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ORIGINAL ARTICLE

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Real-world outcomes using PD-1 antibodies and BRAF + MEK inhibitors for adjuvant melanoma treatment from 39 skin cancer centers in Germany, Austria and Switzerland

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Abstract

Background: Programmed death-1 (PD-1) antibodies and BRAF + MEK inhibitors are widely used for adjuvant therapy of fully resected high-risk melanoma. Little is known about treatment efficacy outside of phase III trials. This real-world study reports on clinical outcomes of modern adjuvant melanoma treatment in specialized skin cancer centers in Germany, Austria and Switzerland.

Methods: Multicenter, retrospective study investigating stage III–IV melanoma patients receiving adjuvant nivolumab (NIV), pembrolizumab (PEM) or dabrafenib + trametinib (D + T) between 1/2017 and 10/2021. The primary endpoint was 12-month recurrence-free survival (RFS). Further analyses included descriptive and correlative statistics, and a multivariate linear-regression machine learning model to assess the risk of early melanoma recurrence.

Results: In total, 1198 patients from 39 skin cancer centers from Germany, Austria and Switzerland were analysed. The vast majority received anti PD-1 therapies (n = 1003). Twelve-month RFS for anti PD-1 and BRAF + MEK inhibitor-treated patients were 78.1% and 86.5%, respectively (hazard ratio [HR] 1.998 [95% CI 1.335–2.991]; p = 0.001). There was no statistically significant difference in overall survival (OS) in anti PD-1 (95.8%) and BRAF + MEK inhibitor (96.9%) treated patients ($p > 0.05$) during the median follow-up of 17 months. Data indicates that anti PD-1

treated patients who develop immune-related adverse events (irAEs) have lower recurrence rates compared to patients with no irAEs (HR 0.578 [95% CI 0.443–0.754], $p = 0.001$). BRAF mutation status did not affect overall efficacy of anti PD-1 treatment ($p > 0.05$). In both, anti PD-1 and BRAF + MEK inhibitor treated cohorts, data did not show any difference in 12-month RFS and 12-month OS comparing patients receiving total lymph node dissection (TLND) versus sentinel lymph node biopsy only ($p > 0.05$). The recurrence prediction model reached high specificity but only low sensitivity with an AUC = 0.65. No new safety signals were detected. Overall, recorded numbers and severity of adverse events were lower than reported in pivotal phase III trials.

Conclusions: Despite recent advances in adjuvant melanoma treatment, early recurrence remains a significant clinical challenge. This study shows that TLND does not reduce the risk of early melanoma recurrence and should only be considered in selected patients. Data further highlight that variables collected during clinical routine are unlikely to allow for a clinically relevant prediction of individual recurrence risk.

INTRODUCTION

In recent years, systemic melanoma treatment has made enormous progress. Starting with the CTLA-4-inhibitor ipilimumab (IPI) approved in 2011, several new and effective drugs are now available and have reshaped the therapeutic landscape for melanoma patients.[1] In addition to treatment of unresectable and metastatic disease, modern melanoma treatment now includes systemic adjuvant therapy for high-risk patients in fully resected AJCC stages III–IV. Today, three therapy regimens are available for adjuvant treatment: Two programmed death-1 (PD-1) antibodies nivolumab (NIV) and pembrolizumab (PEM), and the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib (D + T).[2]

Data from the pivotal phase III randomized clinical trials KEYNOTE-054, CheckMate-238, and Combi-AD highlight that all three adjuvant melanoma therapies significantly reduce the risk of melanoma recurrence. CheckMate-238 investigated efficacy and safety of NIV versus IPI in the adjuvant treatment of fully resected melanoma stage IIIB to IV (AJCC 2009). Results show a significant improvement in recurrence-free survival (RFS) (12-month RFS: 70.5% vs. 60.8% and 4-year RFS: 51.7% vs. 41.2%) and a favourable safety profile of NIV compared to IPI with drug-related adverse events (AEs) grade III and higher being reported in 14.4% of patients versus 45.9% with IPI.[3,4] The KEYNOTE-054 study compared PEM to placebo in the adjuvant therapy of fully resected melanoma stage IIIA-C (AJCC 2009). Results also show a significant improvement of RFS (12-month RFS: 75.4% vs. 61.0% and 3-year RFS: 63.7% vs. 44.1%) and drug-related AEs grade III and higher of 14.7% for PEM versus 3.4% for placebo.[5,6] The COMBI-AD trial evaluated the efficacy of the adjuvant combination of D + T versus placebo in fully resected melanoma stage III patients. Again, a significant improvement of RFS compared to placebo (12-months RFS: 88% vs. 56% and 5-year RFS: 52% vs. 36%) and similar treatment-related AEs compared to its use in advanced disease were achieved.[7,8] Despite the efficacy of modern adjuvant melanoma treatment, recurrence and particularly early recurrence remains a significant clinical challenge. Additionally, only limited data are available to date assessing real-world outcomes using modern adjuvant treatment.

This retrospective study investigates real-world outcomes of melanoma patients receiving adjuvant anti PD-1 or BRAF + MEK inhibitor treatment for fully resected stage III–IV disease in specialized skin cancer centers in the DACH-region (Germany, Austria, and Switzerland). The primary endpoint of the study was 12-month RFS for anti PD-1 and BRAF + MEK inhibitor-treated patients. Further analyses included 12-month overall survival (OS), AEs, and descriptive statistics of clinical, histological, and molecular variables. Additionally, this study uses a machine learning model to predict early melanoma recurrence using variables routinely collected during clinical practice.

METHODS

Patients and study design

We retrospectively enrolled patients with completely resected stage IIIA–D and IV melanoma who received adjuvant treatment with PD-1 antibodies or BRAF + MEK inhibitors in one of the collaborating skin cancer centers in the DACH region (Germany, Austria, and Switzerland) between January 2017 and October 2021 outside of a clinical trial. All patients were treated according to national guidelines. Recommendations in all three national guidelines were found to be similar. Inclusion criteria were histologically confirmed diagnosis of melanoma, tumour stage according to AJCC 2017 (8th edition), and complete resection before adjuvant treatment. Total lymph node dissection (TLND) after positive sentinel lymph node biopsy (SLNB) was not mandatory, however patients had to be considered tumour-free by the respective skin cancer center. RFS was defined as the time from start of therapy to the date of the

first recurrence, new primary melanoma, or death from any cause. For patients alive without disease recurrence, RFS was censored on the date of last patient contact. Further analyses included OS, AEs and sub-group analyses of RFS depending on various clinical, laboratory or histological parameters. OS was defined as time from start of therapy until death. Subgroup analysis included, among others, BRAF-mutation status, disease stage, body mass index (BMI), sex and TLND. AEs were identified and rated by the respective centers according to the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE). We also checked if treatment outcome was different between patients who would have met inclusion criteria published for the pivotal phase III trials compared to patients who would not have been included. A detailed list of these criteria is provided in the Appendix S1. This study was approved by the ethical committee of the Technical University of Munich.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 27) and included descriptive statistics, and logistic regression models. Subgroup analyses were performed using Cox regression. Missing data was censored. To identify predictive variables of early melanoma recurrence in PD-1-treated patients, we employed a regression model including only features with <20% missing values. Categorical values were ordinal encoded for ordinal data or one-hot encoded for non-ordinal data. Data was split into training and test sets in an 80:20 ratio. Missing data was imputed using the median for numeric and categorical data and using the mode for binary data with the exception of the sex variable, which was imputed randomly maintaining the distribution between male and female present in the raw data. Numeric and ordinal data was transformed using a Min-Max-scaler and, where data was distributed non-normally, by Box–Cox-transformation. The regression model was fit using a ridge regression procedure and cross validation with five repeats. Subsequently, hyperparameter optimization was performed via a grid search. All steps were performed in python using the scikit-learn package.

RESULTS

Patients

In total, 1361 patients from 39 centers in Germany, Austria and Switzerland receiving either NIV, PEM or D + T for adjuvant melanoma treatment were submitted, of which 1198 could be included in this analysis (Figure S1). Median age of patients was similar between treatment groups with 59 (17–89), 63 (15–89) and 57 (13–87) years for NIV, PEM and D + T, respectively. This study included 462 patients age >65 (405 patients treated with PD-1 antibodies and 57 patients treated with BRAF + MEK inhibitors). More male than female patients were part of this study (Table 1). Most patients presented with excellent performance status (ECOG ≤ 1). Assessing all patient characteristics of this study, 72.9% of NIV, 65.5% of PEM, and 63.7% of D + T-treated patients would have met published inclusion criteria (see Appendix S1: Material and methods) used in the respective phase III clinical trials for the three adjuvant melanoma treatment modalities.

Tumour and disease characteristics

The predominant histological tumour type was nodular melanoma followed by superficial spreading melanoma. Median tumour thickness was calculated with 2.6 mm (0.15–20.0 mm) for NIV and 2.8 mm (0.2–60.0 mm) for PEM, 2.8 mm (0.4–12.0 mm) for D + T. A significant proportion of tumours were ulcerated in all three treatment groups: NIV 40.4%, PEM 37.5% and D + T 40.5%. Lymphatic disease (lymph node involvement, in transit and satellite metastases) was equally distributed between the three groups. In transit/satellite metastases were present in 25.8%, 22.7% and 23.6 for NIV, PEM and D + T. Clinically detectable lymph node metastasis was present in 45.8% of NIV treated, 49.5% of PEM treated, and 43.6% of D + T-treated patients. In line with differences in the approval text of the three treatments in the DACH region, there was a trend to higher numbers of stage IV patients in the NIV (12.5%) versus PEM (5%) and D + T (2.6%) group. BRAF (V600) mutations were detected in 45.2% of all patients (Table 1). PD-L1 expression levels, measured in combined positive score values, were only performed in 14.2% of patients in the anti PD-1 and BRAF + MEK inhibitor treated groups.

Treatment and survival

Sentinel lymph node biopsy was performed in 63.8%, 67.9% and 67.7% of patients treated with NIV, PEM and D + T. TLND with or without prior SLNB, was done in 42.3% in the NIV group, 37.2% in the PEM group, and 38.4% in the D + T group. Considering that clinically detectable lymph node metastasis and stage IV disease does not require SLNB, most patients received nodal surgery. A small number of patients (NIV: 12.5%, PEM: 8.8% and D + T: 9.2%) received adjuvant interferon alpha therapy before starting modern adjuvant treatment. 15.2%, 18.6% and 18.5% of patients receiving NIV, PEM and D + T also received radiation therapy (Table 2). Median time from last surgery to adjuvant treatment was calculated with 2 months in all three cohorts. The majority of patients received anti PD-1-based adjuvant therapy (n = 1003). At the time of analysis, 588 (88.6%) patients from the NIV group, 246 (72.6%) from the PEM group and 150 (76.9%) from the D + T group completed therapy. The median follow-up period was 14 (0–45) months for NIV treated, 14 (0–53) months for PEM treated, and 11 (0–41) months for D + T-treated patients.

TABLE 1 Patient and tumour characteristics

	Nivolumab (*N* = 664)	Pembrolizumab (*N* = 339)	Dabrafenib + trametinib (*N* = 195)
Age			
Median – years (range)	59 (17–89)	63 (15–89)	57 (13–87)
>65 years – no. (%)	245 (36.9)	160 (47.2)	57 (29.2)
Not reported	1 (0.2)	1 (0.3)	0 (0)
Sex			
Male	360 (54.2)	184 (54.3)	109 (55.9)
Female	263 (39.6)	129 (38.1)	70 (35.9)
Not reported	41 (6.2)	26 (7.7)	16 (8.2)
BMI (kg/m^2) – no. (%)			
<20	14 (2.1)	4 (1.2)	2 (1.0)
20–25	124 (18.7)	65 (19.2)	45 (23.1)
25–30	166 (25.0)	95 (28.0)	32 (16.4)
>30	132 (19.9)	48 (14.2)	17 (8.7)
Not reported	228 (34.3)	127 (37.5)	99 (50.8)
ECOG – no. (%)			
≤1	619 (93.2)	302 (89.4)	181 (92.8)
>1	9 (1.4)	5 (1.5)	–
Not reported	36 (5.4)	32 (9.4)	14 (7.2)
Type of tumour[a] – no. (%)			
SSM	180 (27.1)	103 (30.4)	58 (29.7)
NM	227 (34.2)	179 (39.2)	73 (37.4)
LMM	9 (1.4)	8 (2.4)	5 (2.6)
Other	188 (28.3)	82 (24.1)	45 (23.1)
Not reported	71 (10.7)	27 (8.0)	15 (7.7)
Thickness (mm) – no. (%)			
<1.0	60 (9.0)	27 (8.0)	19 (9.7)
1.01–2.0	141 (21.2)	68 (20.1)	44 (22.6)
2.01–4.0	194 (29.2)	113 (33.3)	60 (30.8)
>4.01	170 (25.6)	92 (27.1)	45 (23.1)
Not reported	99 (14.9)	39 (11.5)	27 (13.8)
Ulceration – no. (%)			
Yes	268 (40.4)	127 (37.5)	79 (40.5)
No	299 (45.0)	167 (49.3)	88 (45.1)
Not reported	97 (14.6)	45 (13.3)	28 (14.4)
Mutation – no. (%)			
BRAF V600E	175 (26.4)	100 (29.5)	152 (77.9)
BRAF V600K	27 (4.1)	5 (1.5)	18 (9.2)
BRAF V600 other	25 (3.8)	15 (4.4)	25 (12.9)
NRAS	113 (17.0)	63 (18.6)	–
Mutation not reported	41 (6.2)	23 (6.8)	–
Lymphatic disease[a] – no. (%)			
≤1 pos. Lymph nodes	470 (70.8)	242 (71.4)	137 (70.3)
2–3 pos. Lymph nodes	131 (19.7)	66 (19.5)	38 (19.5)
≥4 pos. Lymph nodes	37 (5.6)	22 (6.5)	14 (7.2)
Clinically occult	200 (30.1)	109 (32.2)	72 (36.9)
Clinically detectable	304 (45.8)	168 (49.5)	85 (43.6)

TABLE 1 (Continued)

	Nivolumab (*N* = 664)	Pembrolizumab (*N* = 339)	Dabrafenib + trametinib (*N* = 195)
Extra capsular disease	69 (10.4)	46 (13.6)	18 (9.2)
In transit/satellite metastasis	171 (25.8)	77 (22.7)	46 (23.6)
Not reported	26 (3.9)	9 (2.7)	6 (3.1)
Stage[b] – no. (%)			
IIIA	60 (9.0)	47 (13.9)	26 (13.3)
IIIB	182 (27.4)	87 (25.7)	45 (23.1)
IIIC	327 (49.2)	182 (53.7)	112 (57.4)
IIID	12 (1.8)	6 (1.8)	6 (3.1)
IV	83 (12.5)	17 (5.0)	5 (2.6)
Not reported	–	–	1 (0.5)
Stage IV[b] – distant metastasis – no. (%)			
M1a	34 (5.1)	6 (1.8)	3 (1.5)
M1b	21 (3.2)	6 (1.8)	1 (0.5)
M1c	12 (3.2)	3 (0.9)	–
M1d	9 (1.4)	1 (0.3)	–
M undefined	7 (1.1)	1 (0.3)	1 (0.5)
Not reported	–	–	1 (0.5)

Abbreviations: BMI, body mass index; CPS, combined positive score; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Multiple entries possible.
[b]According to AJCC classification, 8th Edition.

Twelve-month RFS was 72.1% in the NIV group, 78.0% in the PEM group and 86.5% in the D + T group (Figure 1a). Median time to recurrence was calculated with 6 (0–39), 6 (1–53) and 10 (1–31) months for NIV, PEM and D + T. Since NIV and PEM are both PD-1 directed antibodies, and we did not detect any significant differences regarding patient characteristics and RFS between the two drugs, patients treated with NIV and PEM were combined to represent melanoma patients with adjuvant PD-1 antibody treatment for further analyses. Twelve-month RFS fall all patients receiving PD-1 directed treatment was 74.1% and 86.5% for BRAF + MEK inhibitor treatment (HR 1.998 [95% CI 1.335–2.991]; $p = 0.001$) (Figure 1b).

During the observation period, 341 (34.0%) patients relapsed under PD-1 therapy: Local recurrence was reported in 103 (30.2%) patients, regional lymph node (LN) metastases only were found in 80 (23.5%) patients, and distant metastases (with or without LN metastases) in 210 (61.6%) patients. Data did not show any organ preference for distant metastases. Under D + T therapy, 45 (23.1%) patients recurred. Eleven (24.4%) patients developed local recurrence, and LN metastases only, 31 (68.9%) patients developed distant metastases with or without LN metastases. Most patients with disease recurrence received subsequent systemic treatment consisting of combined checkpoint blockade, anti PD-1 monotherapy or BRAF + MEK targeting (Table 3). There was no statistically significant difference in 12-month OS between NIV, PEM and D + T-treated patients (Figure 1c; NIV = 95.9%, PEM = 98.2% and D + T = 96.9%) and no difference in OS when the two PD-1 antibodies were combined for analyses and compared to adjuvant BRAF + MEK treatment ($p > 0.05$) (Figure 1d).

Adverse events

There were no significant differences in the AEs profile and frequency between NIV- and PEM-treated patients (Table S1). We did not detect any new safety signals. 60.1% of patients receiving PD-1-based adjuvant therapy developed any grade AEs. Grade ≥3 AEs were reported in 11.2%. Thyroid gland-related AEs (13.0%), fatigue (6.1%) and rashes (5.4%) were among the most frequently diagnosed AEs, however, <0.5% were considered grade ≥3. The only AEs rated grade ≥3 affecting more than 1% of patients involved the liver (hepatitis in 1.5%) and the colon (colitis in 1.3%). The vast majority of AEs in the anti PD-1 treated group were considered immune-related AEs (508/603, 84.2%). The median time between the start of therapy and the occurrence of any AE was 2.0 (0–17) months for anti PD-1 treatment.

In the BRAF + MEK treated group, 75.9% of patients developed any grade AEs. Grade ≥3 AEs were reported in 11.3%. Pyrexia (19.0%), nausea (8.7%) and fatigue (8.2%) were among the most frequently observed drug related AEs; however, only pyrexia was considered grade ≥3 in 1.5% of cases. A significant fraction of AEs were considered treatment-related AEs (95/148, 64.2%) (Table S1). The median time between the start of therapy and the occurrence of any AEs was 1.0 (0–12) month for BRAF + MEK treatment.

Treatment interruptions due to AEs were noted in 82 (12.3%) NIV-treated patients and lasted for a median duration of 28 (2–125) days. In the PEM cohort 33 (9.7%) patients paused treatment with a median duration of 28 (7–120) days, and in the BRAF + MEK group 64 (32.8%) patients interrupted adjuvant treatment for a median duration of 18 (1–90)

TABLE 2 Treatment

	Nivolumab (*N* = 664)	Pembrolizumab (*N* = 339)	Dabrafenib + trametinib (*N* = 195)
Lymph node surgery – no. (%)			
SLNB only	269 (40.5)	169 (48.1)	92 (47.2)
TLND only	126 (19.0)	59 (17.4)	35 (17.9)
SLNB + TLND	155 (23.3)	67 (19.8)	40 (20.5)
No lymphnode surgery performed	104 (15.7)	38 (11.2)	24 (12.3)
Not reported	10 (1.5)	6 (1.8)	4 (2.1)
Therapy before adjuvans – no. (%)			
Interferon	83 (12.5)	30 (8.8)	18 (9.2)
Radiation therapy	101 (15.2)	63 (18.6)	36 (18.5)
Not reported	6 (0.9)	4 (1.2)	3 (1.5)
Blood results before therapy median[a] (range) – years			
LDH	199 (40–802)	200 (85–618)	197 (114–531)
S100B	50 (0–7250)	57 (0–7600)	58 (0–380)
NLR	2.36 (0.12–44.78)	2.64 (0.9–22.42)	2.27 (0.08–101)
CRP	0.4 (0–41)	0.3 (0–59.7)	0.62 (0.03–48)
Albumin	4.0 (1–34)	4.0 (4–5)	5.0 (4–5)
Blood results before therapy – no. (%)			
LDH > ULN	98 (14.8)	65 (19.2)	33 (16.9)
S100 > ULN	26 (3.9)	12 (3.5)	6 (3.1)
Time intervals and frequencies – median in months (range)			
Time till adjuvans	2.0 (0–17)	2.0 (0–16)	2.0 (0–11)
Treatment duration	9.0 (0–19)	7.0 (0–14)	8.0 (0–14)
FU after start	14.0 (0–45)	14.0 (0–53)	11.0 (0–41)
No. of patients progression free and alive – no. (%)			
12 month RFS	479/664 (72.1)	263/337 (78.0)	166/192 (86.5)
RFS not reported	1 (0.15)	2 (0.6)	3 (1.5)
12 month OS	613/639 (95.9)	329/335 (98.2)	186/192 (96.9)
OS not reported	25 (3.8)	4 (1.2)	3 (1.5)

Abbreviations: CLND, complete lymph node dissection; CRP, C-reactive protein; FU, follow up; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; OS, overall survival; RFS, recurrence-free survival; SLND, sentinel lymph node dissection; ULN, upper limit of the norm.

[a]All laboratory values were collected ±7 days of start of therapy and were available for >70% of patients.

days. On top of that, 94 (14.2%), 40 (11.8%) and 37 (19.0%) patients in the NIV, PEM and D + T cohort permanently discontinued adjuvant treatment due to AEs (Table 3). A detailed description of all reported AEs is provided in Table S1.

Subgroup analyses

Several subgroup analyses were performed for patients receiving anti PD-1 and BRAF + MEK treatment (Figure 2a,b). Patients in more advanced stages of the disease had significantly worse RFS than patients in lower stages (Figure 3a,b). Similarly, ulceration status, the number of involved lymph nodes and clinically detectable lymph node metastases negatively affected outcome in both, anti PD-1 and BRAF + MEK inhibitor treated cohorts. In the anti PD-1 treated group, the presence of immune-related AEs was associated with better 12-month RFS (HR 0.560 [95% CI 0.437–0.718], $p = 0.001$), whereas drAEs in the BRAF + MEK group did not affect RFS ($p > 0.05$). A small but statistically significant difference in 12-month OS was calculated in patients with irAEs compared to no-irAEs receiving PD-1 treatment (HR 0.806 [95% CI 0.709–0.917], $p = 0.001$). OS was not affected by AEs in the BRAF + MEK inhibitor treated cohort ($p > 0.05$; Figure S2). Failure to previous adjuvant interferon-α therapy did not affect RFS in the anti PD-1 and BRAF + MEK inhibitor treated cohorts ($p > 0.05$) (Figure S3). TLND compared with SLNB only did not correlate with melanoma recurrence in anti PD-1 nor BRAF + MEK inhibitor-treated patients ($p > 0.05$; Figure 3c,d). Similarly, there was no association between RFS and age, BMI, sex and a post-hoc analysis of eligibility using published criteria of previous pivotal phase III clinical trials in both cohorts (Figure 2a,b; Appendix S1: Material and methods). Less than 15% of cases were assessed

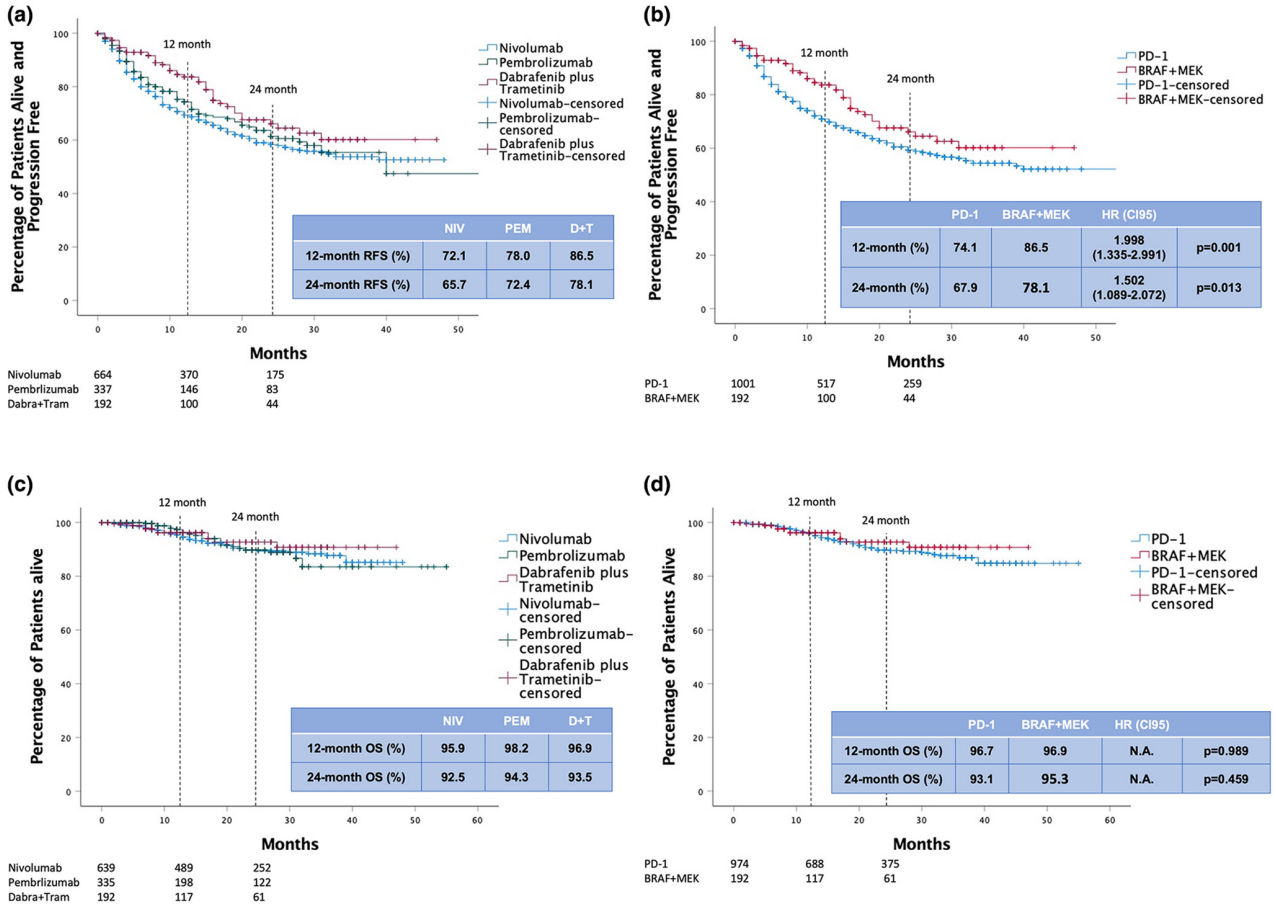


FIGURE 1 Recurrence-free survival (RFS) of patients receiving dabrafenib + trametinib (D + T, red), pembrolizumab (PEM, green), and nivolumab (NIV, blue) (a). Analysis of all patients receiving anti PD-1 and BRAF + MEK inhibitor treatment revealed 12-month RFS of 86.5% for BRAF + MEK versus 74.1% for anti PD-1-treated patients (HR: 1.998, 95% CI: 1.335–2.991; $p = 0.001$) (b). Overall survival (OS) was identical in patients receiving NIV, PEM or D + T (c). There were no differences in OS when all anti PD-1-treated patients were combined and compared to the BRAF + MEK cohort (d).

for PD-L1 expression making sub-group analyses according to PD-L1 status statistically error prone. BRAF (V600) mutant ($n = 347$) and BRAF (V600) wild-type ($n = 589$) patients had similar RFS and OS when receiving adjuvant anti PD-1 treatment (Figure 4). Twelve-month RFS in BRAF (V600) mutant patients receiving adjuvant D + T was significantly better than in BRAF (V600) mutant patients receiving adjuvant anti PD-1-based therapies (HR 2.175 [95% CI 1.421–3.328], $p = 0.001$). However, this difference became smaller over time and did not affect OS (Figure S4).

Machine learning regression model

In further analyses, we investigated the impact of various variables to predict early melanoma recurrence using a machine learning approach (ridge regression procedure with cross validation and hyperparameter optimization via grid search). Since we considered kinase inhibition to be inherently different to immunotherapy and because the majority of patients received anti PD-1-based adjuvant melanoma therapy, we focused only on immune-checkpoint-treated patients for this analysis. The regression model achieved an AUC of 0.65 indicating rather poor predictive capacity (Figure S5A). Blotting precision and recall scores as a function of the decision thresholds and aiming at high specificity shows that the model is able to predict a large number of true-negative patients, however, at the expense of precision (high false-positive rate). In this case (Figure S5B, black dotted line), sensitivity and specificity of the regression model were calculated with 97.2% and 10.1%, respectively. Known coefficients including disease stage, tumour thickness and ulceration, but also new variables including lactate dehydrogenase (thus far mainly validated for advanced disease, but not in the adjuvant setting) and the number of involved lymph nodes at diagnosis were found to be predictors of disease recurrence. Higher age, and higher absolute leucocyte, eosinophil and lymphocyte counts were predictors of lower recurrence risk (Figure S5C). The addition of other variables did not further improve the model.

DISCUSSION

This study covering real-world data from 1198 patients collected at 39 skin cancer centers in Germany, Austria and

TABLE 3 Treatment failures

	Nivolumab (*N* = 664)	Pembrolizumab (*N* = 339)	Dabrafenib + trametinib (*N* = 195)
Treatment interruption due to adverse events[a] – no. (%)	82 (12.3)	33 (9.7)	64 (32.8)
Duration of interruption – median days (range)	28.0 (2.0–125.0)	28.0 (7.0–120.4)	18.0 (1.0–90.0)
End of therapy due to – no. (%)			
Adverse event	94 (14.2)	40 (11.8)	37 (19.0)
Melanoma recurrence	241 (36.3)	100 (29.5)	45 (23.1)
Local recurrence	79 (11.9)	24 (7.1)	11 (5.6)
Lymph node metastasis only	58 (8.7)	22 (6.5)	11 (5.6)
Distant metastasis only	104 (15.7)	40 (11.8)	23 (11.8)
Distant + LN metastasis	47 (7.1)	19 (5.6)	8 (4.1)
Not reported	–	1 (0.3)	–
Time to recurrence (months) – median (range)	6.0 (0–39)	6.0 (1–53)	10.0 (1–31)
Therapy of recurrence – no. (%) of recurrences			
Surgery	129 (53.5)	21 (21.0)	15 (33.3)
Radiation therapy	56 (23.2)	47 (47.0)	19 (42.2)
Systemic therapy	166 (68.9)	83 (83.0)	36 (80.0)
Not reported	14 (5.8)	5 (5.0)	1 (0.45)

Abbreviations: AE, adverse event; LN, lymph node.

[a]Adjuvant treatment was reestablished in all cases.

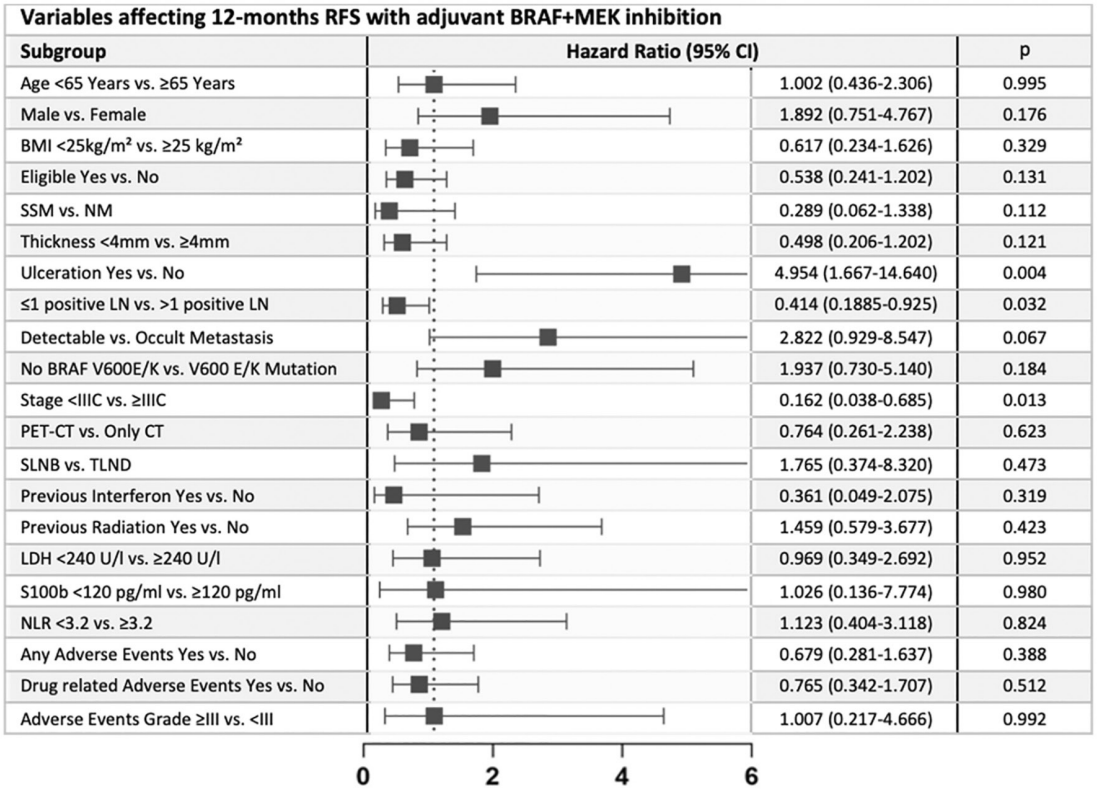
Switzerland receiving modern adjuvant melanoma treatment for fully resected high-risk melanoma demonstrates that early disease recurrence poses a significant clinical challenge. During the observation period of this study, 386/1198 (32.2%) patients recurred of which most of the events were recorded in the first 12 months resulting in 12-month RFS rates of 72.1%, 78.0% and 86.5% for NIV, PEM and D + T, respectively. By that, data from this study met the expectations from the three landmark studies CheckMate 238, Keynote-054 and Combi-AD in which 12-month RFS of 70.5% for NIV, 75.4% for PEM and 88% for D + T were reported.[3,6,8] It is encouraging to see that early treatment efficacy reported in pivotal clinical phase III studies can also be achieved in daily practice, regardless of inclusion and exclusion criteria typically used in clinical trials.

Even though it is tempting to directly compare PD-1 and BRAF + MEK-treated patients in the present study, such comparisons must be done carefully. This study is retrospective in nature and thus subject to certain limitations, particularly when compared to randomized controlled trials. Thus, results always bare the risk of being biased by non-medical aspects of patient care such as reimbursement rules or individual preferences of patients and physicians. It is also evident that the PD-1 and BRAF + MEK patient cohorts are not fully balanced in this study. Yet, results highlight that, even though outcome data using anti PD-1-based checkpoint blockade and BRAF + MEK inhibition have improved RFS significantly compared to historical interferon-α therapy, a significant fraction of high-risk melanoma patients still progress during, or after modern adjuvant therapy.[9,10]

This study focused on early melanoma recurrence, which is most likely a read-out of intrinsic, primary therapy resistance.[11] To identify biomarkers of early recurrence, readily available clinical, histological and laboratory parameters were tested for their predictive potential. Even though some variables including ulceration status and higher disease stage could be statistically confirmed for indicating increased risk of disease recurrence in both PD-1 and BRAF + MEK-treated patients (Figure 2), no individual variable, showed a clinically meaningful correlation with 12-month RFS. Interestingly, and similar to results in patients receiving treatment for advanced disease, irAEs were indicators of improved 12-month RFS in the adjuvant anti PD-1 group.[12,13] DrAEs had no effect on RFS with adjuvant BRAF + MEK inhibitor treatment (Figure S2). Again, these data must be interpreted with care, as it is possible that the reporting of AEs is less stringent in daily clinical routine compared to a randomized controlled trial. In the present study, lower numbers and less severe AEs compared to data from randomized controlled trials were submitted. Yet, these data might also indicate that some AEs reported in pivotal clinical trials are only of limited clinical relevance in daily routine.

Since single variables were unable to robustly predict early disease recurrence, a multivariate machine learning regression model using a collection of variables was trained to predicting early melanoma recurrence risk. This model was weak in detecting patients at high risk (AUC = 0.65). With a negative predictive value of 86.7% the algorithm was able to robustly predict true negatives for early disease recurrence, however, at the expense of high numbers of false positives (positive predictive value 37.6%). While it is possible that results can be improved with even larger data sets, findings also highlight the limits of variables collected in routine settings to predict patients at high risk of early disease recurrence.

(a)



(b)

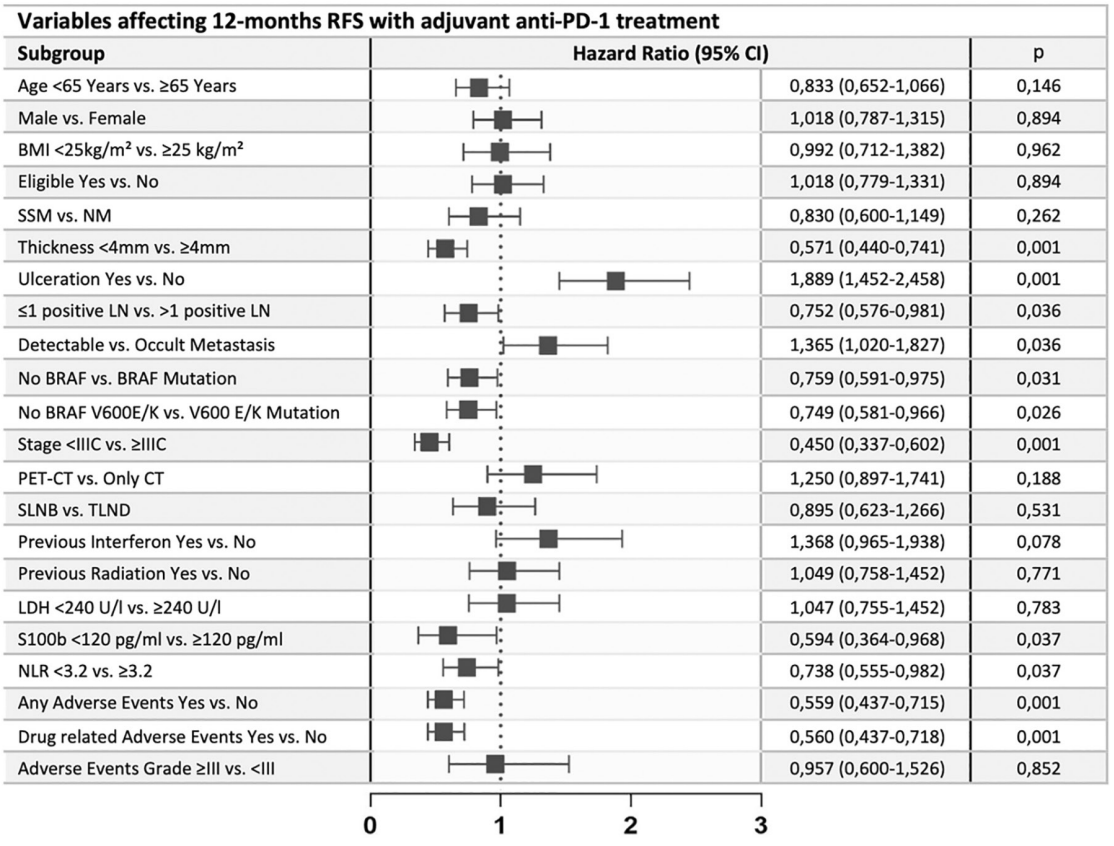


FIGURE 2 Variables investigated for their potential to affect recurrence-free survival (RFS) in patients receiving adjuvant anti PD-1 (a) and adjuvant BRAF + MEK treatment (b).

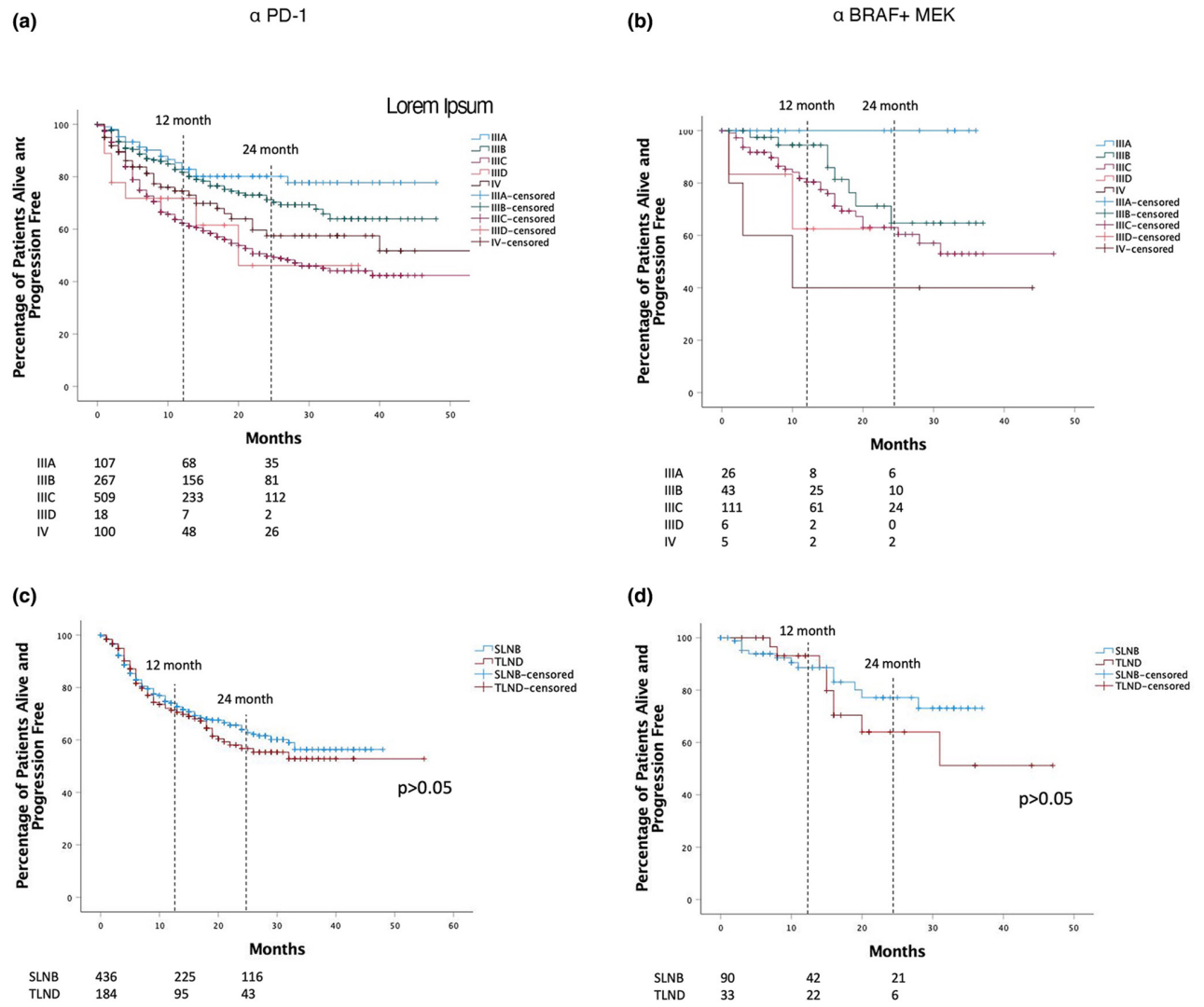


FIGURE 3 Recurrence-free survival (RFS) according to disease stage in patients receiving adjuvant anti PD-1 treatment (a) and adjuvant BRAF + MEK treatment (b). Comparison of patients who received total lymph node dissection (TLND) or sentinel lymph node biopsy only (SLNB) revealed no differences in RFS in the PD-1 (c) and BRAF + MEK (d) treatment groups.

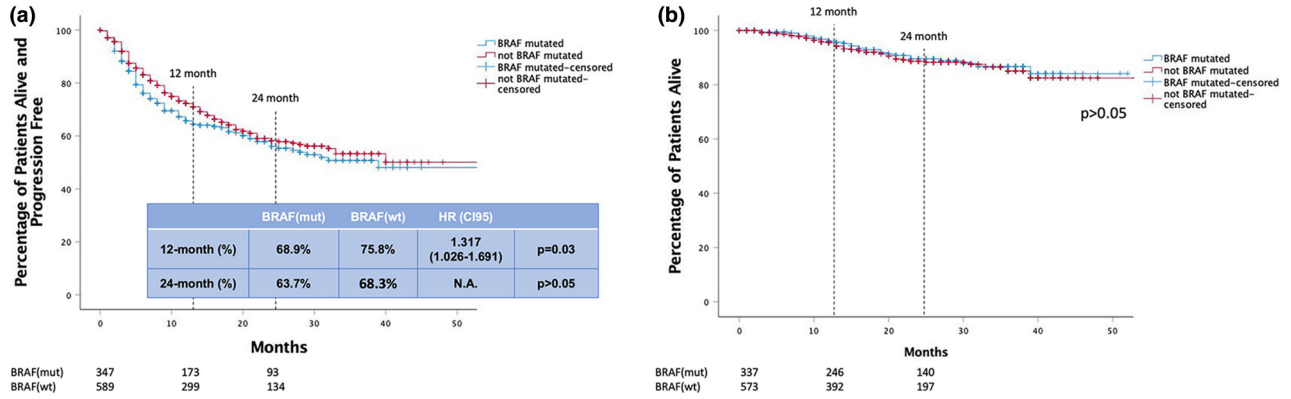


FIGURE 4 Recurrence-free survival (RFS) and overall survival (OS) with adjuvant PD-1 antibody treatment in patients according to their BRAF (V600) mutation status: Despite small differences at month 12, overall RFS (a) and OS (b) were similar in BRAF (V600) mutant and BRAF (V600) wild-type patients.

An important finding of this study is that TLND did not affect 12-month RFS in either the anti PD-1 treated or BRAF + MEK inhibitor treated cohorts. The fact that several skin cancer centers did not perform TLND in every case of positive SLNB is indicative of a DACH-wide shift in melanoma patient care. Data from this study supports

that radical surgery should only be considered in selected patients.[14–16]

Results did not show any new safety signals for any of the investigated drugs. Overall, AEs were more common in BRAF + MEK inhibitor compared to anti PD-1-treated patients, which is in line with previous publications.[17]

In this study, PD-1 blockade dominated the adjuvant melanoma treatment landscape; however, all adjuvant treatment options for high-risk melanoma patients are valuable and enrich patients' treatment options. From indirect comparisons of the three landmark studies we have learned that, even though adjuvant BRAF + MEK inhibition shows superior RFS at 12 months, early differences in RFS level out over time.[18] At 3 years, RFS curves in all three studies flatten with RFS of 58% (NIV), 63.7% (PEM) and 58% (D + T), indicating similar long-term benefits of modern adjuvant melanoma therapy. It is likely, that patients in the present real-world study will experience comparable treatment outcomes over time. First, yet immature, 24-month RFS and OS data indicate that real-world treatment outcomes follow similar trajectories as results from pivotal phase III clinical trials.

Treatment decisions are based on several (individual) variables and preferences of patients and physicians alike, including a risk assessment of the induction of potentially life-changing AEs all of which might have influenced the results of this work.[19] It is also worth noticing that this study only included patients from skin cancer centers in the DACH-region. Limitations of this study further include its retrospective design and that a small number of patients was still receiving adjuvant treatment at the time of data cut-off (October 2021). However, most patients completed treatment and additional analyses comparing the entire cohort of this study to all patients who already completed treatment did not reveal significant differences.

Strengths of this study are the size of the study cohort, the large collection of variables covering patient and tumour characteristics, laboratory findings, as well as real-world treatment, outcome and real-world safety data, all of which provide new insights into the characteristics of high-risk melanoma patients receiving modern adjuvant melanoma therapy. Additionally, this study included a small number of patients receiving off label adjuvant melanoma treatment including BRAF + MEK inhibition for fully resected stage IV disease. This highlights, that patients and physicians also opt to use modern adjuvant treatments outside of what has been tested in large clinical trials in carefully selected situations.

CONCLUSION

This study provides real-world insights into early efficacy and safety outcomes using adjuvant anti PD-1 and BRAF + MEK inhibitor treatment for high-risk melanoma patients and supports their use in clinical routine. Data shows that TLND does not improve 12-month RFS and OS in SLNB-positive patients receiving modern adjuvant treatment.

AUTHOR CONTRIBUTIONS

KS and CP designed and executed the study and wrote the manuscript. SK, CP and AB performed the statistical analyses. All other coauthors collected and contributed patient data for the study and proof-read the manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

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

ETHICAL APPROVAL

This study was approved by the Ethical Committee of the Technical University of Munich. All authors consent to publication of the present manuscript.

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REFERENCES

1. Steininger J, Gellrich FF, Schulz A, Westphal D, Beissert S, Meier F. Systemic therapy of metastatic melanoma: on the road to cure. Cancers. 2021;13:1430.
2. Dimitriou F, Long GV, Menzies AM. Novel adjuvant options for cutaneous melanoma. Ann Oncol. 2021;32:854–65.
3. Ascierto PA, Del Vecchio M, Mandalá M, Gogas H, Arance AM, Dalle S, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21:1465–77.
4. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377:1824–35.
5. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. J Clin Oncol. 2020;38:3925–36.
6. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378:1789–801.
7. Dummer R, Hauschild A, Santinami M, Atkinson V, Mandalà M, Kirkwood JM, et al. Five-year analysis of adjuvant dabrafenib plus trametinib in stage III melanoma. N Engl J Med. 2020;383:1139–48.
8. Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017;377:1813–23.
9. Ives NJ, Suciu S, Eggermont AMM, Kirkwood J, Lorigan P, Markovic SN, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Eur J Cancer. 2017;82:171–83.
10. Eggermont AM, Suciu S, Testori A, Kruit WH, Marsden J, Punt CJ, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer. 2012;48:218–25.
11. Owen CN, Shoushtari AN, Chauhan D, Palmieri DJ, Lee B, Rohaan MW, et al. Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy. Ann Oncol. 2020;31:1075–82.
12. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6:38.
13. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer. 2019;7:306.
14. Stadler R, Leiter U, Garbe C. Lack of survival benefit in sentinel lymph node-positive melanoma with immediate complete lymphadenectomy – a review. J Dtsch Dermatol Ges. 2019;17:7–13.
15. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer NH, Berking C, et al. Final analysis of DeCOG-SLT trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol. 2019;37:3000–8.
16. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376:2211–22.
17. Longo C, Pampena R, Lallas A, Kyrgidis A, Stratigos A, Peris K, et al. Adjuvant therapy for cutaneous melanoma: a systematic review and network meta-analysis of new therapies. J Eur Acad Dermatol Venereol. 2020;34:956–66.
18. Toor K, Middleton MR, Chan K, Amadi A, Moshyk A, Kotapati S. Comparative efficacy and safety of adjuvant nivolumab versus other treatments in adults with resected melanoma: a systematic literature review and network meta-analysis. BMC Cancer. 2021;21:3.
19. Lodde G, Forschner A, Hassel J, Wulfken LM, Meier F, Mohr P, et al. Factors influencing the adjuvant therapy decision: results of a real-world multicenter data analysis of 904 melanoma patients. Cancer. 2021;13:2319.

SUPPORTING INFORMATION

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

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