 5 Comparison of older (>63 years) and younger (≤63 years) patients regarding different treatment or melanoma associated factors such as assessment of the duration of therapeutic visits ($p = 0.009$), the bother by the need of a venous access ($p = 0.004$), worries about the occurrence or deterioration of adverse events ($p < 0.001$) or restriction by them ($p = 0.01$), treatment-related restriction in leisure time activities ($p = 0.01$) or in work and daily life ($p = 0.002$) and thoughts about melanoma in the previous week ($p < 0.01$). Evaluation of duration of therapeutic visits: 0 adequate, 10 too long; evaluation of the rest: 0 not at all, 10 very much. *$p < 0.05$, **$p < 0.01$

adjuvant nivolumab and pembrolizumab on treatment and over follow-up.[25,26] Thus, additional comparative studies, which also consider the duration of individual treatments, should verify if TT and ICI affect QOL to an unequal extent and even differently in the real-world than in clinical trials.

In a recent German multicentre study by Lodde et al.,[27] patients were asked why they declined adjuvant melanoma treatment, which revealed fear of an impaired QOL and of AEs as two of the three most-cited reasons. In our study, we considered patients who were already on treatment and observed that adjuvant TT patients were more likely to report current AEs. However, they did not, just as ICI-treated patients, indicate a relevant fear of the occurrence or deterioration of AEs. Furthermore, the most frequent patients' reason to decline systemic adjuvant treatment in the study of Lodde et al.[27] was higher age. Accordingly, the median age of patients in their study, who opted for an adjuvant treatment (61.8 years), was less than that of patients, who decided against adjuvant therapy (76.3 years). In contrast in our study of patients currently receiving systemic therapy, those older than 63 years worried significantly less about AEs and evaluated various PROs better than the younger. Remarkably, older studies in cancer patients have demonstrated that age was positively associated with QOL and patient satisfaction.[28,29] Hence, we hypothesize that those older melanoma patients who opt for treatment might represent a certain group, which is characterized by betting coping with their disease and higher satisfaction with their therapy.

An unexpected finding of our study was the fact that the subjectively perceived strain of taking daily pills did not differ between patients treated with dabrafenib/trametinib or encorafenib/binimetinib. Although this comparison contained only a small number of patients and was made independently of therapeutic subgroups, it suggests that the number of daily pills is not overly important to melanoma patients, if therapeutically indicated.

Our study suggests that in the unresectable/metastatic setting, shorter ICI treatment intervals might be selected more often to keep patients under closer monitoring. Present data indicated that the longer 4- or 6-week intervals for nivolumab or pembrolizumab, respectively, have a comparable outcome to shorter intervals, but clinical trials evaluating consequences on efficacy or dosing in partly even longer intervals are still ongoing.[30–33] These studies might be an additional basis for less frequent ICI administration in clinical routine. On the other hand, the results of our cross-sectional study show that patients largely agreed with the modalities of their current therapy. Longer treatment intervals, therefore, do not necessarily increase the patients' comfort but may also contain a greater patient risk due to a delayed diagnosis of AEs. A small German study just recently noticed that pembrolizumab was the most commonly chosen drug in adjuvant therapy.[34] This is consistent with our data, since here also pembrolizumab was the most frequently administered adjuvant therapy. Interestingly, the single ICI drug with the highest patients' belief in treatment success in our study was also pembrolizumab. Of note,

in the unresectable/metastatic setting, TT-treated patients believed less in their current treatment than those with ICI, which might be explained by their higher number of previous therapies.

Our study has several limitations. Because of its design as a cross-sectional study, no follow-up data was provided. Also, the moment of participation during the individual course of treatment and efficacy data were not considered. The sample size of our study is comparatively small, and the study population was not sampled randomly but depending on the availability of patients leading to an imbalance of ICI and TT patients. Furthermore, questionnaires were filled out by the treated patients themselves, and their answers were not verified with the information of their medical records. Lastly, the solely participation of specialized and largely university skin centres in this study might have potentially biased its results.

Despite all these limitations, our analysis provides significant new findings that deserve attention: Patients with advanced melanoma mainly evaluated their treatment positively. ICI might be preferred over TT in the adjuvant setting due to its less negative impact on QOL. Most patients agreed with the frequency of ICI applications and the number of daily TT pill intake. In melanoma, older on-treatment patients seem to deal better with their disease and have a pronounced treatment satisfaction.

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CONFLICT OF INTEREST

A.T. has received consultant's honoraria or travel support from Bristol-Meyers Squibb (BMS), GlaxoSmithKline (GSK), Kyowa Kirin, Merck Sharp & Dohme (MSD), Novartis, Pierre-Fabre Pharmaceuticals, and Recordati Rare Diseases (RRD), outside the scope of the submitted work. J.C.H. discloses advisory boards (self) with GSK, MSD, Pierre Fabre, Sunpharma; advisory boards (institution) with BMS, Immunocore, Novartis, Nektar, Philogen; contracted research with 4SC, BioNTech, BMS, Genentech/Roche, Idera, Immunocore, Iovance, Nektar, Novartis, Philogen, Pierre Fabre, Regeneron, Sanofi; honoraria from BMS, MSD, Novartis, Pierre Fabre, Roche, Sanofi, Sunpharma; and research funding to institution from BMS, Sunpharma. I.G. declares speaker and advisory board honoraria from Almirall Hermal, BMS, MSD, Novartis, Pierre Fabre, Roche, Sanofi Genzyme, and Sun Pharma; and travel support from BMS, MSD, and Novartis. R.G. has served as an invited speaker for Roche, BMS, MSD, Novartis, Amgen, Merck Serono, Almirall Hermal, Sunpharma, Sanofi, Pierre-Fabre; on advisory boards for BMS, Roche, Novartis, Almirall Hermal, MSD, Amgen, Sun Pharma, Sanofi, Pierre-Fabre, 4SC, MerckSerono, Pfizer, Immunocore; and has received research grants from Novartis, Pfizer, Johnson & Johnson, Amgen, Merck-Serono, Sun Pharma, Sanofi; and travel/meeting support from Roche, BMS, Sun Pharma, Merck-Serono, Pierre-Fabre. M.S. has received consultant or speaker fees or travel grants from BMS, MSD, Roche, Kyowa Kirin, Novartis, Sanofi Genzyme, Pierre Fabre, Sun Pharma, Immunocore. M.V.H. has received travel grants from Pierre Fabre, and speaker honoraria from MSD, BMS, Roche, Novartis, and Pierre Fabre. P.D. has received consultant or speaker honoraria from Abbvie, BMS, MSD, Novartis, Pfizer, Pierre Fabre, Roche, and Sanofi Aventis. S.H. has served as consultant or/and has received honoraria from BMS, MSD, Kyowa Kirin and Sun Pharma and received travel support from Pierre-Fabre. B.S. is on the advisory board or has received honoraria from Immunocore, Almirall, Pfizer, Sanofi, Incyte, Novartis, Roche, BMS, and MSD, research funding from Novartis, Pierre Fabre, BMS, and MSD, and travel support from Novartis, Roche, BMS, Pierre Fabre Pharma, MSD, and Amgen, outside the submitted work. S.H. has received speaker and advisory board honoraria from BMS, MSD, Novartis, Pierre Fabre, Sanofi Genzyme, and Sun Pharma. M.Z. discloses for the last three years honoraria concerning melanoma for participation in advisory boards for BMS, as well as honoraria for lectures or financial support for congress participation from MSD, Novartis, and Pierre Fabre. R.K.C.M. has received consultant's honoraria or travel support from BMS, MSD, Novartis, and Pierre-Fabre Pharmaceuticals, outside the scope of the submitted work. V.H. has received honoraria or travel support from BMS, MSD, Novartis, and Roche. P.T. has received honoraria from 4SC, Almirall, Biofrontera, BMS, Kyowa Kirin, Novartis, MSD, Pierre-Fabre, Merck Serono, Sanofi, Roche; and travel support from BMS and Pierre-Fabre. C.P. has received consultant's honoraria or travel support from BMS, MSD, Novartis, Pierre-Fabre, Roche, Sanofi, Sun Pharma, Almirall, and PelPharma. M.R.G. has received honoraria from Roche, MSD, BMS, Merck KGaA, Novartis, Pierre Fabre, and Sun Pharma. P.K. has received travel and lecture grants from Novartis, Teva, and Lilly. S.E. has received speaker honoraria from Amgen, BMS, MSD, Roche, Novartis, Sanofi, Pierre-Fabre, Therakos, Cinogy. J.K.T. has received travel grants from Kyowa Kirin, Pierre Fabre, and Sun Pharma; and speaker honoraria from MSD, BMS, Roche, Novartis, Sanofi Aventis, RRD, OncoBeta, and Pierre Fabre. The other authors declare they have no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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