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Influence of adjuvant therapies on organ-specific recurrence of cutaneous melanoma: A multicenter study on 1383 patients of the prospective DeCOG registry ADOReg

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Abstract

This study investigated whether adjuvant treatments in stage III cutaneous melanoma (CM) influenced patterns of recurrence. Patients with primary ($n = 1033$) or relapsed CM ($n = 350$) who received adjuvant therapies with Nivolumab (N), Pembrolizumab (P), or Dabrafenib and Trametinib (D + T) were extracted from the prospective multicenter real-world skin cancer registry ADOReg. Endpoints were progression-free survival (PFS), distant metastasis-free survival (DMFS), organ-specific DMFS, and overall survival (OS). For primary cases, D + T indicated an improved PFS (1- and 2-year PFS: 90.9%; 82.7%) as compared to P (81.0%, 73.9%; $p = .0208$), or N (83.8%, 75.2%; $p = .0539$). *BRAF*-mutated(mut) CM demonstrated significantly lower PFS ($p = .0022$) and decreased DMFS ($p = .0580$) when treated with immune checkpoint inhibitor (ICI) instead of D + T. Besides, *NRAS*-mut CM tended to perform worse than wt CM upon ICI (PFS: $p = .1349$; DMFS: $p = .0540$). OS was similar between the groups. Relapsed cases showed decreased PFS, DMFS, and OS in comparison to primary (all: $p < .001$), without significant differences between the subgroups. Organ-specific DMFS was significantly altered for primary cases with bone ($p = .0367$) or brain metastases ($p = .0202$). In relapsed CM, the frequency of liver (D + T: 1.5%; P: 12%; N: 9%) and LN metastases (D + T: 1.5%; P: 12%; N: 10.2%) was significantly lower with adjuvant D + T than ICI. *NRAS*-mut CM showed increased recurrence in

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primary and relapsed cases. These data show that adjuvant D + T is superior to ICI in primary *BRAF*-mut CM.

KEYWORDS

adjuvant treatment, immune checkpoint inhibition, melanoma, targeted therapy, therapy resistance

What's New?

While adjuvant therapies might differ in protecting against metastases to certain organs, only few clinical studies report on organ-specific recurrence. This large real-world, multicenter retrospective study on melanoma recurrence despite adjuvant therapy provides evidence that primary and relapsed cutaneous melanoma (CM) have distinct patterns of recurrence. Primary but not relapsed *BRAF*-mutated CM showed improved progression-free and distant metastasis-free survival when treated with adjuvant targeted therapy compared to immune checkpoint inhibitors (ICIs). In relapsed CM, the frequency of liver and lymph node metastasis was significantly lower with adjuvant-targeted therapy than with ICIs.

1 | INTRODUCTION

Cutaneous melanoma (CM) is a malignancy that develops from melanocytes of the skin. It is an example of organotropic metastasis, as it commonly spreads to the skin, lymph node (LN), lung, liver, and brain.[1] The prognosis of metastatic CM has been improved by immune checkpoint inhibitors (ICIs), antibodies against programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or targeted therapies (TTs) with BRAF/MEK inhibitors (BRAFi/MEKi).[2,3] However, organ-specific metastases diminish therapy responses. Liver metastasis is well documented as a poor prognostic factor for ICI[4,5] or TT.[6] Brain metastases reduce both the duration of overall response to BRAFi/MEKi and progression-free survival (PFS).[7] Moreover, response to ICI is decreased in patients with symptomatic brain metastases.[8]

To prevent metastatic disease, ICIs or TTs are applied in an adjuvant setting. Anti-PD-1 inhibition with Nivolumab or Pembrolizumab or TT with Dabrafenib and Trametinib significantly increases relapse-free survival (RFS) in stage III CM with locoregional metastasis or stage IV CM after resection of metastases.[9–11] Besides stage III, adjuvant ICI is also approved for stage IIB and IIC high-risk CM, as it shows increased distant metastasis-free survival (DMFS) and lower risk of recurrence.[12–15] However, around 25%–34% of patients suffer from melanoma recurrence with distant metastases despite adjuvant ICI.[16,17] Interestingly, adjuvant ICI seems to influence patterns of metastasis. Adjuvant therapy with Pembrolizumab in stage III/IV significantly decreases lung or LN metastasis as compared to placebo, whereas no significant reduction is seen for liver, bone, or brain metastasis.[16] Likewise, in stage IIB/IIC, a strong reduction of the number of patients with lung metastases as first distant site is found upon adjuvant Pembrolizumab. In contrast, the numbers of brain, LN, liver, or bone metastases are similar between the adjuvant Pembrolizumab and placebo group.[12] For adjuvant treatment with Nivolumab, no comparisons with placebo can be drawn from the CheckMate 238 trial.[17] As demonstrated in the CheckMate 76K study, adjuvant Nivolumab in stage IIB and IIC effectively reduced local and distant recurrence.[15] This effect is confirmed for skin, lung, and LN metastasis. This analysis is currently limited by the low number of recurrences.[15] Regarding adjuvant TT with Dabrafenib and Trametinib, relapses more frequently occur after the end of treatment, with two thirds being diagnosed as metastatic disease.[18]

We hypothesized that the protective properties of adjuvant ICI or TT in stage III/IV CM might have influenced the organ-specific pattern of melanoma recurrence. Therefore, 1383 patients from the prospective skin cancer registry ADOReg who received adjuvant treatment with Dabrafenib and Trametinib, Nivolumab, or Pembrolizumab were analyzed.

2 | MATERIALS AND METHODS

2.1 | Data collection and study population

A retrospective multicenter analysis was performed on a data set obtained from the prospective multicenter skin cancer registry ADOReg of the German Dermatologic Cooperative Oncology Group (DeCOG). Patients with CM who received adjuvant treatment with ICI (anti-PD-1 inhibitors Pembrolizumab or Nivolumab) or TT (BRAFi/MEKi Dabrafenib and Trametinib) in stage III by AJCCv8 were selected. Acral lentiginous (ALM), uveal (UM), or mucosal melanoma (MM) were excluded. A total of 1383 patients were included, whose data were entered into the ADOReg by 52 skin cancer centers. Only patients were included who received adjuvant treatment after approval by the regulatory authorities (EMA): 07/2018 Nivolumab, 07/2018 Dabrafenib and Trametinib, 10/2018 Pembrolizumab. Therefore, adjuvant therapies were initiated between July 2018 and October 2022. Data cutoff was November 1, 2022. Detailed information on patient and tumor characteristics and the course of treatment were extracted.

2.2 | Outcomes

Endpoints of this study were overall survival (OS) which was defined as interval between the date of first diagnosis and death. PFS was defined as time between initiation of adjuvant therapy and disease progression (in-transit, LN, or distant metastasis). DMFS was defined as time between the onset of adjuvant therapy and detection of stage IV disease. Time periods for PFS, DMFS, or OS were censored for patients who did not relapse, develop distant metastasis, or survive, respectively, and the dates of last follow-up were used. For relapsed cases, time to recurrence (TTR) from the first diagnosis of CM until progression into stage III disease was calculated. Furthermore, organ-specific DMFS was calculated for patients of both cohorts.

2.3 | Statistical analysis

SAS Analytics software, release 9.4 (SAS Institute Inc., NC, USA) was used for statistical analyses. The therapy groups were compared regarding the following variables: year of birth, age at diagnosis, gender, tumor subtype, BRAF status, localization of CM, Breslow thickness, number of mitoses, ulceration, stage according to AJCC, completion of sentinel LN dissection (SLND), and status of sentinel LN. For these comparisons, X^2 tests, Fisher's exact tests, one-way ANOVA, or Kruskal–Wallis tests were performed, as appropriate. In case of significance or statistical tendency ($p < .10$), pairwise comparisons with a X^2 test, Fisher's exact test, Scheffe test, or Wilcoxon two-sample test were added. The following time points were retrieved from the data set: date of first diagnosis of CM, date of stage III disease, date of stage IV disease, and date of organ-specific metastases. Kaplan–Meier curves were computed, and survival curves were compared by log-rank tests. Based on the Cox proportional hazards model, univariable and multivariable analyses were performed to assess an influence of the subgroup characteristics on PFS in primary CM. Test results with $p < .05$ were considered as statistically significant. Graphical displays were created with Microsoft Excel (Microsoft, WA, USA) and GraphPad Prism 9 (GraphPad, MA, USA).

3 | RESULTS

3.1 | Description of the study cohorts

A total of 2614 patients with stage III CM were extracted from the ADOReg database (Figure 1). Cases who received adjuvant ICI (anti-PD-1 inhibitor: Pembrolizumab [P] or Nivolumab [N]) or TT (BRAFi/MEKi: Darbafenib and Tramentinib [D + T]) were selected. The study population was separated whether they were diagnosed with stage III CM de novo (primary cases; $n = 1033$) or after secondary progression into stage III (relapsed cases; $n = 350$).

3.2 | Patient characteristics of primary CMs (de novo stage III)

Primary cases were mostly diagnosed with nodular CM ($n = 433$) and were alive at time of data cutoff (94.58%). Among the patients tested, a *BRAF* mutation was found in 56.3% and an *NRAS* mutation in 33.7%. Three quarter were treated with ICI, either Nivolumab ($n = 466$; 45.1%) or Pembrolizumab ($n = 274$; 26.5%), while around one quarter received Dabrafenib and Trametinib ($n = 293$; 28.3%) (Table 1). The median follow-up time was 23.4 months for Dabrafenib and Trametinib, 28.9 months for Nivolumab, and 24.8 months for Pembrolizumab. Patients who received adjuvant TT were significantly younger (D + T:

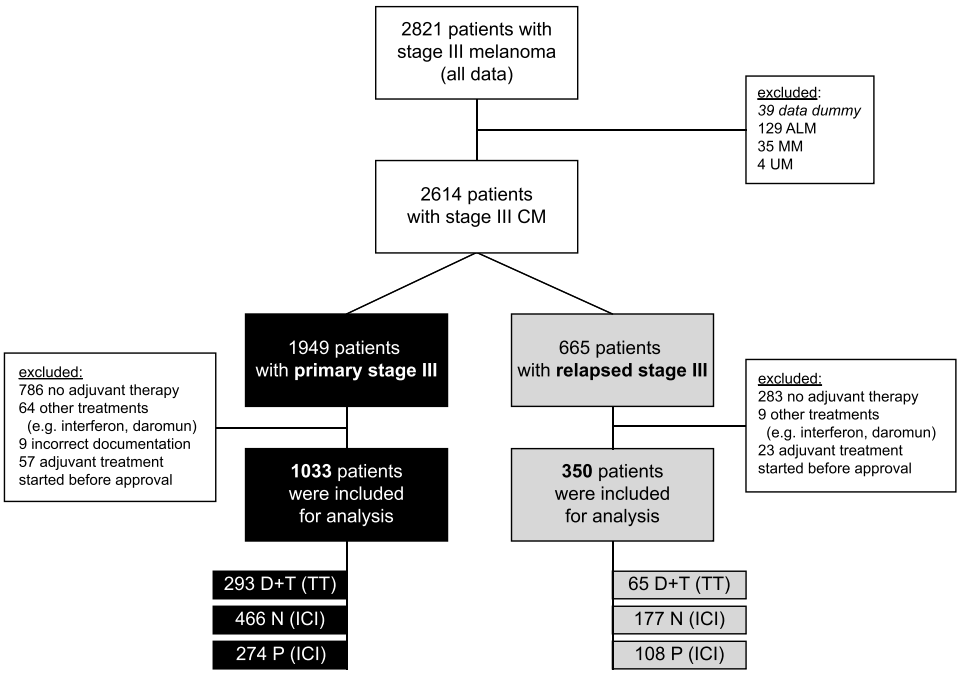


FIGURE 1 Patient selection flow chart. Stage III melanoma patients were extracted from the ADOReg registry ($n = 2821$). A total of 2614 patients with stage III CM were identified after exclusion of certain histological subtypes (ALM, MM, and UM). Patients were then allocated whether they were initially diagnosed with stage III CM ($n = 1949$) or during follow-up in case of a relapse of CM ($n = 665$). Last, only patients with approved adjuvant treatments (Dabrafenib and Trametinib [D + T], Nivolumab [N], or Pembrolizumab [P]) were included in the final data analysis. ALM, acral lentiginous melanoma; CM, cutaneous melanoma; MM, mucosal melanoma; UM, uveal melanoma.

TABLE 1 Subgroup analysis of primary CMs.

	Dabrafenib/Trametinib	Nivolumab	Pembrolizumab	*p* Value
Number of patients	293	466	274	
Follow-up time (months)	23.4	28.9	24.8	
Age	57.6 (±14.3)	60.9 (±13.8)	62.9 (±13.6)	<.0001 D + T vs. N: **.0059** D + T vs. P: **<.0001** N vs. P: .1697
Gender				
Male	54.95% (161)	61.80% (288)	56.20% (154)	.1225
Female	45.05% (132)	38.20% (178)	43.80% (120)	
Tumor subtype				
NMM	41.98% (123)	41.20% (192)	43.07% (118)	**.0436**
SSM	34.81% (102)	26.82% (125)	29.93% (82)	D + T vs. N: **.0160**
LMM	0.34% (1)	1.72% (8)	2.55% (7)	D + T vs. P: .1046
Unclassified[a]	22.87% (67)	30.26% (141)	24.45% (67)	N vs. P: .3335
Breslow thickness	3.73 (±3.35)	3.96 (±3.27)	4.06 (±3.41)	.4079
Ulceration (yes)	36.86% (108)	39.91% (186)	37.59% (103)	.2402
Number of mitoses	3.94 (±3.62)	4.39 (±5.48)	4.79 (±4.46)	.1828
AJCC stage				
III unspecified[a]	0.34% (1)	0.64% (3)	0% (0)	.0809
IIIA	21.84% (64)	15.02% (70)	16.42% (45)	D + T vs. N: **.0328**
IIIB	33.79% (99)	33.26% (155)	32.12% (88)	D + T vs. P: .0856
IIIC	40.27% (118)	48.71% (227)	49.27% (135)	N vs. P: .8657
IIID	3.75% (11)	2.36% (11)	2.19% (6)	
SLND (yes)	80.20% (235)	72.32% (337)	72.99% (200)	**.0383** D + T vs. N: **.0141** D + T vs. P: **.0423** N vs. P: .8425
SLN positive	94.89% (223)	88.72% (299)	87.50% (175)	**.0150**
Mean no. of positive SLN	1.16	1.09	1.08	.2708
BRAF mutation	97.61% (286)	31.12% (145)	25.91% (71)	**<.0001** D + T vs. N: **<.0001** D + T vs. P: **<.0001** N vs. P: .0966
NRAS mutation	0.34% (1)	16.3% (76)	21.90% (60)	**<.0001** D + T vs. N: **<.0001** D + T vs. P: **<.0001** N vs. P: .2145
Adjuvant radiotherapy	8.53% (25)	9.44% (44)	10.95% (30)	.6145
AWD/NED	94.88% (278)	94.42% (440)	94.53% (259)	.9797
DC	5.12% (15)	5.58% (26)	5.47% (15)	
Localization[b]				
Head/neck	9.56% (28)	9.01% (42)	10.95% (30)	.1725
Trunk	40.96% (120)	37.34% (174)	35.77% (98)	
Upper extremity	15.02% (44)	17.60% (82)	20.44% (56)	
Lower extremity	24.57% (72)	23.39% (109)	26.28% (72)	

(Continues)

TABLE 1 (Continued)

	Dabrafenib/Trametinib	Nivolumab	Pembrolizumab	*p* Value
LN	4.44% (13)	3.43% (16)	1.82% (5)	
Other	5.46% (16)	9.23% (43)	4.74% (13)	

Abbreviations: AWD, alive with disease; CM, cutaneous melanoma; DC, deceased; LMM, lentigo maligna melanoma; LN, lymph node; NED, no evidence of disease; NMM, nodular melanoma; SLN, sentinel lymph node; SLND, sentinel lymph node dissection; SSM, superficial spreading melanoma.
[a]Not otherwise specified/ not documented.
[b]Grouped according to ICD-10 codes, please refer to Table S1 for details.

57.6 years; N: 60.9 years; P: 62.9 years; D + T vs. N: $p = .0059$; D + T vs. P: $p < .0001$). Female and male patients were equally distributed among all treatment groups ($p = .1225$). The major tumor subtype in all subgroups was nodular melanoma (NMM). Superficial spreading melanoma (SSM) and unclassified CM were unequally distributed ($p = .0436$), with a higher frequency of SSM in patients with Dabrafenib and Trametinib, while unclassified cases were more frequent in the Nivolumab cohort. The tumor thickness (Breslow) ($p = .4079$), ulceration ($p = .2402$), and numbers of mitoses ($p = .1828$) were equally distributed among the subgroups. According to the AJCC stage, patients with Dabrafenib and Trametinib had lower stages than in the Nivolumab ($p = .0328$) or the Pembrolizumab cohort ($p = .0856$). No differences in the localization of the primary CM were found, as these were localized mostly at the trunk or the lower extremity ($p = .1725$) (Table S1). SLND was increasingly performed in patients with Dabrafenib and Trametinib as compared to both ICI-treated subgroups (D + T vs. N: $p = .0141$; D + T vs. P: $p = .0423$). The numbers of positive sentinel LN were similar between all subgroups ($p = .2708$). As expected, mutations of *BRAF* were more frequent in the TT subgroup, while mutations of NRAS were increased in the ICI subgroups. The Nivolumab subgroup tended to show higher numbers of *BRAF* mutations in relation to Pembrolizumab ($p = .0966$). Ninety-nine (9.6%) of all patients also received adjuvant radiotherapy upfront TT or ICI ($p = .6145$).

3.3 | Treatment course of adjuvant therapies for primary CMs

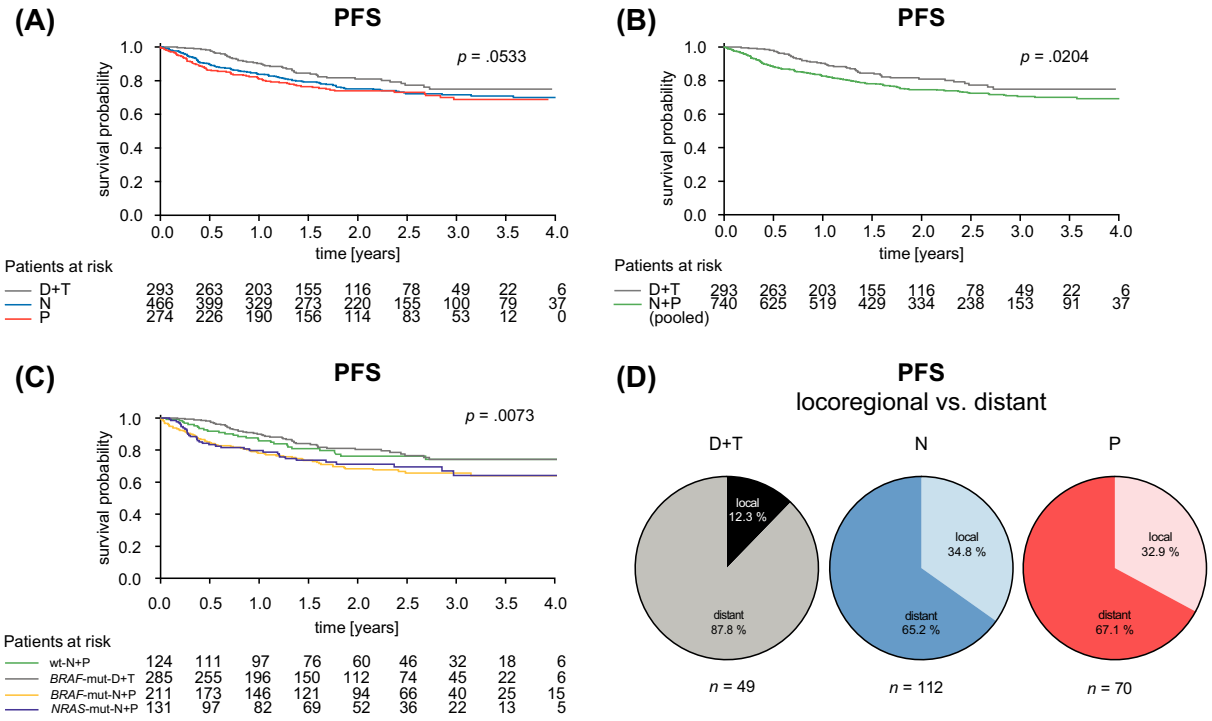
The mean time from first diagnosis of stage III CM to adjuvant treatment initiation ranged from 5.2 months in the Pembrolizumab group to 6.1 months in the Dabrafenib and Trametinib group ($p = .2165$) (Table S2). For 729 patients (70.6%), data of the treatment duration were available (Table S3). Adjuvant therapies were administered less than 1 year in all groups, the mean time was 8.6 months, respectively ($p = .1954$). Most commonly, treatment was stopped at the regular endpoint (35.3%), due to toxicity (13.4%), disease progression (10.8%), or patient's request (4.3%) (Tables S4 and S5). Treatment was still ongoing in 304 patients (29.4%) at the time of data cutoff.

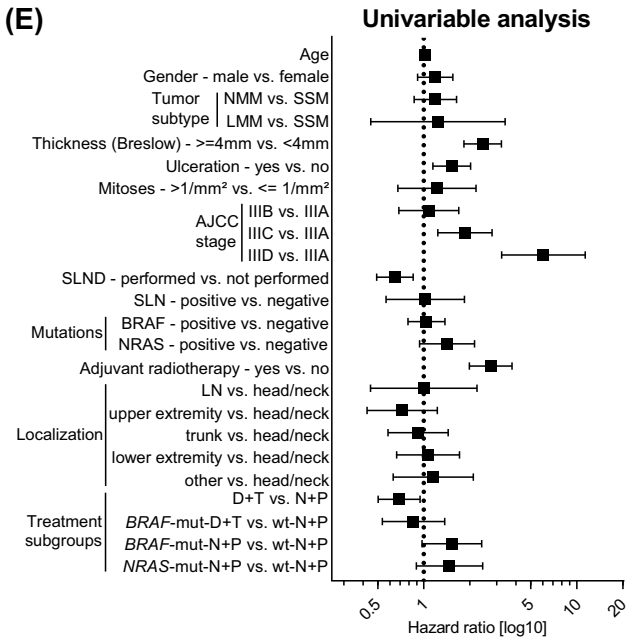
Two hundred and thirty-one patients (22.4%) with primary stage III CM suffered from melanoma recurrence, either locoregional disease with in-transit metastasis or LN macrometastasis, or stage IV disease. The censored 1-year and 2-year PFS were 90.3% and 81.0% for Dabrafenib and Trametinib, 83.8% and 75.2% for Nivolumab and 81.0% and 73.9% for Pembrolizumab ($p = .0533$), respectively (Figure 2A). A significant difference between the cases treated with Dabrafenib and Trametinib was found in relation to all ICI-treated cases (N + P: 82.8%, 74.7%) ($p = .0204$) (Figure 2B). PFS was similar between Nivolumab and Pembrolizumab treated patients ($p = .5084$). After stratification by *BRAF* and *NRAS* status, the curves significantly differed from each other ($p = .0073$) (Figure 2C). There was no difference between wildtype (wt) CM treated with ICI and *BRAF*-mutated (mut) cases with TT ($p = .5627$). Notably, *BRAF*-mut CM showed significantly lower PFS when treated with ICI as compared to TT ($p = .0022$). Among the ICI treatment cohorts, *BRAF*-mut ($p = .0656$) or *NRAS*-mut ($p = .1349$) patients tended to perform worse than wt cases. Progression was most frequently detected at distant sites (D + T: 87.76%; N: 65.18%; P: 67.14%), while locoregional disease was diagnosed less (D + T: 12.24%; N: 34.82%; P: 32.86%) (Figure 2D). Univariable and multivariable analyses (Figure 2E,F) revealed significant influences of the age ($p = .0260$), tumor thickness ($p = .0029$), stage (IIID vs. IIIA: $p = .0103$), and adjuvant radiotherapy ($p < .0001$) on PFS. The tumor stage was differed between the subgroups ($p = .0196$) (Table S6A–C). However, separate analyses of the PFS for each substage (IIIA–IIID) showed no differences (Figure S1A–D). Altogether, after adjusting for age, tumor thickness, stage and adjuvant radiotherapy, adjuvant TT significantly improved PFS as compared to ICI (hazard ratio: 0.705; $p = .0457$).

3.4 | Organ-specific DMFS and pattern of recurrence despite adjuvant treatment of primary CMs

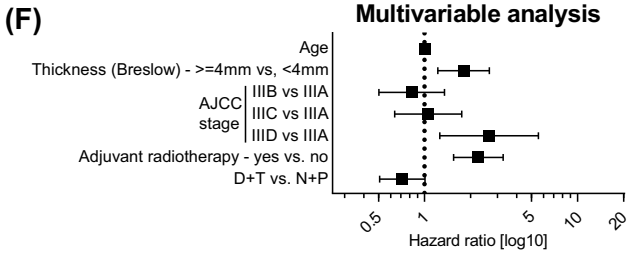
Stage IV disease was reported in 182 patients (17.6%) (Table S7). The censored 1-year and 2-year DMFS were 91.1% and 83.0% for Dabrafenib and Trametinib, 88.8% and 82.9% for Nivolumab and 85.2% and 79.5% for Pembrolizumab, respectively ($p = .2760$) (Figure 3A and Figure S2A). Death was reported in 56 patients of primary cases. The censored 1-year and 2-year OS were 98.5% and 95.0% for Dabrafenib and Trametinib, 97.3% and 95.0% for Nivolumab and 98.0% and 94.5% for Pembrolizumab, respectively ($p = .9645$) (Figure S2B,C). Stratification by the mutational status revealed differences for DMFS ($p = .0549$), but not OS ($p = .4866$) (Figure S3A,B). *BRAF*-mut CM tended to develop metastatic disease earlier with ICI than TT ($p = .0580$), while no difference was found between *BRAF*-mut with TT and wt patients with ICI ($p = .3600$). *NRAS*-mut patients tended to

perform worse than wt cases upon ICI ($p = .0540$). Organ-specific DMFS was analyzed (Figure 3B). The survival of patients with metastasis to the bones ($p = .0367$) or the brain ($p = .0202$) significantly differed between the cohorts, while it was similar for patients with metastasis to the skin, distant LN, lungs, liver, or other sites (Figure S4A–G). The mean time from start of adjuvant therapy to the





Hazard ratio	95 % CI	p value
1.010 / year	1.001 - 1.020	**.0327**
1.188	0.911 - 1.551	.2040
1.190	0.866 - 1.636	.2838
1.236	0.450 - 3.398	.6810
2.425	1.829 - 3.215	**< .0001**
1.523	1.146 - 2.025	**.0037**
1.218	0.677 - 2.191	.5096
1.079	0.687 - 1.694	.7412
1.855	1.233 - 2.791	**.0030**
6.051	3.224 - 11.355	**< .0001**
0.648	0.492 - 0.853	**.0020**
1.022	0.567 - 1.842	.9424
1.040	0.787 - 1.374	.7855
1.421	0.940 - 2.146	.0955
2.736	1.986 - 3.770	**< .0001**
1.001	0.449 - 2.227	.9984
0.723	0.426 - 1.227	.2295
0.918	0.584 - 1.443	.7106
1.065	0.664 - 1.709	.7936
1.153	0.632 - 2.105	.6424
0.690	0.503 - 0.946	**.0212**
0.855	0.535 - 1.368	.5142
1.525	0.974 - 2.389	.0651
1.472	0.894 - 2.425	.1288



Hazard ratio	95 % CI	p value
1.012 / year	1.001 - 1.023	**.0260**
1.801	1.222 - 2.653	**.0029**
0.824	0.503 - 1.349	.4414
1.057	0.638 - 1.750	.8299
2.641	1.257 - 5.549	**.0103**
2.247	1.547 - 3.263	**< .0001**
0.705	0.501 - 0.993	**.0457**

FIGURE 2 Legend on next page.

development of skin metastases was 377.4 d, 411.9 d for LN metastases, 390.9 d for lung metastases, 457.7 d for liver metastases, 400.1 d for bone metastases, 522.4 d for brain metastases, and 401.2 d for unspecific sites. While LN metastases were found after 441.0 d in patients treated with Dabrafenib and Trametinib, these occurred significantly earlier in patients who received adjuvant Pembrolizumab (after 301.1 d) ($p = .0317$). Lung metastases occurred significantly earlier in patients treated with Pembrolizumab (after 306.2 d) as compared to Dabrafenib and Trametinib (after 459.8 d) ($p = .0307$). In patients with Pembrolizumab bone metastases were detected significantly earlier (after 194.2 d) as compared to Dabrafenib and Trametinib (after 481.4 d) ($p = .0170$). Brain metastases tended to occur earlier in patients with adjuvant Pembrolizumab (after 385.9 d) as compared to Nivolumab (after 627.7 d) ($p = .0642$).

Besides, organ-specific recurrence rates were calculated in relation to all patients treated with the respective adjuvant therapy (Figure 3C,D). Lung metastases were detected in 91, brain metastases in 66, LN metastases in 53, liver metastases in 46, bone metastases in 32, and skin metastases in 27 patients. Fifty-two patients showed metastases at sites not further specified. Only for skin metastases a tendency towards a higher frequency was seen in patients who received adjuvant Nivolumab ($p = .1526$). The organ-specific DMFS did not significantly differ among the subgroups after stratification by *BRAF* or *NRAS* mutations (Figure S5A,B).

In most of the patients (8.8%), only one metastatic site was reported. Metastasis to two organs was found in 2.7%, metastasis to three organs in 1.8%, and metastasis to four sites in 1.9%. Metastasis to more than four organ sites was unlikely (Table S8). As second-line therapies, most of the patients ($n = 113$) received ICI with Nivolumab and Ipilimumab (56.6%) or TT with Encorafenib and Binimetinib (15.0%) (Tables S9 and S10).

3.5 | Patient characteristics of relapsed CM cases

Three hundred and fifty patients suffered from a relapse of CM (Table 2). These were previously diagnosed with a stage 0, I, or II CM, then progressed into stage III disease and qualified for adjuvant treatment.

Most patients suffered from SSM ($n = 124$) or NMM ($n = 119$). 88.0% were alive at data cutoff. Among the tested patients, a *BRAF* mutation was found in 46.5% and an *NRAS* mutation in 35.8%. Adjuvant therapy with Nivolumab was initiated in 177 patients (50.6%), 108 patients (30.9%) received Pembrolizumab, and 65 patients were treated with Dabrafenib and Trametinib (18.6%). The median follow-up time was 21.2 months for Dabrafenib and Trametinib, 29.0 months for Nivolumab, and 24.9 months for Pembrolizumab. Patients with adjuvant TT were significantly younger in comparison to Pembrolizumab ($p = .0154$), while no differences were found between the other subgroups (D + T: 55.6 years; N: 58.7 years; P: 62.2 years). The genders were equally distributed among all subgroups. In patients treated with Dabrafenib and Trametinib, higher rates of SSM and NMM were reported, while cases with ICI showed increased numbers of lentigo maligna melanoma (LMM) or unclassified CM (D + T vs. N: $p = .0348$; D + T vs. P: $p = .0297$). The tumor characteristics (ulceration, Breslow's thickness) were similar between all subgroups. The numbers of mitoses were higher in the Pembrolizumab subgroup than in the Dabrafenib and Trametinib ($p = .0479$), or Nivolumab ($p = .0245$) groups. CMs in the Dabrafenib and Trametinib subgroup were most frequently localized at the trunk, while CM of the ICI cohorts was predominantly detected at the lower extremity ($p = .0384$) (Table S11). Most relapsed cases had a stage II CM at baseline. SLND was performed in 52.9%. Adjuvant radiotherapy was applied in 21.1% on average. As expected, mutations of *BRAF* were more frequent in the TT subgroup, while mutations of *NRAS* were increased in the ICI subgroups. Stage IIIB CM was most common among relapsed cases ($n = 178$; 50.9%), followed by stage IIIC ($n = 142$; 40.6%).

The uncensored TTR, from first diagnosis of CM until progression into stage III, indicated that patients of the Dabrafenib and Trametinib subgroup tended to be diagnosed with stage III disease later ($p = .0620$) (Figure 4A and Table S12). The mean time from initial diagnosis of CM until recurrence with stage III was 3.94 years for the Dabrafenib and Trametinib subgroup, 2.76 years for the Nivolumab

FIGURE 2 PFS of patients with stage III CM at first diagnosis (primary cases). (A) Censored PFS from start of respective adjuvant therapy until melanoma recurrence (in-transit, LN macrometastasis, or distant metastasis) was modeled. Kaplan–Meier curves are shown. The PFS of patients with Dabrafenib and Trametinib (D + T) is shown in gray, Nivolumab (N) in blue, and Pembrolizumab (P) in red. Curves were compared by log-rank tests: all groups: $p = .0533$; D + T versus N: $p = .0539$; D + T versus P: $p = .0208$; N versus P: $p = .5084$. (B) The PFS of patients with Dabrafenib and Trametinib is shown in gray; patients with Nivolumab and Pembrolizumab were pooled and are presented in green. Curves were compared by log-rank tests: all groups: $p = .0204$. (C) The PFS of primary cases after stratification by the mutational status of *BRAF* and *NRAS* and the corresponding treatment are presented. Nivolumab and Pembrolizumab-treated patients were pooled (N + P). Patients with wt CM who received Nivolumab or Pembrolizumab are displayed in green, *BRAF*-mut cases with Dabrafenib and Trametinib in gray, *BRAF*-mut cases with Nivolumab or Pembrolizumab in orange, and *NRAS*-mut cases with Nivolumab or Pembrolizumab in purple. Curves were compared by log-rank tests: all groups: $p = .0073$; wt-N + P versus *BRAF*-mut-D + T: $p = .5627$; *BRAF*-mut-D + T versus *BRAF*-mut-N + P: $p = .0022$; wt-N + P versus *BRAF*-mut-N + P: $p = .0656$; wt-N + P versus *NRAS*-mut-N + P: $p = .1349$. (D) Pie charts itemize details on melanoma recurrence despite adjuvant therapy. The percentages of patients with locoregional (in-transit or LN macrometastasis) or distant metastasis are presented per treatment cohort. Patients who recurred both locoregional and at distant sites were grouped into the distant metastasis category. (E, F) Univariable (E) and multivariable analyses (F) were performed with a Cox proportional hazards model to assess an influence of the subgroup characteristics on PFS in primary CM. The variables ulceration and NRAS mutation were not included in the multivariable analyses because of a high number of missing values. Forest plots illustrate corresponding hazard ratios (squares) and 95% confidence intervals (CIs) (bars). CM, cutaneous melanoma; LN, lymph node; PFS, progression-free survival.

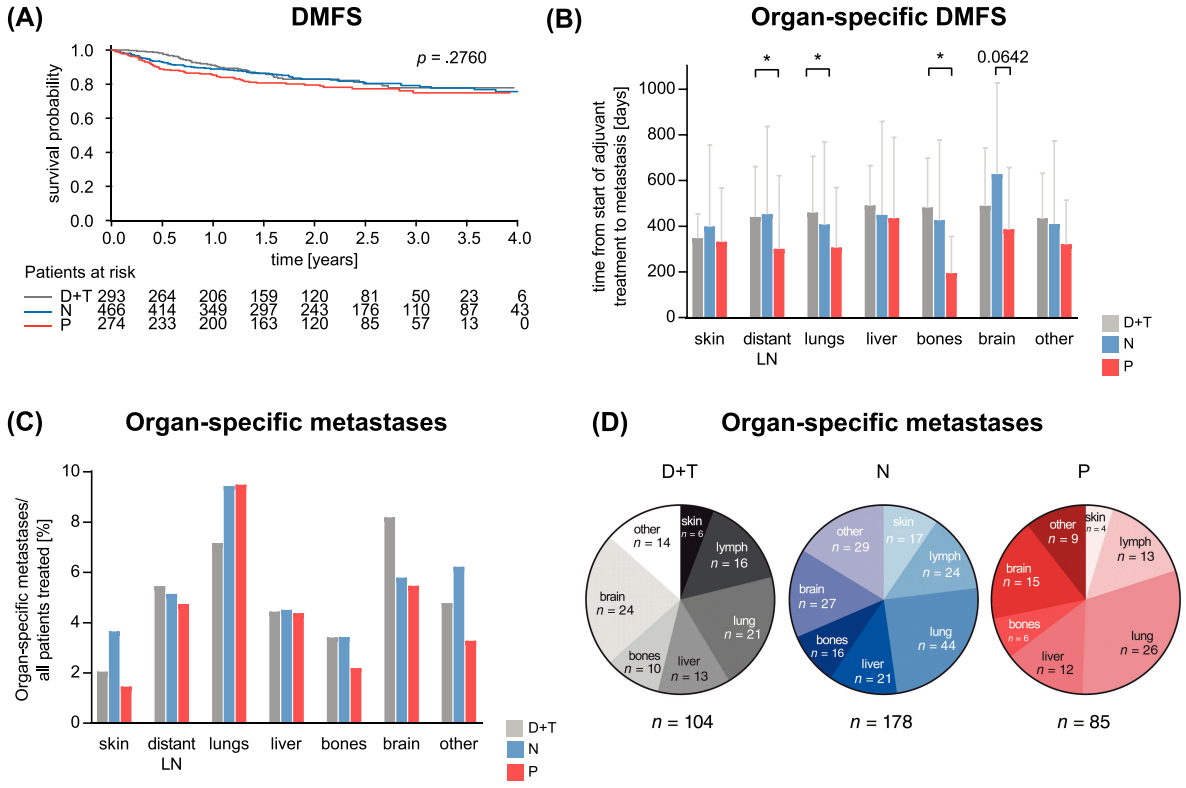


FIGURE 3 Organ-specific DMFS and recurrence pattern of primary CMs despite adjuvant treatment. (A) Censored DMFS from start of respective adjuvant therapy until stage IV disease (distant metastasis only) was modeled. Kaplan–Meier curves are shown. No statistical inhomogeneity of the curves was found ($p = .2760$, Log-rank test). The DMFS of patients with Dabrafenib and Trametinib (D + T) is shown in gray, Nivolumab (N) in blue, and Pembrolizumab (P) in red. B. The mean time (days) from start of respective adjuvant treatments to the development of organ-specific metastases is presented per site and subgroup.*Skin*: D + T: 347.5 d, N: 398.7 d, P: 332.0 d ($p = .8835$, Kruskal–Wallis test). *Distant LN*: D + T: 441.0 d, N: 452.5 d, P: 301.1 d ($p = .1097$, Kruskal–Wallis test); D + T versus N: $p = .4560$ (Kruskal–Wallis test); D + T versus P: $p = .0317$ (Kruskal–Wallis test); N versus P: $p = .1522$ (Kruskal–Wallis test). *Lungs*: D + T: 459.8 d, N: 408.0 d, P: 306.2 d ($p = .1076$, Kruskal–Wallis test); D + T versus N: $p = .1758$ (Kruskal–Wallis test); D + T versus P: $p = .0307$ (Kruskal–Wallis test); N versus P: $p = .3369$ (Kruskal–Wallis test). *Liver*: D + T: 490.7 d, N: 450.1 d, P: 435.1 d ($p = .3737$, Kruskal–Wallis test). *Bones*: D + T: 481.4 d, N: 426.6 d, P: 194.2 d ($p = .0697$, Kruskal–Wallis test); D + T versus N: $p = .3428$ (Kruskal–Wallis test); D + T versus P: $p = .0170$ (Kruskal–Wallis test); N versus P: $p = .1216$ (Kruskal–Wallis test). *Brain*: D + T: 489.3 d, N: 627.7 d, P: 385.9 d ($p = .1353$, Kruskal–Wallis test); D + T versus N: $p = .3454$ (Kruskal–Wallis test); D + T versus P: $p = .1658$ (Kruskal–Wallis test); N versus P: $p = .0642$ (Kruskal–Wallis test). *Other*: D + T: 434.6 d, N: 409.8 d, P: 321.3 d ($p = .4426$, Kruskal–Wallis test). (C) The percentages of patients with site-specific metastasis as related to all patients with respective adjuvant treatment are presented per site and subgroup. *Skin*: $p = .1526$ (chi-square test). *Distant LN*: $p = .9278$ (chi-square test). *Lungs*: $p = .5033$ (chi-square test). *Liver*: $p = .9966$ (chi-square test). *Bones*: $p = .5992$ (chi-square test). *Brain*: $p = .3247$ (chi-square test). *Other*: $p = .2047$ (chi-square test). (D) Pie charts display the numbers of involved sites among all stage IV patients per subgroup. CM, cutaneous melanoma; DMFS, distant metastasis-free survival; LN, lymph node.

group, and 2.43 years for the Pembrolizumab group, respectively. Adjuvant treatment was started 5.7 months after diagnosis of relapsed CM on average between all subgroups. Pembrolizumab was started significantly earlier (4.3 months) as compared to either Dabrafenib and Trametinib (9.1 months; $p = .0185$) or Nivolumab (5.3 months; $p = .0168$) (Table S13).

3.6 | Treatment course of adjuvant therapies for relapsed CMs

Data on the treatment course were provided for 260 patients (74.3%). On average, all adjuvant therapies were given for 8.2 months (Table S14). The treatment was discontinued at the regular endpoint (31.8%), disease progression (18.6%), or intolerable toxicity (14.0%). At data cutoff, 90 patients (25.7%) were still on therapy (Tables S15 and S16).

Ninety-five of 350 relapsed cases (27.1%) suffered from a secondary tumor recurrence, which was either locoregional (in-transit or LN metastases) or distant (progression into stage IV). The censored PFS was similar between all subgroups ($p = .7233$) (Figure 4B). The censored 1-year and 2-year PFS were 73.5% and 56.5% for Dabrafenib and Trametinib, 76.5% and 68.0% for Nivolumab, and 73.9% and 60.4% for Pembrolizumab, respectively. Forty-two of 350 (12.0%) patients died despite adjuvant treatment. Melanoma recurrence was detected predominantly as distant metastatic disease (D + T: 93.75%;

TABLE 2 Subgroup analysis of relapsed cases.

	Dabrafenib/Trametinib	Nivolumab	Pembrolizumab	*p* Value
Number of patients	65	177	108	
Follow-up time (months)	21.2	29.0	24.9	
Age	55.6 (±14.9)	58.7 (±14.6)	62.2 (±13.9)	**.0126** D + T vs. N: .3310 D + T vs. P: **.0154** N vs. P: .1458
Gender				
Male	56.92% (37)	59.32% (105)	64.81% (70)	.5241
Female	43.08% (28)	40.68% (72)	35.19% (38)	
Tumor subtype				
NMM	41.54% (27)	32.77% (58)	31.48% (34)	.1328
SSM	43.08% (28)	33.90% (60)	33.33% (36)	D + T vs. N: **.0348**
LMM	0% (0)	5.08% (9)	4.63% (5)	D + T vs. P: **.0297**
Unclassified[a]	15.38% (10)	28.25% (50)	30.56% (33)	N vs. P: .9789
Breslow thickness	3.07 (±3.34)	2.89 (±2.86)	3.08 (±2.72)	.2815
Ulceration (yes)	40.0% (26)	35.03% (62)	34.26% (37)	.5743
Number of mitoses	2.38 (±2.83)	2.16 (±2.23)	3.91 (±4.46)	**.0485** D + T vs. N: .9949 D + T vs. P: **.0479** N vs. P: **.0245**
AJCC stage at 1st diagnosis				
0	0% (0)	1.69% (3)	0% (0)	.3315
IA	12.31% (8)	10.73% (19)	7.41% (8)	
IB	24.62% (16)	26.55% (47)	22.22% (24)	
IIA	16.92% (11)	19.21% (34)	24.07% (26)	
IIB	18.46% (12)	20.90% (37)	30.56% (33)	
IIC	20.00% (13)	16.38% (29)	9.26% (10)	
Unclassified	7.69% (5)	4.52% (8)	6.48% (7)	
AJCC stage at relapse				
III unspecified[a]	0% (0)	2.82% (5)	3.70% (4)	.9424
IIIA	4.62% (3)	3.95% (7)	5.56% (6)	
IIIB	53.85% (35)	50.85% (90)	49.07% (53)	
IIIC	38.46% (25)	40.68% (72)	41.67% (45)	
IIID	3.08% (2)	1.69% (3)	0% (0)	
SLND (yes)	55.38% (36)	49.15% (87)	57.41% (62)	.5584
BRAF mutation	100% (65)	24.29% (43)	24.07% (26)	<.0001 D + T vs. N: **<.0001** D + T vs. P: **<.0001** N vs. P: .6491
NRAS mutation	0% (0)	17.51% (31)	28.70% (31)	**.0003** D + T vs. N: **.0013** D + T vs. P: **<.0001** N vs. P: .1018
Adjuvant radiotherapy	20.00% (13)	20.90% (37)	22.22% (24)	.9359
AWD/NED	90.77% (59)	86.44% (153)	88.89% (96)	.2458
DC	9.32% (6)	13.56% (24)	11.11% (12)	

TABLE 2 (Continued)

	Dabrafenib/Trametinib	Nivolumab	Pembrolizumab	*p* Value
Localization[b]				
Head/neck	10.77% (7)	12.99% (23)	23.15% (25)	**.0384**
Trunk	41.54% (27)	26.55% (47)	28.70% (31)	
Upper extremity	18.46% (12)	24.29% (43)	17.59% (19)	
Lower extremity	26.15% (17)	36.16% (64)	29.63% (32)	
Other	3.08% (2)	0.56% (1)	0.93% (1)	

Abbreviations: AWD, alive with disease; DC, deceased; LMM, lentigo maligna melanoma; NED, no evidence of disease; NMM, nodular melanoma; SLND, sentinel lymph node dissection; SSM, superficial spreading melanoma.

[a]Not otherwise specified/ not documented.

[b]Grouped according to ICD-10 codes, please refer to Table S11 for details.

N: 86.96%; P: 84.85%), while locoregional progression was found less (D + T: 6.25%; N: 13.04%; P: 15.15%) (Figure 4C). The censored 1-year and 2-year DMFS were 75.4% and 67.2% for Dabrafenib and Trametinib, 79.5% and 72.0% for Nivolumab, and 75.9% and 64.3% for Pembrolizumab, respectively ($p = .7411$) (Figure 4D). The censored 1-year and 2-year OS was 98.0% and 71.9% for Dabrafenib and Trametinib, 94.0% and 84.9% for Nivolumab, and 92.2% and 86.2% for Pembrolizumab, respectively ($p = .9295$) (Figure S6A). Stratification by mutational status revealed an improved TTR of the *BRAF*-mut-D + T subgroup ($p = .0075$), while PFS ($p = .2418$), DMFS ($p = .3554$), and OS ($p = .9815$) were similar among all subgroups (Figure S6B–E). Overall, relapsed cases showed significantly reduced PFS ($p < .0001$), DMFS ($p < .0001$), and OS ($p < .0001$) in comparison to primary CM (Figure S7A–C).

3.7 | Organ-specific DMFS and pattern of recurrence despite adjuvant treatment of relapsed CM

Eighty-six patients (24.6%) progressed into stage IV. The mean time from first diagnosis until stage IV was 1582.9 days among all patients. It was significantly longer in Nivolumab treated patients as compared to patients with Pembrolizumab ($p = .0072$) (Table S17). No statistical differences were detected between the other subgroups. Organ-specific DMFS of relapsed CM was similar with respect to the metastatic sites (Figure 4E and Figure S8A–G). The mean time from start of adjuvant therapy to detection of organ-specific metastasis was 385.2 d for skin metastases, 344.7 d for LN metastases, 300.8 d for lung metastases, 280.8 d for liver, 288.0 d for bone, 398.9 d for brain metastases, and 348.4 d for other sites, respectively. Patients with adjuvant Pembrolizumab showed a tendency towards earlier diagnosis of brain metastasis as compared with Nivolumab (291.4 d vs. 474.9 d; $p = .1811$), while no difference was found in relation to Dabrafenib and Trametinib (291.4 d vs. 354.1 d; $p = .6272$).

Organ-specific recurrence rates for relapsed CMs were analyzed (Figure 4F,G). Lung metastases were detected in 41 patients, metastases to unspecified sites in 36, brain metastases in 36, LN metastases in 32, liver metastases in 30, bone in 23, and skin metastases in 11 patients, respectively. The percentage of patients with liver metastasis was significantly lower in patients with Dabrafenib and Trametinib (1.5%) as compared to Pembrolizumab (12.0%, $p = .0142$) or Nivolumab (9.0%, $p = .0430$). Furthermore, the percentage of LN metastasis was significantly smaller in patients treated with Dabrafenib and Trametinib (1.5%) as compared to Pembrolizumab (12.0%, $p = .0184$) or Nivolumab (10.2%, $p = .0291$). Notably, *NRAS*-mut CM showed increased organ-specific recurrence rates, especially for distant LN, liver, and bones (Figure S9A,B).

Only one metastatic site was involved in most patients (6.9%) on average between all groups. Two organs were involved in 5.4%, three organs in 4.6%, and four organs in 4.0% (Table S18). After disease progression, most of the patients received dual-ICI with Nivolumab and Ipilimumab (28.4%), TT with Dabrafenib and Trametinib (9.5%), or TT with Encorafenib and Binimetinib (9.5%) (Tables S19 and S20).

4 | DISCUSSION

This multicenter retrospective study focused on the organ-specific recurrence patterns of stage III CM after adjuvant TT (Dabrafenib and Trametinib) or ICI (Nivolumab or Pembrolizumab). Organ-specific metastases, such as brain or liver metastases, are poor prognostic factors and promote further therapy resistance in the palliative setting.[4–8] Adjuvant therapies might differ in its protection against metastasis to certain organs. Only few clinical studies report on organ-specific recurrence in detail.

Data of 1383 stage III CM patients were retrieved from the ADOReg database. It was differentiated between primary stage III CM and cases with secondary melanoma progression into stage III, referred to as relapsed CM. On average, adjuvant therapies were administered 262.6 d in primary and 248.2 d in relapsed stage III CM. Treatments were stopped when the regular endpoint was reached (primary: 35.3%; relapsed: 31.7%), toxicity developed (primary: 13.4%; relapsed: 14.0%), or disease progression was detected (primary: 10.8%; relapsed: 18.6%). This is in accordance with retrospective observational studies.[19,20]

22.4% of all primary and 27.1% of all relapsed cases suffered from melanoma recurrence with in-transit, LN, or distant metastasis. Progression into stage IV disease was diagnosed in 17.6% of primary and

24.6% of relapsed cases. Primary cases with adjuvant Dabrafenib and Trametinib showed improved censored PFS (1-year PFS: 90.3%; 2-year PFS: 81.0%) as compared to Pembrolizumab (1-year and 2-year PFS: 81.0% and 73.9%; $p = .0208$) or Nivolumab (1-year and 2-year PFS: 83.8% and 75.2%; $p = .0539$). A benefit for TT as compared to ICI was also demonstrated after adjusting for influential

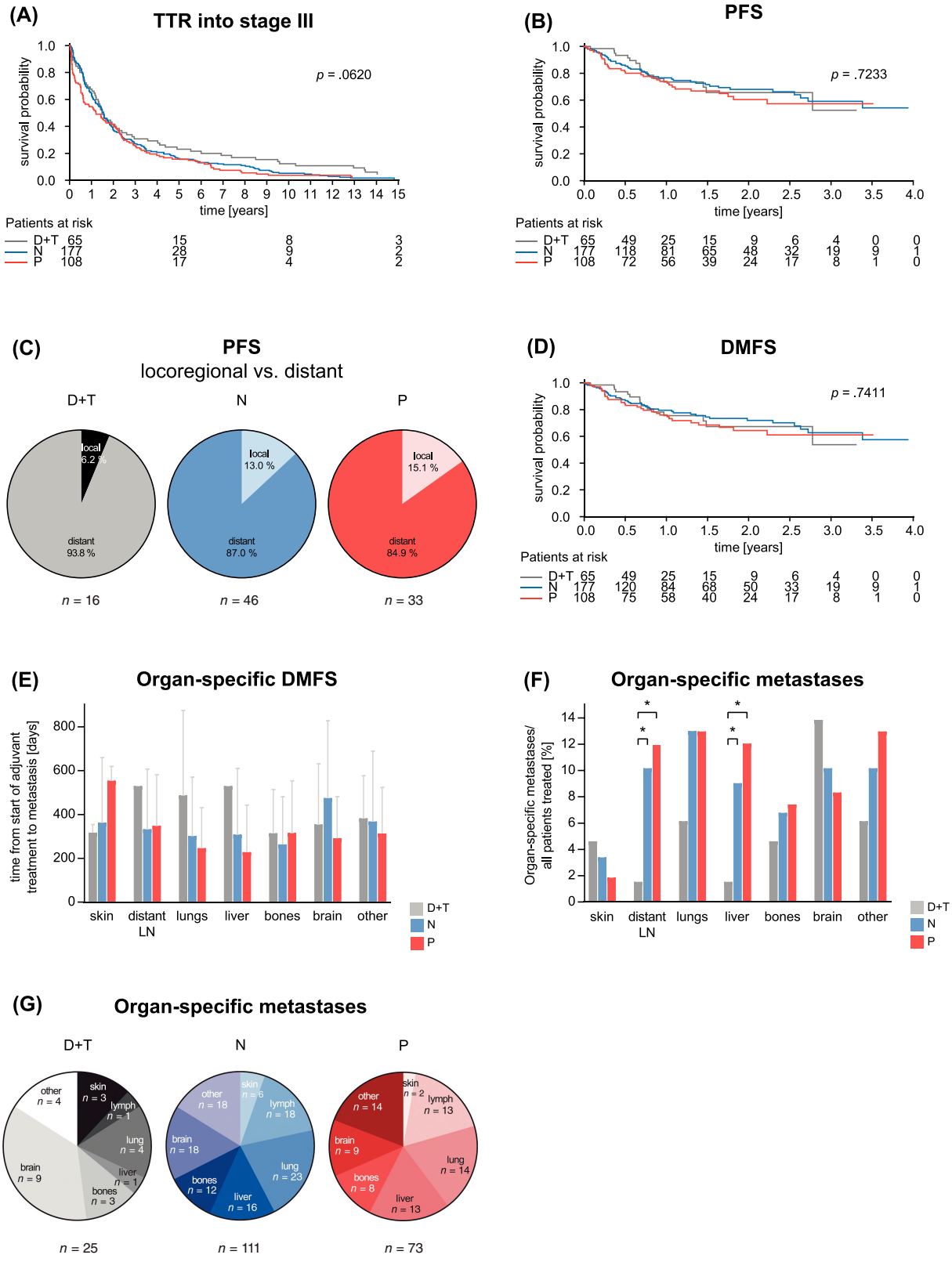


FIGURE 4 Legend on next page.

factors in a multivariable analysis ($p = .0457$). Furthermore, stratifications by *BRAF* and *NRAS* mutations demonstrated significantly lower PFS of *BRAF*-mut patients with ICI as compared to *BRAF*-mut cases with TT ($p = .0022$). Wt cases with ICI and *BRAF*-mut patients with TT performed similarly ($p = .5627$). Besides, *NRAS*-mut cases tended to perform worse than wt CM with ICI ($p = .1349$). Censored OS was similar among the subgroups (censored 1-year and 2-year OS: D + T: 98.5% and 95.0%; N: 97.3% and 95.0%; P: 98.0% and 94.5%). In relapsed CM, censored PFS (1-year and 2-year PFS: D + T: 73.5% and 56.5%; N: 76.5% and 68.0%; P: 73.9% and 60.4%) and censored OS (1-year and 2-year OS: D + T: 98.0% and 71.9%; N: 94.0% and 84.9%; P: 92.2% and 86.2%) were significantly decreased as compared to primary CM ($p < .001$), without significant differences between the subgroups.

This is in line with real-world data of stage III CM that report a PFS of 72.1% at 12 months for adjuvant treatment with Nivolumab, 78.0% for Pembrolizumab, and 86.5% for Dabrafenib and Trametinib.[21] Other studies confirm this data, report a favorable PFS of adjuvant TT in relation to ICI and demonstrate a benefit of *BRAF*-mut cases when treated with TT as compared to ICI.[22,23] In contrast to our analysis, these studies do not discriminate between primary and relapsed stage III CM and pool patients with Nivolumab and Pembrolizumab to anti-PD-1 treated cohorts. Studies of Polish or Dutch cohorts also report an advantage of adjuvant TT against adjuvant ICI.[24,25] All studies confirm published data from the registrational studies of Dabrafenib and Trametinib (COMBI-AD) with an estimated 3-year PFS of 58% and a 5-year PFS of 52%,[9,26] Nivolumab (CheckMate 238) with a 4-year PFS of 51.7% and 5-year PFS of 50%,[27,28] or Pembrolizumab (KEYNOTE-054) with an estimated 3.5-year and 5-year PFS of 59.8% and 55.4%.[16,29]

Stage IV disease was diagnosed in 182 (17.6%) patients of primary and 86 (24.6%) of relapsed cases. The censored 2-year DMFS was 83.0% in primary and 67.2% in relapsed CM for patients with Dabrafenib and Trametinib, 82.9% and 72.0% for Nivolumab and 79.5% and 64.3% for Pembrolizumab, respectively. DMFS did not differ between the subgroups in both primary and relapsed cases (primary: $p = .2760$; relapsed: $p = .7411$). But, in the primary cohort, *BRAF*-mut CM with ICI tended to develop metastatic disease earlier than *BRAF*-mut with TT ($p = .0580$) and *NRAS*-mut cases tended to perform worse than wt CM upon ICI ($p = .0540$). Placzke et al. describe a DMFS of 70.2% at 1 year.[25] Regarding Dabrafenib and Trametinib, 35% of patients in the COMBI-AD trial have metastatic disease at 5 years.[17] No details on melanoma recurrence to specific sites are published by the COMBI-AD study, as it censored patients at locoregional recurrence. At a follow-up of 3.5 years of the KEYNOTE-054 trial, 68% of patients with adjuvant Pembrolizumab do not show any distant metastases.[16] At 5 years, a DMFS of 60.6% in the pembrolizumab group is reported as compared to 44.5% in the placebo subgroup.[29] At 4 years of follow-up of the CheckMate 238 trial, a DMFS of 61.6% for Nivolumab and 56.3% for Ipilimumab is calculated.

In our analysis, metastases were reported at common distant sites such as the lungs, brain, LN, liver, or skin. In primary cases, metastasis to LN ($p = .0317$), lungs ($p = .0307$), and bones ($p = .0170$) occurred significantly earlier with Pembrolizumab as compared to adjuvant TT. This is in line with the worse PFS of adjuvant ICI as compared to TT. Regarding brain metastasis, a trend toward earlier detection in the Pembrolizumab subgroup in comparison to the Nivolumab cohort was found ($p = .0642$). Notably, organ-specific survival of patients with bone ($p = .0367$) or brain metastasis ($p = .0202$) significantly differed

FIGURE 4 TTR into stage III, PFS, DMFS, and organ-specific DMFS of patients with relapsed stage III CM. (A) TTR from date of first diagnosis (stage I or II CM) until progression into stage III is plotted with Kaplan–Meier curves. As these patients received adjuvant therapies afterward, respective treatment groups are separated. The patients who received subsequent adjuvant therapy with Dabrafenib and Trametinib (D + T) are shown in grey, Nivolumab (N) in blue, and Pembrolizumab (P) in red. A tendency toward improved TTR is detected for the subgroup that received Dabrafenib and Trametinib in comparison to both Nivolumab and Pembrolizumab ($p = .0620$, Log-rank test). (B) Censored PFS from start of respective adjuvant therapy until melanoma recurrence (in-transit, LN macrometastasis, or distant metastasis) was modeled. Kaplan–Meier curves are shown. No statistical differences between the subgroups were found ($p = .7233$, Log-rank test). The PFS of patients with Dabrafenib and Trametinib is shown in grey, Nivolumab in blue, and Pembrolizumab in red. (C) Pie charts demonstrate details on melanoma recurrence despite adjuvant therapy. The percentages of patients with locoregional (in-transit or LN macrometastasis) or distant metastasis are presented per treatment cohort. Patients who recurred both locoregional and at distant sites were grouped into the distant metastasis category. (D) Censored DMFS from start of respective adjuvant therapy until stage IV disease (distant metastasis only) was modeled. Kaplan–Meier curves are shown. No statistical inhomogeneity of the curves was found ($p = .7411$, Log-rank test). The DMFS of patients with Dabrafenib and Trametinib is shown in grey, Nivolumab in blue, and Pembrolizumab in red. (E) The mean time (days) from start of respective adjuvant treatments to the development of organ-specific metastases is presented per site and subgroup. *Skin*: D + T: 317.3 d, N: 362.8 d, P: 554.0 d ($p = .3596$, Kruskal–Wallis test). *Distant LN*: D + T: 529.0 d, N: 332.1 d, P: 347.8 d ($p = .6065$, Kruskal–Wallis test). *Lungs*: D + T: 486.5 d, N: 301.6 d, P: 246.5 d ($p = .1076$, Kruskal–Wallis test). *Liver*: D + T: 529.0 d, N: 308.3 d, P: 227.9 d ($p = .4319$, Kruskal–Wallis test). *Bones*: D + T: 314.7 d, N: 263.5 d, P: 314.9 d ($p = .7554$, Kruskal–Wallis test). *Brain*: D + T: 354.1 d, N: 474.9 d, P: 291.4 d ($p = .4043$, Kruskal–Wallis test). *Other*: D + T: 382.0 d, N: 368.0 d, P: 313.7 d ($p = .7785$, Kruskal–Wallis test). (F) The percentage of patients with site-specific metastasis as related to all patients with respective adjuvant treatment is presented per site and subgroup.*Skin*: $p = .5799$ (chi-square test). *Distant LN*: $p = .0540$ (chi-square test); D + T versus N: $p = .0269$ (chi-square test); D + T versus P: $p = .0142$ (chi-square test); N versus P: $p = .6233$ (chi-square test). *Lungs*: $p = .3032$ (chi-square test). *Liver*: $p = .0548$ (chi-square test); D + T versus N: $p = .0430$ (chi-square test); D + T versus P: $p = .0142$ (chi-square test); N versus P: $p = .4168$ (chi-square test). *Bones*: $p = .7632$ (chi-square test). *Brain*: $p = .5113$ (chi-square test). *Other*: $p = .3599$ (chi-square test). (G) Pie charts display the exact numbers of involved sites among all stage IV patients per subgroup. CM, cutaneous melanoma; DMFS, distant metastasis-free survival; LN, lymph node; OS, overall survival; PFS, progression-free survival; TTR, time to recurrence.

between the three groups. After the relapse of CM, the choice of adjuvant treatment did not affect the timing of recurrence to specific sites, as no difference in organ-specific DMFS was detected for relapsed CM. Also, the survival of patients with organ-specific metastases was similar. However, the percentage of liver metastasis was significantly lower when relapsed patients received adjuvant TT (1.5%) as compared to both Pembrolizumab (12.0%, $p = .0142$) and Nivolumab (9.0%, $p = .0430$). This might be crucial for further therapeutic options, as liver metastases poorly respond to ICI.[4,5] Furthermore, LN metastasis was detected significantly less in patients who received Dabrafenib and Trametinib (1.5%) as compared to Pembrolizumab (12.0%, $p = .0184$) or Nivolumab (10.2%, $p = .0291$). Interestingly, stratification by the mutational status of the subgroups showed higher recurrence rates for *NRAS*-mut CM, especially among the relapsed cohort. While primary CM predominantly spread in an oligometastatic pattern, metastasis at two to four distant sites was frequently detected in the relapsed cases of our study.

Lodde et al. describe a higher percentage of brain metastases in patients with primary CM who received adjuvant TT in comparison to *BRAF*-mut CM with adjuvant ICI.[22] In the CheckMate 238 trial, metastasis to the lungs (Nivolumab: 32%; Ipilimumab: 39.8%) or LN (Nivolumab: 26.7%; Ipilimumab: 33.7%) is found more frequently, while metastasis to the liver (Nivolumab: 16%; Ipilimumab: 14.3%) or brain (Nivolumab: 12%; Ipilimumab: 15.3%) occurs less.[17] Patients with melanoma recurrence, despite adjuvant treatment with either Nivolumab or Ipilimumab, do not significantly differ in the metastatic patterns.[17] Adjuvant treatment with Pembrolizumab strongly reduces metastatic spread to LN (12.6% [Pembrolizumab] vs. 18% [placebo]) and the lungs (13.2% [Pembrolizumab] vs. 21.4% [placebo]).[29] As first metastatic sites, despite adjuvant treatment with Pembrolizumab, the lungs (13.2%) and LN (12.6%) are mainly involved, while metastasis to the liver (7.8%), brain (5.6%), and bone (4.1%) are less.[29]

Registrational trials report higher percentages of organ-specific recurrences. This might be caused by a documentation bias of this registry study, as patients within registrational trials are often followed up in a more stringent manner. Besides, analyses on metastatic patterns were limited by small numbers of reported distant sites which affected statistical power and general conclusions. Last, the high percentage of censored data led to an underestimation of PFS, DMFS, and OS. This is a typical problem of real-world data of adjuvant treatment, as patients very often do not reach endpoints such as recurrence or death.

Altogether, our study demonstrates an improved PFS upon adjuvant TT in comparison to ICI in primary, but not in relapsed stage III CM. PFS, DMFS, and OS were significantly lower in the relapsed cohort, underscoring disease dynamics. The adjuvant regimen influenced the pattern of secondary melanoma recurrence, as the organ-specific DMFS until brain or bone metastases significantly differed between the subgroups of primary cases. In relapsed CM, the percentages of liver and LN metastasis were significantly lower with adjuvant TT than ICI. These data show that adjuvant TT is superior to ICI in primary, *BRAF*-mut CM. Besides, *NRAS*-mut CM should be carefully monitored during adjuvant therapy, since these demonstrated increased melanoma recurrence in both primary and relapsed cases.

AUTHOR CONTRIBUTIONS

SAW and JUt designed the overall concept. SU and JUt supervised the study. Data were acquired and provided by IvW, KCKl, KCKä, MW, DS, LZ, PM, FriM, CP, CB, MVH, RH, AK, RG, JUl, FraM, CG, ED, UL, BS, SU, and JUt. Data analysis was performed by SAW, LK, and CW. The manuscript was written by SAW, LK, and JUt. It was scientifically revised by CB, RG, and SU. All authors have read and approved this manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

SAW received honoraria from Bristol Myers Squibb, Novartis, and Sun Pharma outside the submitted work. IvW received Honoraria from Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Stemline, and Kyowa Kirin outside the submitted work. Consultant or Advisory Role: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Stemline, and Kyowa Kirin outside the submitted work. Travel, Accommodations from Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Stemline and Kyowa Kirin outside the submitted work. KCKl reports consultancy and speaker honoraria or travel grants from Bristol Myers Squibb, Kyowa Kirin, Novartis, Pierre Fabre, Sun Pharmaceutical, and Vetter Pharma outside the submitted work. KCKä serves as consultant to Philogen, BMS, MSD, Sanofi Aventis, and Immunocore and received travel grants and speaker fees from Philogen, Pierre Fabre, BMS, MSD, Sun Pharma, Sanofi Aventis, Novartis, and Medac and has received research support by Novartis. MW received grants from Bristol Myers Squibb and Merck Sharp & Dohme, consulting fees from Merck Sharp & Dohme, Immunocore and Novartis, lecture honoraria from Bristol Myers Squibb and Merck Sharp & Dohme and Pierre Fabre, and advisory board honoraria from Merck Sharp & Dohme. DS reports partial financial support from Bristol Myers Squibb for the conduct of this study and drug supply (nivolumab and ipilimumab) support; grants (or contracts) from Amgen, Array/Pfizer, Bristol- Myers Squibb, MSD, Novartis and Roche; consulting fees from 4SC, Amgen, Array Biopharma, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Haystick, Immunocore, InFlarX, Innocent, LabCorp, Merck Serono, MSD, Nektar, NeraCare, Novartis, OncoSec, Pfizer, Philogen, Pierre Fabre, Replimune, Roche, Sandoz, Sanofi/Regeneron, and Sun Pharma; honoraria from Bristol Myers Squibb, MSD/Merck, Merck Serono, Novartis, Roche, Sanofi, and Sun Pharma; support for attending meetings or travel support from Bristol Myers Squibb, MSD, Merck Serono, Novartis, Pierre Fabre, and Sanofi; participation on drug safety monitoring or advisory boards for 4SC, Amgen, Array Biopharma, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Immunocore, InFlarX, Merck Serono, MSD, Nektar, NeraCare, Novartis, OncoSec, Pfizer, Philogen, Pierre Fabre, Replimune, Roche, Sandoz, Sanofi/Regeneron, and SunPharma; leadership roles for DeCOG, German Cancer Society, Hiege-Stiftung, Deutsche Hautkrebsstiftung, NVKH e.V., and EuMelaReg. LZ served as consultant and has received honoraria from BMS, MSD, Novartis, Pierre Fabre, Sanofi, and SunPharma and travel support from MSD, BMS, Pierre Fabre, Sanofi, SunPharma, and Novartis, outside the submitted work. PM declares research grants from Bristol Myers Squibb, Merck Sharp & Dohme, and Novartis; speakers and advisory board honoraria from Bristol Myers Squibb, Beiersdorf, Merck Sharp & Dohme, Roche, Amgen, Regeneron, Delcath, Pierre Fabre, Sun Pharma, Immunocore, Sanofi, and Novartis outside the submitted work, and travel support from Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Sun Pharma, and Pierre Fabre, outside the submitted work. FriM has received travel support or/and speaker's fees or/and advisor's honoraria by Novartis, Roche, BMS, MSD, Pierre Fabre, Sanofi, and Immunocore and research funding from Novartis and Roche. 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RG received honoraria for lectures/advice from Bristol Myers Squibb, Roche Pharma, MerckSharpDohme, Novartis, Merck-Serono, Amgen, Almirall Hermal, Pierre Fabre, Sun Pharma, Immunocore, 4SC, Delcath, and Sanofi/Regeneron; support for participation in meetings from SUN Pharma, Boehringer Ingelheim, and Pierre Fabre; research support from Novartis, Sanofi/Regeneron, Merck Serono, Amgen, SUN Pharma, KyowaKirin, and Almirall Hermal. JUl received honoraria and travel support from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi, and SUN Pharma outside the submitted work. FraM served as consultant and/or has received honoraria from Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Sanofi Genzyme, Sun Pharma, and travel support from Novartis, Sun Pharma, Roche, Pierre Fabre, and Merck Sharp & Dohme, outside the submitted work. CG is on the advisory board or has received honoraria from Almirall, Amgen, Beiersdorf, BioNTech, Bristol Myers Squibb, Immunocore, Janssen, MSD Sharp & Dohme, Novartis, Pierre Fabre Pharma, Regeneron, Roche, Sanofi Genzyme, SUN Pharma and Sysmex, research funding

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DATA AVAILABILITY STATEMENT

All data are provided in this manuscript, including figures and Supporting Information. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The ADOReg was approved by the Medical Ethics Committee of the University Duisburg-Essen (14-5921-BO), and written informed consent for participation was obtained from all patients. The study (ADJU-OS) was approved by the scientific board of the ADOREg.

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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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