ORIGINAL ARTICLE

First-line therapy-stratified survival in BRAF-mutant melanoma: a retrospective multicenter analysis

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Abstract

Background Inhibition of the mitogen-activated protein kinase (MAPK) pathway as well as programmed death 1 receptor (PD-1) blockade was shown to prolong overall survival (OS) in patients with advanced B-Raf proto-oncogene (BRAF)-mutant melanoma. However, due to the lack of head-to-head trials, it remains unclear if one of these therapeutic approaches should be preferred in first-line therapy. Here, we present a retrospective analysis comparing anti-PD-1 monotherapy with BRAF/MAPK/ERK kinase (MEK) combined inhibition used as first-line agents in a real-world clinical setting.

Patients and methods Clinical data, routine blood counts and lactate dehydrogenase (LDH) levels of 301 patients with unresectable or metastatic melanoma harboring an activating mutation in BRAF (V600E/K) were included. Of these, 106 received anti-PD-1 antibodies, while 195 patients were treated with a selective BRAF inhibitor combined with an MEK inhibitor as palliative first-line therapy. Patients were sub-grouped according to previously described predictive and prognostic markers.

Results OS was significantly longer in patients receiving anti-PD-1 monotherapy compared to patients receiving combined MAPK inhibitors. Subsequent therapies were comparable among these groups. The difference in OS was less pronounced in patients with high LDH levels and visceral metastatic spread.

Conclusion First-line treatment with a PD-1 blocking antibody might be associated with longer OS than first-line inhibition of the MAPK pathway in patients with advanced melanoma harboring mutant BRAF. These hypothesis-generating data need to be confirmed or rejected in prospective, randomized trials.

Keywords Melanoma · BRAF · First-line treatment · PD-1 · MAPK

Abbreviations

BRAF	B-Raf proto-oncogene
BRAFi	BRAF inhibitors
CI	Confidence interval
CTLA-4	Cytolytic T lymphocyte-associated antigen-4
HR	Hazard ratio
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MAPKi	MAPK inhibitors
MEK	MAPK/ERK kinase
MEKi	MEK inhibitors
NCT	National Clinical Trial
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death 1 receptor
PD-L1	Programmed death ligand 1
ULN	Upper limit of normal

Introduction

Approximately, 50% of all melanomas harbor an activating mutation in B-Raf proto-oncogene (BRAF) affecting the codon 600, with consequent activation of the mitogen-activated protein kinase (MAPK) pathway [1]. In patients with advanced BRAFV600E/K-mutated melanomas, inhibition of the MAPK pathway has shown a high response rate and prolongation of overall survival (OS) [2]. Therapeutically, combinations of selective BRAF inhibitors (BRAFi) (vemurafenib or dabrafenib) and MAPK/ERK kinase (MEK) inhibitors (MEKi) (cobimetinib or trametinib) have become a standard of care in these patients [3, 4]. Programmed death 1 receptor (PD-1) blockade with monoclonal antibodies (nivolumab, pembrolizumab) has demonstrated an objective response rate (ORR) of ~ 40% and to prolong survival in patients with advanced melanoma [5, 6]. Here, the efficacy of this form of therapy was shown both in patients with mutated BRAF and in patients without such an activating mutation [7]. Thus, patients with advanced melanoma harboring mutated BRAFV600E/K can benefit from MAPK inhibitors (MAPKi) as well as PD-1 blockade. However, it remains unclear which, if any, modality should be used as preferred first-line therapy to yield maximum patient benefit. No prospective head-to-head data are currently available to address this everyday challenge in the treatment of patients with BRAF-mutated advanced melanoma.

Exploratory analyses of prospective clinical trials as well as retrospective biomarker studies have identified several markers associated with benefit from MAPKi or PD-1 blockade. For instance, elevated lactate dehydrogenase (LDH) is associated with worse outcome both in the context of MAPKi and PD-1 blockade [8, 9]. For programmed death ligand 1 (PD-L1) expression, a positive correlation with the ORR of PD-1 blockade and OS has been observed [5, 10, 11]. Patients considered to be PD-L1 negative, however, still show clinical responses. For patients receiving MAPKi, controversial data on the predictive value of PD-L1 expression exist [12–14]. To date, it remains unclear if any biomarker exists that is predictive for either therapeutic approach that could help to guide the treatment of BRAFV600-mutant melanoma patients regarding first-line therapy and prospective, clinical trials are still underway.

To optimize patient benefit, data that may support the use of either PD-1 blockade or MAPKi as first-line therapy in patients with advanced BRAF-mutated melanoma, are urgently needed. With data from prospective clinical trials pending, we conducted a multicenter retrospective analysis to investigate the outcome of patients undergoing either measure as first-line therapy.

Materials and methods

Patient cohort

Patients with advanced (unresectable or metastatic) melanoma harboring mutant BRAF (V600E/K) were included in this retrospective analysis. Participating clinical sites provided data of patients who received either dual MAPKi (vemurafenib plus cobimetinib or dabrafenib plus trametinib) or single-agent PD-1 blocking antibody (nivolumab or pembrolizumab) as first-line therapy for advanced disease. No further restrictions applied regarding patient selection. The American Joint Committee on Cancer (AJCC) 2009 classification was used to categorize patients [15]. Demographic, as well as clinical data were collected for all identified patients from patient records. Data were obtained as documented at the start of first-line therapy. Laboratory values were obtained within 4 weeks before start of systemic therapy. Elevated LDH was defined as any value above the local upper limit of normal (ULN).

Definition of end points and data acquisition

OS was calculated from the start of first-line therapy. Patients who were still living were censored at the last documented follow-up. Patients who died from reasons other than progressive melanoma were censored at the date of death. Median follow-up was calculated by inverted censoring [16]. Patients were categorized according to the pattern of metastasis into three different groups as reported previously [9]: (i) unresectable or distant soft tissue and/or lymph node metastases only, (ii) pulmonary metastases and (iii) visceral metastases other than or in addition to lung.

Statistical analysis

Statistical analyses were performed by applying the Chi square test or Wilcoxon rank sum test using SPSS (IBM, version 23). Survival analysis was conducted using the Kaplan–Meier method; the log-rank test was used for curve comparison. The Cox proportional-hazards model was used for multivariate analyses. Differences were considered statistically significant for p values < 0.05.

Results

Study population

Clinicopathological characteristics of patients included in this study are shown in Table 1. All patients showed an activating somatic mutation in BRAF (BRAFV600E/K). In the

Table 1 Clinicopathological characteristics of patients with metastatic malignant melanoma included in this study

	All	PD-1	MAPKi	p
Individual patients	$n = 301$ (%)	$n = 106$ (%)	$n = 195$ (%)	
First-line therapy received				
Pembrolizumab	65 (21.6)	65 (61.9)		n.a
Nivolumab	41 (13.6)	41 (38.1)		
Dabrafenib/trametinib	157 (52.2)		157 (80.5)	
Vemurafenib/cobimetinib	38 (12.6)		38 (19.5)	
Subsequent therapy with				
Anti-PD-1 monotherapy	60 (19.9)	1 (0.9)	59 (30.3)	
Dual MAPKi	49 (16.3)	37 (34.9)	12 (6.2)	
Anti-CTLA-4 monotherapy	28 (9.3)	5 (4.7)	23 (11.8)	**< 0.0001**[#]
Dual anti CTLA-4/PD-1	29 (9.6)	5 (4.7)	24 (12.3)	
Unknown[a]	20 (6.6)	2 (1.9)	18 (9.2)	
Other/none	115 (38.2)	56 (52.8)	59 (30.3)	
BRAF-status				
Mutant (V600E/K)	301 (100)	106 (100)	195 (100)	n.a
Sex				
Male	184 (61.1)	67 (63.2)	117 (60.0)	0.59[#]
Female	117 (38.9)	39 (36.8)	78 (40.0)	
Age (years)				
(Median, [range])	58 [18–88]	60 [21–86]	58 [18–88]	**0.008**[##]
Elevated LDH				
Yes	104 (34.6)	20 (18.9)	84 (43.1)	**< 0.0001**[#]
No	197 (65.4)	86 (81.1)	111 (56.9)	
Metastatic pattern				
Lymph node or soft tissue only	51 (16.9)	22 (20.8)	29 (14.9)	**0.0031**[#]
Pulmonary	35 (11.6)	20 (18.9)	15 (7.7)	
Other visceral	215 (71.4)	64 (60.4)	151 (77.4)	

Bold values indicate *p*-values lower than 0.05

n.a. not applicable, [#]by X^2 test, [##]by Wilcoxon rank sum test.

[a]Unknown if subsequent PD-1 blockade or MAPKi was received

PD-1 group, 65 of 106 (61.9%) received pembrolizumab, while the remaining 41 patients (38.1%) were treated with nivolumab. In patients receiving dual MAPKi as first-line therapy, dabrafenib plus trametinib was employed in 80.5% of patients, while 19.5% received vemurafenib combined with cobimetinib. Distribution of sex was similar between the PD-1 and MAPKi groups. In contrast, patients with visceral metastases and elevated LDH were significantly more common in the MAPKi group. Importantly, a similar proportion of patients in either cohort received the alternate treatment modality as subsequent therapy (Table 1). In the MAPKi group, 33.3% of patients received PD-1 blockade subsequently, while 34.9% patients in the PD-1 group received dual MAPKi therapy at a later stage.

Overall survival according to first-line treatment

As shown in Fig. 1a, left panel, Kaplan–Meier estimates of OS were compared between patients in the PD-1 group ($n = 106$) and in the MAPKi group ($n = 195$). Median OS was 29.1 months [95% confidence interval (CI) 24.9–33.2] in the PD-1 group and 12.4 months (95% CI 8.6–14.4) in the MAPKi group ($p < 0.001$). Median follow-up for survival was 22.3 (95% CI 20.7–23.8) for the PD-1 group and 25.8 months (95% CI 16.4–35.1) for the MAPKi group. Figure 1a, right panel, shows OS after subgrouping according to the specific treatment patients received. No differences were found within the PD-1 (nivolumab vs. pembrolizumab) and MAPKi (dabrafenib plus trametinib vs. vemurafenib plus cobimetinib) treatment groups.

Demographic and clinical subgroup analyses of overall survival

Differences in patients' characteristics between treatment groups are shown in Table 1. Sex and age distribution were similar for both groups. For patients with normal LDH, regardless of first-line therapy, median OS was 26.9 months,
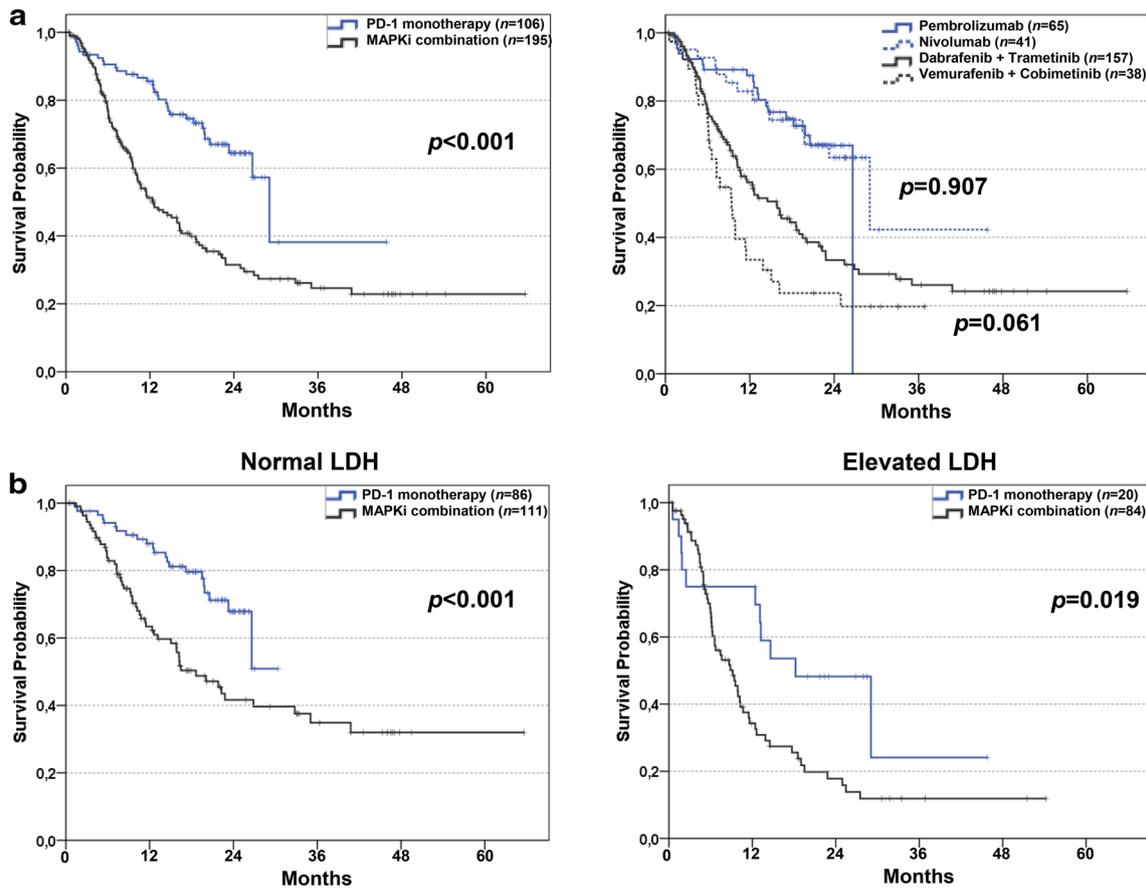
Fig. 1 Overall survival of BRAF-mutated melanoma patients stratified by first-line therapy. **a** Kaplan–Meier curves for OS of BRAF mutated patients receiving any PD-1 blocking antibody as monotherapy ($n=106$; 35.2%) or any dual MAPKi ($n=195$; 64.8; **a** left). Overall survival of BRAF mutated patients receiving pembrolizumab ($n=65$; 21.6%) or nivolumab ($n=41$; 13.6%) or vemurafenib plus cobimetinib ($n=38$; 12.6%) or dabrafenib plus trametinib ($n=157$; 52.2%) as first-line therapy (**a** right). **b** OS is shown for patients with normal LDH levels at the start of any PD-1 blocking antibody monotherapy ($n=86$; 43.7%) or any dual MAPKi ($n=111$; 56.3%; **b** left). OS is shown for patients with elevated LDH levels at the start of any PD-1 blocking antibody monotherapy ($n=20$; 19.2%) or any dual MAPKi ($n=84$; 80.8%; **b** right). Vertical lines indicate censored values; p values were calculated by log rank testing

while patients with elevated LDH showed a median OS of 9.9 months (data not shown). Figure 1b, left panel, shows OS in patients with normal LDH after stratification according to therapy. When LDH levels were normal, median OS was significantly shorter for MAPKi-treated patients than for patients receiving PD-1 blockade (18.6 vs. 26.6 months, $p < 0.001$). In patients with elevated LDH, a similar observation was made (Fig. 1b, right panel). Median OS was 9.2 months in patients with elevated LDH receiving MAPKi as compared to 18.2 months in patients receiving PD-1 blockade ($p = 0.019$). As depicted in Fig. 2a, OS was significantly longer in anti-PD-1-treated than in MAPKi-treated patients, regardless of the metastatic pattern.

Biomarker-based subgroup analyses of overall survival

We and others have previously reported biomarkers predicting outcome in patients undergoing PD-1 blockade or MAPKi [8, 9]. By analyzing several biomarkers, including peripheral eosinophils (Supplementary Fig. 1a) and lymphocytes (Supplementary Fig. 1b), we could not identify a biomarker-defined patient subgroup in which MAPKi was associated with improved survival compared to PD-1 blockade. In multivariate analysis of the overall cohort without stratification by first-line therapy, LDH, metastatic pattern and frequency of peripheral eosinophils were found to be

a

Soft tissue/lymph node — PD-1 monotherapy (*n*=22); MAPKi combination (*n*=29); *p*=0.016

Lung — PD-1 monotherapy (*n*=20); MAPKi combination (*n*=15); *p*=0.022

Other visceral metastases — PD-1 monotherapy (*n*=64); MAPKi combination (*n*=151); *p*<0.001

b

Factor	HR (95%-CI)	*p*
LDH normal	1	
LDH elevated	2.1 (1.5 − 3.0)	0.000
Soft-tissue/pulmonal metastases only	1	
other metastases	3.0 (1.9 − 4.9)	0.000
Low eosinophils	1	
High eosinophils	0.6 (0.4 − 0.9)	0.005
Low lymphocytes	1	
High lymphocytes	0.8 (0.5 − 1.1)	0.16

c 0 - 1 points — PD-1 monotherapy (*n*=36); MAPKi combination (*n*=117); *p*=0.08

d 2 - 3 points — PD-1 monotherapy (*n*=70); MAPKi combination (*n*=78); *p*<0.001

Fig. 2 Subgroup analyses of overall survival based on metastatic pattern or age groups. **a** Kaplan–Meier curves for OS are shown for BRAF mutated melanoma patients treated with PD-1 blocking antibodies (*n*=22; 43.1%) or dual MAPKi (*n*=29; 56.9%) with metastases located in lymph nodes/soft tissue (**a** left), patients treated with PD-1 blocking antibodies (*n*=20; 57.1%) or dual MAPKi (*n*=15; 42.9%) with metastases limited to lung (**a** middle) or other visceral organs (**a** right) treated with PD-1 blocking antibodies (*n*=64; 29.8%) or dual MAPKi (*n*=151; 70.2%). **b** Table showing hazard ratios (HR) for death after stratification of all 301 patients according to four biomarkers. Hazard ratios, 95% CI and *p* values were calculated by multivariate Cox proportional hazards model. **c** Factors identified as independent by multivariate Cox proportional hazards model (LDH levels, metastatic pattern, eosinophil levels) were used to develop a point model where patients are stratified according to the total number of favorable factors (normal LDH, no visceral metastases other than lung, eosinophils count > 1.5%). Kaplan–Meier curves for OS are shown for BRAF mutated melanoma patients treated with PD-1 blocking antibodies (*n*=36; 23.5%) or dual MAPKi (*n*=117; 76.5%) with 0 or 1 points. **d** Kaplan–Meier curves for OS are shown for BRAF mutated melanoma patients treated with PD-1 blocking antibodies (*n*=70; 47.3%) or dual MAPKi (*n*=78; 52.7%) with two or three points. Vertical lines indicate censored values; *p* values were calculated by log rank testing (**a, c, d**)

independently associated with patient prognosis (Fig. 2b). Next, we tested the association of OS and models incorporating three independent prognostic factors (normal LDH, no visceral metastasis other than lung, eosinophils count > 1.5%). As depicted in Fig. 2d, patients with two to three favorable markers showed superior OS when receiving PD-1 blockade as first-line therapy as compared to MAPKi, while OS was similar in patients with zero to one favorable markers after stratification by first-line therapy (Fig. 2c).

Discussion

In this study, we observed an association between first-line therapy with PD-1 blocking agents with OS in advanced BRAFV600E/K-mutant melanoma. This association was found in comparison to MAPKi-treated patients and was evident in several analyzed subgroups. In patients with poor prognostic features, first-line PD-1 blockade and combined MAPKi were associated with similar OS. Importantly, the proportion of patients subsequently receiving the alternate therapeutic regime was comparable between both groups. Although this is a retrospective study, it provides hypothesis-generating data on treatment sequence in advanced BRAFV600-mutant melanoma.

So far, only a single study addressing a similar question has been published [17]. In contrast to our study, Johnson et al. found no association with OS when comparing patients who received PD-1 blockade prior to or after MAPKi. However, their cohort contained patients receiving BRAFi monotherapy as well as combined MAPKi and included ~ 50% of patients who were not treatment naïve. Furthermore, patients were included who had received combined ipilimumab and nivolumab as well as atezolizumab, an anti-PD-L1 antibody with limited data in patients with metastatic melanoma. In contrast, we have gathered data from a more homogenous group treated with approved drugs as first-line therapy. Since ipilimumab combined with nivolumab has been approved

most recently, we did not include such patients due to limited follow-up time. Comparing landmark OS rates in our MAPKi group to data from prospective clinical trials [18], survival rates were lower in our study. This difference might be explained by the enrollment criteria needed to be fulfilled in these trials and differences regarding subgrouping patients according to LDH and metastatic spread for OS analyses. Due to these differences, a direct comparison between OS data is not possible and warrants further investigations.

Since there is no evidence to support a specific treatment sequence for BRAF-positive patients [19], the European Society of Medical Oncology (ESMO) [20] and National Comprehensive Cancer Network (NCCN) melanoma guidelines (Version 2.2018) give no recommendation about the sequencing of systemic treatments. Recommendations for first-line therapy in BRAFV600-mutant metastatic melanoma are currently extrapolated from prospective clinical trials and based on patient-centered factors. In addition to patient preference, expected treatment-related adverse events (AE), disease-related symptoms and the extent of metastatic spread were suggested to guide clinicians when recommending PD-1 blockade or MAPKi to patients [21, 22]. In our cohort, these considerations are reflected by a high representation of patients with elevated LDH and visceral metastases among those who received MAPKi as first-line therapy. Even though we could not observe superior OS in this subgroup, the higher response rate as compared to PD-1 blockade needs to be considered in treatment recommendations. In patients with symptomatic metastases, MAPKi can quickly induce remission and, for instance, provide pain relief [23]. Besides these clinical features, tumor biology could impact treatment outcome of MAPKi and PD-1 blockade. For instance, a patient with a PD-L1-positive, BRAFV600-mutated melanoma harboring an additional Rac family small GTPase 1 (RAC1)^{P29S} mutation is prone to receive immunotherapy and not targeted therapy first line [4, 24]. Thus, first-line therapy in BRAFV600-mutant melanoma needs to be discussed in a patient-by-patient manner integrating clinical and molecular data until prospective clinical trials like National Clinical Trial (NCT) 02224781 or NCT 02631447 can provide data confirming or dismissing any possible advantage for patients undergoing a specific treatment schedule.

As of today, single agent PD-1 blockade remains the standard of care for patients with advanced melanoma. While adding the cytolytic T lymphocyte-associated antigen-4 (CTLA-4) blocking agent ipilimumab to nivolumab yields a numerically higher response rate and better OS in the prospective CheckMate 067, the trial was not designed to show statistical superiority of the combination [4]. However, ongoing trials employing new combinations aim at replacing PD-1 monotherapy. For instance, NCT 03470922 is designed to show improved progression-free survival (PFS) of the lymphocyte activation gene 3 (LAG3) blocker relatlimab, combined with nivolumab compared to nivolumab. Although early data on relatlimab are promising [25], the recent failure of combined indoleamine 2,3-dioxygenase (IDO) inhibition and pembrolizumab [26] indicates that PD-1 monotherapy has set the bar high for new combinations. Until new data and drugs become available, PD-1 monotherapy will continue to play a major role in melanoma therapy.

The retrospective nature of our study implies several limitations. Mainly, patients with poor prognostic features (elevated LDH, visceral metastases) are significantly enriched in the MAPKi cohort. Confounding can be avoided by stratification in prospective clinical trials like NCT 02224781, comparing dual MAPKi with combined PD-1/CTLA-4 blockade in previously untreated patients with advanced melanoma. To address this issue, OS analyses in our study were conducted in subgroups from both cohorts sharing the same prognostic feature. Due to the disbalance in the frequency of some prognostic features, some of these subgroups are rather small. However, our study supports the practice that patients without poor prognostic features could benefit more from first-line PD-1 blockade than from dual MAPKi.

Conclusion

Our data show significantly better OS for advanced BRAF-mutant melanoma patients receiving PD-1 blockade as first-line therapy compared to patients receiving MAPKi in all subgroups. Limitations apply due to the retrospective nature of our study. Additionally, it should be acknowledged that other parameters apart from patient survival, such as symptom control, must be considered when making treatment decisions for treatment-naïve patients with advanced BRAFV600E/K-mutant melanoma. Our data from a large multicenter cohort provide additional information to guide the decision-making process until prospective clinical trials addressing the treatment sequence in BRAF-mutant melanoma are reported.

Compliance with ethical standards

Conflict of interest Bastian Schilling reports advisory roles for or has received honoraria from Pierre Fabre Pharmaceuticals, Incyte, Novartis, Roche, Bristol-Myers Squibb (BMS) and Merck Sharp & Dohme (MSD), research funding from BMS, Pierre Fabre Pharmaceuticals and MSD, and travel support from Novartis, Roche, BMS, Pierre Fabre Pharmaceuticals and Amgen. Christoffer Gebhardt reports advisory roles for or has received honoraria from Pierre Fabre Pharmaceuticals, Beiersdorf, BMS, MSD, Novartis, Roche and Sysmex, and travel support from BMS, MSD, Novartis and Roche. Jessica C. Hassel reports advisory roles for Pierre Fabre and Sanofi, and honoraria from BMS, MSD, Novartis, Roche and Pfizer. Anja Gesierich reports advisory roles for BMS, MSD, Novartis, Roche and Pfizer, has received honoraria from MSD and BMS, and travel support from BMS, MSD, Novartis and Roche. Ralf Gutzmer reports advisory roles for Roche, BMS, MSD, Amgen, Almirall, Leo, Pfizer, Novartis, GlaxoSmithKline (GSK), Incyte, Merck and Pierre-Fabre, has received honoraria from Roche, BMS, MSD, GSK, Novartis, Merck, Almirall, Amgen, Galderma, Astra-Zeneca and Pierre-Fabre, research funding from Novartis, Johnson & Johnson and Pfizer, honoraria from Roche, BMS, MSD, GSK, Novartis, Merck, Almirall, Amgen, Galderma, Astra-Zeneca and Pierre-Fabre, and travel support from Roche, BMS, MSD, GSK, Novartis, Merck, Almirall, Amgen, Galderma, Astra-Zeneca and Pierre-Fabre. Elisabeth Livingstone reports advisory roles for Roche, BMS, Novartis and Actelion, has received honoraria from Roche, BMS, MSD, Amgen, Novartis, Boehringer-Ingelheim (BI) and medac, and travel support from Roche, BMS, MSD, Amgen, Novartis, BI and medac. Panagiotis T. Diamantopoulos reports honoraria from Novartis and Roche, and travel support from Roche, Novartis, Janssen and Amgen. Helen Gogas reports honoraria from BMS, Roche, MSD, Novartis, Amgen and Pierre Fabre, and research funding from BMS, Roche, MSD and Novartis. Simone M. Goldinger reports advisory roles for Roche, Novartis, MSD and BMS, and has received travel support from Roche, Novartis, MSD and BMS. Joanna Mangana reports advisory roles for Merck and Pfizer, has received research funding from BMS, and travel support from MSD. Claus Garbe reports advisory roles for Amgen, BMS, MSD, Philogen, Roche and LEO Pharma, has received honoraria from Novartis, Amgen, BMS, MSD, Philogen, Roche and LEO Pharma, and research funding from Novartis, BMS and Roche. Dirk Schadendorf has received honoraria from Roche Pharma, BMS, Novartis, Merck Serono, MSD, Amgen, Incyte, LEO, Pfizer, Pierre Fabre, Array, Astra Zeneca, Regeneron, Philogen, Sanofi and Mologen, and research funding from Novartis and BMS. Christian Blank reports advisory roles for BMS, MSD, Roche, Novartis, GSK, Lilly, Pfizer and Genmab, and has received research funding from Novartis and BMS. Benjamin Weide has received honoraria from Merck/MSD, BMS, Philogen, Curevac, Roche, Novartis and Amgen, research funding from MSD and BMS, and travel support from MSD and BMS. All other authors declare no conflicts of interest.

Ethical approval Retrospective collection of anonymous patient data was performed during routine clinical care. This study was approved by the Ethics Committee, University of Tübingen (approvals 524/2012BO2 and 234/2015BO2).

Informed consent For anonymous publication of retrospective data acquired during routine clinical care, individual informed consents were not obtained.

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