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Original research

Real-World efficiency of pembrolizumab in metastatic melanoma patients following adjuvant anti-PD1 treatment

Michael Weichenthal [a,b,*], Inge Marie Svane [c,d], Johanna Mangana [e,f], Ulrike Leiter [g], Friedegund Meier [h,i], Christina Ruhlmann [j], Dimitrios Ziogas [k], Reinhard Dummer [e,f], Pablo Cerenzuela [l], Jose Luis Manzano [m], Marc Bender [n], Shan Jiang [o], Paolo Antonio Ascierto [p], Iva Gavrilova [q], Lidija Kandolf [r], Helen Gogas [k], Peter Mohr [s], Dirk Schadendorf [t,u,v,w], Eva Ellebaek [c,d]

[a] *Skin Cancer Center Kiel, University Hospital Schleswig-Holstein, Kiel, Germany*
[b] *Department of Dermatology, Medical Documentation and Statistics Unit, University of Kiel, Germany*
[c] *Department of Oncology, National Center for Cancer Immune Therapy (CCIT-DK), Copenhagen, Denmark*
[d] *University Hospital, Herlev and Gentofte, Denmark*
[e] *Department of Dermatology, University Hospital Zurich, Zurich, Switzerland*
[f] *Faculty of Medicine, University of Zurich, Zurich, Switzerland*
[g] *University Tübingen, Department of Dermatology, Tübingen, Germany*
[h] *Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[i] *Skin Cancer Center at the University Cancer Centre Dresden and National Center for Tumor Diseases, Dresden, Germany*
[j] *Department of Oncology, Odense University Hospital, Odense, Denmark*
[k] *First Department of Medicine, National and Kapodistrian University of Athens, Greece*
[l] *Hospital Virgen de la Arrixaca, Oncología Médica, El Palmar, Spain*
[m] *Hospital Universitari Germans Trias i Pujol, Barcelona, Spain*
[n] *Skin Cancer Center, Division of Molecular Cell Biology, Elbe Kliniken Stade, Buxtehude, Germany*
[o] *Merck Sharp & Dohme LLC, New Jersey, USA*
[p] *Department of Skin Cancers, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy*
[q] *Oncodermatology Department, National Oncology Center, Sofia, Bulgaria*
[r] *Department of Dermatology, Faculty of Medicine, Military Medical Academy, Belgrad, Serbia*
[s] *Dermatologic Center Buxtehude, Buxtehude, Germany*
[t] *Department of Dermatology, Venereology and Allergology, University Hospital Essen, Essen, Germany*
[u] *Westdeutsches Tumorzentrum WTZ, University Hospital Essen, Germany*
[v] *National Center for Tumor Diseases (NCT-West), Campus Essen, Essen, Germany*
[w] *University Alliance Ruhr, Research Center One Health, University Duisburg-Essen, Essen, Germany*

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ABSTRACT

Background: Postoperative treatment of patients with either BRAF/MEK inhibitors or anti-PD1 antibodies in the adjuvant setting results in improved recurrence free survival and has therefore become a standard of care for most patients with resected stage III melanoma. For patients who need systemic treatment after failure of adjuvant immune checkpoint inhibitors, there is insufficient evidence regarding efficacy of a retreatment with anti-PD1 antibodies.

Methods: From the European Melanoma Treatment Registry (EUMelaReg) we have identified 74 patients and evaluated the clinical characteristics and outcome of anti-PD1 retreatment with pembrolizumab in these patients. The primary objectives were overall response rate and progression-free survival stratified by type of recurrence, i.e. whether recurrence occurred while on adjuvant anti-PD1, or later during follow up. In addition, the analysis was stratified for patients, who terminated adjuvant treatment early due to side effects.

Results: The ORR of pembrolizumab retreatment in 1st line after recurrence (n=51) was 37.3 %, which did not differ significantly between type of recurrence (40.9 % in early vs. 34.5 % in late recurrence). Patients who discontinued adjuvant anti-PD1 for toxicity had a higher ORR (52.9 %) compared to patients who completed the

* Correspondence to: Skin Cancer Center Kiel, University Hospital Schleswig-Holstein, Arnold-Heller-Str.3, 24105 Kiel, Germany.
E-mail address: MWeichenthal@dermatology.uni-kiel.de (M. Weichenthal).

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treatment (37.5 %) or discontinued due to disease progression (23.1 %). PFS in 1st line retreatment was comparable between the groups with a median PFS (95 % CI) of 7.4 (2.3-NR) months and 6.1 (3.4–13.1) months in early and late recurrence, respectively.
Conclusion: Retreatment with pembrolizumab may be a valuable treatment option after failure of adjuvant immunotherapy, in particular in patients who have stopped adjuvant treatment for side effects.

1. Introduction

The development of immune checkpoint inhibitors (ICI) has changed the treatment of unresectable and metastatic melanoma dramatically in recent years and improved the outcome of patients significantly compared to former treatment standards. [1,2] In treatment-naive metastatic melanoma, treatment with anti-PD1 (programmed cell death protein 1) antibodies results in overall remission rates of about 40 % [3,4] and also, long-term overall survival rates at 5 years around 40 %, both of which constitute a notable improvement as compared to the historically dismal prognosis of metastatic melanoma. The Keynote-054 phase III trial comparing pembrolizumab (pembro) to placebo demonstrated a significant recurrence-free survival (RFS) benefit using pembro for one year in fully resected stage III patients. [5] When compared to ipilimumab (ipi) in a phase III study, single-agent nivolumab (nivo) also showed both favorable efficacy and tolerability in the adjuvant setting. [6]

While adjuvant anti-PD1 treatment does improve RFS in resected high-risk melanoma patients, a proportion of these patients will develop recurrence despite adjuvant treatment, many of them with unresectable or metastatic disease. Overall, in stage IIIA to IIID about 38 % of patients will develop a recurrence according to the long-term result of the Keynote-054 trial. [7] This may occur while still on 12 months of adjuvant treatment or later during follow-up (FU) and is referred to as early and late ICI resistance. [8]

In case of non-resectable failure or metastatic disease following adjuvant anti-PD1 treatment it is unclear whether the efficacy of a rechallenge with anti-PD1 is impacted by preceding ICI failure during or after adjuvant therapy. Only few studies investigated the efficacy of non-adjuvant anti-PD1 retreatment of patients who have relapsed after adjuvant anti-PD1 therapy and the available data are sparse.

This observational study was performed to study the efficacy of non-adjuvant pembro in melanoma patients who have failed from adjuvant anti-PD1 therapy.

2. Methods

2.1. Study design and patient selection

Patient data were used from the European Melanoma Registry (EUMelaReg; www.eumelareg.org), which is a disease entity-based treatment registry dedicated to melanoma that collects real-world diagnostic information and treatment patterns of patients across Europe. The country registries that contributed patient-level data to this study were Bulgaria, Denmark, Germany, Greece, Israel, Italy, Poland, Spain, and Switzerland.

Patients with the following characteristics were included to the analysis: adult patients with non-resectable stage III or stage IV melanoma who were treated with non-adjuvant pembro after failure from adjuvant anti-PD1 treatment; cutaneous melanoma including acral and melanoma of unknown primary (MUP) subtype; no participation in a clinical trial with anti-PD1 usage in advance setting. Combined anti-PD1/CTLA4 (cytotoxic T-lymphocyte-associated Protein 4) as 1st line (1 L) treatment for metastatic disease was only allowed, if pembro was given in a later line as rechallenge after progressive disease. No restriction was made for patients receiving BRAF/MEK inhibitors (BRAF/MEKi) in 1 L. The data cut was September 2023.

2.2. Statistical considerations and analysis

Descriptive statistics were used to summarize baseline study cohort characteristics. Data are presented as number of observations and percentage for categorical variables. Continuous variables are presented as mean, standard deviation, median, minimum, and maximum. TOT, PFS, FU, and OS, time-to-event analyses were conducted using the Kaplan-Meier method to generate plots and to estimate median time-to-event in months with 95 % confidence interval (CI), and events rates with 95 % CI at landmark time-points. TOT is defined as time from the date of start of treatment until the date of end of treatment (EoT). TOT for treatments documented as ongoing at data cut-off were censored with the date of last contact (applicable in the non-adjuvant setting). PFS is defined as time from start of non-adjuvant pembro retreatment to date of first progression according to physician's assessment or death due to any cause. Patients were censored at the start of next treatment. If neither a subsequent treatment nor death was documented, a patient was censored with the date of last contact. OS is defined as time from the start date of first non-adjuvant pembro treatment to date of death due to any cause. The OS for subjects not known to have died was censored at the last date the patient was known to be alive. FU time was calculated by Kaplan Meier analysis from start of first non-adjuvant pembro treatment to date of last contact with "inverse" censoring for death events.

3. Results

3.1. Patient characteristics

3.1.1. Demographics at time of recurrence

A total of 74 eligible patients who were treated with non-adjuvant pembro after failure from adjuvant anti-PD1 treatment met the inclusion criteria and were identified from the EUMelaReg database for this study. Demographics and patient characteristics are summarized in Table 1. Clinical characteristics at non-adjuvant pembro treatment are shown in Table 2.

The most common reason for adjuvant treatment discontinuation was disease progression (44.6 %), followed by treatment completion (23.0 %), and toxicity (25.7 %) (Table 1). Disease recurrence from adjuvant anti-PD1 treatment occurred in 44 (59.5 %) patients while on adjuvant anti-PD1 therapy or within 12 weeks after EoT (early recurrence subgroup), 30 (40.5 %) patients relapsed >12 weeks after end of adjuvant treatment (late recurrence subgroup).

The median time from first recurrence on anti-PD1 treatment to start of non-adjuvant pembro was 5.0 (95 % CI: 0.1–53–3) months in the total population. Among those with 1 L anti-PD1 treatment (1 L cohort) after early recurrence, 12 (54.2 %) patients had resectable locoregional recurrence and were re-exposed only after having experienced another non-resectable further stage for recurrence. This is also reflected by a delay of > 3 months before retreatment in these patients. Additional 10 (45.5 %) patients received immediate treatment (within ≤ 3 months) with just single agent pembro after early recurrence due to individual reasons such as comorbidity, age, or impaired performance status (Table 1).

Patients who had pembro retreatment in a later line (n=23) (later line cohort) had a median time from first recurrence to start of non-adjuvant pembro of 11.9 (95 % CI: 3.6–53.3) months. These patients received other regimens in 1 L, mainly combined ICI or BRAF/MEKi, and

Table 1
Baseline demographics at adjuvant anti-PD1 treatment.

Baseline demographics	Pembro in 1 L: Early vs. late recurrence in adjuvant setting		Pembro in later line	Total
	Early recurrence*	Late recurrence **		
	(N=22)	(N=29)	(N=23)	(N=74)
Gender				
Female	10 (45.5 %)	12 (41.4 %)	8 (34.8 %)	30 (40.5 %)
Male	12 (54.5 %)	17 (58.6 %)	15 (65.2 %)	44 (59.5 %)
Age at 1st line (years)				
Median (Range)	77.0 (27.0–85.0)	71.0 (20.0–87.0)	59.0 (37.0–83.0)	68.5 (20.0–87.0)
Melanoma type				
Cutaneous	21 (95.5 %)	25 (86.2 %)	21 (91.3 %)	67 (90.5 %)
MUP	1 (4.5 %)	4 (13.8 %)	2 (8.7 %)	7 (9.5 %)
Recurrence at adjuvant Tx				
During treatment	22 (100.0 %)	-	21 (91.3 %)	43 (58.1 %)
≤ 12 weeks after EOT	-	-	1 (4.3 %)	1 (1.4 %)
> 12 weeks after EOT	-	29 (100.0 %)	1 (4.3 %)	30 (40.5 %)
Reason for end of adjuvant Tx				
Disease progression	13 (59.1 %)	-	20 (87.0 %)	33 (44.6 %)
Completed	5 (22.7 %)	11 (37.9 %)	1 (4.3 %)	17 (23.0 %)
Toxicity	3 (13.6 %)	14 (48.3 %)	2 (8.7 %)	19 (25.7 %)
Other***	1 (4.5 %)	4 (13.8 %)	-	5 (6.8 %)
Time from first recurrence to start non-adjuvant Tx				
Median (Range) (months)	4.0 (0.1–26.4)	1.3 (0.1–19.3)	11.9 (3.6–53.3)	5.0 (0.1–53.3)
≤ 3 months	10 (45.5 %)	24 (82.8 %)		34 (45.9 %)
> 3 months	12 (54.5 %)	5 (17.2 %)	23 (100.0 %)	40 (54.1 %)
ToT at adjuvant Tx (months)				
Median (95 % CI)	3.3 (0.1–14.0)	8.3 (0.1–12.7)	2.8 (0.1–10.6)	3.5 (0.1–14.0)
RFI at adjuvant Tx (months)				
Median (95 % CI)	3.5 (0.1–11.9)	21.2 (3.9–46.9)	2.7 (0.4–14.5)	5.8 (0.1–46.9)

N, number of patients; MUP, melanoma of unknown primary; EOT, end of treatment; SD, standard deviation; CI, confidence interval; ToT, time on treatment; RFI, recurrence free interval; Tx, treatment.
* Early recurrence: recurrence occurred during treatment or within 12 weeks after end of treatment.
** Late recurrence: recurrence >12 weeks after end of treatment
*** Adjuvant therapy ended due to investigators decision/patient's wish/other.

pembro in a later line.

3.1.2. Demographics at time of retreatment

At the time of pembro retreatment, patients had a median age of 68.5 (20.0–87.0) years, 59.5 % were male, and most were diagnosed with cutaneous melanoma (90.5 %) (Table 1). A BRAF V600 mutation was present in 21.6 % of the patients (Table 2). The number of metastatic sites was higher in later line (56.5 % for ≥ 3 sites) than in 1 L cohort with ≥ 3 sites in 18.2 % (early recurrence) and 13.8 % (late recurrence), respectively (Table 2).

Stage IV melanoma was reported for 81.1 % of the patients with M1c being the most frequent subgroup (33.8 %), and 10.8 % had brain metastases (M1d). Patients may have had a shift in stage from recurrence to 1 L due to further disease progression, in particular in those retreated with pembro in later line. In 1 L cohort, stage IV M1c/d was present in 40.9 % (early recurrence) and 24.1 % (late recurrence), respectively, while those in later line had 73.9 % M1c/d (Table 2).

Eastern Cooperative Oncology Group (ECOG) scores at time of retreatment were similar despite type of recurrence and reason for EoT, mostly grade 0 or 1. Lactate dehydrogenase (LDH) was elevated in 36.5 %, and patients in 1 L with early recurrence more often had an elevated serum LDH level at retreatment than patients with late recurrence (47.7 % vs. 20.0 %).

Table 2
Clinical characteristics at non-adjuvant pembro treatment.

Tumor characteristics at time of retreatment	Pembro in 1 L: Early vs. late recurrence in adjuvant setting		Pembro in later line	Total
	Early recurrence*	Late recurrence **		
	(N=22)	(N=29)	(N=23)	(N=74)
AJCC staging (8th edition)				
Stage III	6 (27.3 %)	6 (20.7 %)	2 (8.7 %)	14 (18.9 %)
Stage IV			1 (4.3 %)	1 (1.4 %)
Stage IV-M1a	5 (22.7 %)	7 (24.1 %)	2 (8.7 %)	14 (18.9 %)
Stage IV-M1b	2 (9.1 %)	9 (31.0 %)	1 (4.3 %)	12 (16.2 %)
Stage IV-M1c	8 (36.4 %)	7 (24.1 %)	10 (43.5 %)	25 (33.8 %)
Stage IV-M1d	1 (4.5 %)	-	7 (30.4 %)	8 (10.8 %)
BRAF mutation present				
Yes	3 (13.6 %)	4 (13.8 %)	9 (39.1 %)	16 (21.6 %)
No	19 (86.4 %)	25 (86.2 %)	14 (60.9 %)	58 (78.4 %)
ECOG				
0	12 (54.5 %)	18 (62.1 %)	10 (43.5 %)	40 (54.1 %)
1	6 (27.3 %)	8 (27.6 %)	8 (34.8 %)	22 (29.7 %)
≥ 2	1 (4.5 %)	1 (3.4 %)	2 (8.7 %)	4 (5.4 %)
Unknown	3 (13.6 %)	2 (6.9 %)	3 (13.0 %)	8 (10.8 %)
LDH				
Normal	11 (50.0 %)	20 (69.0 %)	6 (26.1 %)	37 (50.0 %)
Elevated	7 (31.8 %)	6 (20.7 %)	14 (60.9 %)	27 (36.5 %)
Missing	4 (18.2 %)	3 (10.3 %)	3 (13.0 %)	10 (13.5 %)
Line of Tx				
1	22 (100.0 %)	29 (100.0 %)		51 (68.9 %)
2	-	-	9 (39.1 %)	9 (12.2 %)
≥ 3	-	-	14 (60.9 %)	14 (18.9 %)
Number of metastatic sites				
1	10 (45.5 %)	17 (58.6 %)	5 (21.7 %)	32 (43.2 %)
2	8 (36.4 %)	8 (27.6 %)	5 (21.7 %)	21 (28.4 %)
≥ 3	4 (18.2 %)	4 (13.8 %)	13 (56.5 %)	21 (28.4 %)

N, number of patients; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; Tx, treatment.
* Early recurrence: recurrence occurred under treatment or within 12 weeks after end of treatment.
** Late recurrence: recurrence within >12 weeks after end of treatment.

3.2. Treatment outcomes

3.2.1. Clinical responses and outcomes in 1 L

In total, 51 patients received 1 L pembro retreatment after adjuvant anti-PD1 therapy. ORR in the total group was 37.3 %, which did not differ significantly between type of recurrence (34.5 % in late vs. 40.9 % in early recurrence). The relative distribution of the particular responses showed more complete responses (CR) in late recurrences (20.7 % vs. 13.6 %), while primary progressive disease rates were similar (34.5 % vs. 36.4 %) (Table 3A).

ORR of 1 L cohort stratified by reason for end of adjuvant treatment were higher for patients who discontinued adjuvant anti-PD1 for toxicity (52.9 %) compared to patients who completed treatment (37.5 %) or discontinued due to disease progression (23.1 %) (Table 3B).

The median PFS (95 % CI) of 1 L cohort was 7.43 (2.3-not reached [NR]) months in patients with early recurrence and 6.12 (3.4–13.1) months in patients with late recurrence after adjuvant anti-PD1 treatment, respectively, and did not differ significantly (p=0.06) (Fig. 1A). Stratification by EoT reason for adjuvant anti-PD1 treatment showed lower PFS (95 % CI) for patients discontinuing treatment due to progression (2.57 [1.9–9.1] months) compared to patients who completed treatment (10.1 [2.9-NR] months) or discontinued due to toxicity (8.32 [3.8–15.5] months) (Fig. 1B). However, differences were not significant (p=0.029). OS (95 % CI) from start of pembro retreatment was 24.2 (16.7-NR) months in patients receiving treatment in 1 L after adjuvant treatment failure. It was slightly shorter in patients with early recurrence from adjuvant anti-PD1 (22.2 [13.9-NR] months), as it was in patients who discontinued adjuvant treatment due to recurrence (13.9 [3.5-NR] months). This was not statistically significant in either stratification (Fig. 1C, D). Median ToT (95 % CI) for pembro retreatment did not differ between patients with early (8.62 [1.4–11.1] months) and late recurrence (5.56 [2.8–7.5] months) (p=0.024) (Fig. 1E) but was numerically higher in patients who completed treatment (6.84 [2.8-NR] months) compared for toxicity (6.05 [1.6–12.8] months) and adjuvant treatment stop due to disease progression (6.94 [1.4–10.0] months) (p=0.068) (Fig. 1F).

Table 3A
Outcomes stratified by type of recurrence.

Outcome	Pembro in 1 L: Early vs. late recurrence in adjuvant treatment			Pembro in later line
	Early recurrence* (N=22)	Late recurrence** (N=29)	Total (N=51)	(N=23)
ORR	9 (40.9 %)	10 (34.5 %)	19 (37.3 %)	2 (8.7 %)
DCR	13 (59.1 %)	16 (55.2 %)	29 (56.9 %)	6 (26.1 %)
Best response				
Complete response	3 (13.6 %)	6 (20.7 %)	9 (17.6 %)	2 (8.7 %)
Partial response	6 (27.3 %)	4 (13.8 %)	10 (19.6 %)	
Mixed response	1 (4.5 %)		1 (2.0 %)	1 (4.3 %)
Stable disease	4 (18.2 %)	6 (20.7 %)	10 (19.6 %)	3 (13.0 %)
Progressive disease	8 (36.4 %)	10 (34.5 %)	18 (35.3 %)	11 (47.8 %)
Missing		3 (10.3 %)	3 (5.9 %)	6 (26.1 %)
Median FU (95 % CI)	19.5 (12.9–45.7)	12.8 (10.1–17.5)	14.5 (12.3–21.1)	23.3 (5.1-NR)
Survival* (95 % CI)**				
Median PFS	7.4 (2.3-NR)	6.1 (3.4–13.1)	7.4 (2.3-NR)	1.8 (1.5–4.3)
Median OS	22.2 (13.9-NR)	NR (16.7-NR)	24.2 (16.7-NR)	7.6 (4.3–17.9)
Median ToT	8.6 (1.4–11.1)	5.6 (2.8–7.5)	6.1 (3.0–8.4)	1.8 (0.9–2.9)

N, number of patients; ORR, overall response rate; DCR, disease control rate; FU, follow-up; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; NR, not reached, CI, confidence interval.

* Early recurrence: recurrence occurred under treatment or within 12 weeks after end of treatment.

** Late recurrence: recurrence within >12 weeks after end of treatment.

*** Survival from start of non-adjuvant pembro treatment.

Table 3B
Outcomes stratified by reason for end of adjuvant treatment.

Outcome	Pembro in 1 L: Reason for end of adjuvant treatment			
	Disease Progression (N=13)	Treatment Completed (N=16)	Toxicity (N=17)	Total* (N=51)
ORR	3 (23.1 %)	6 (37.5 %)	9 (52.9 %)	19 (37.3 %)
DCR	6 (46.2 %)	9 (56.3 %)	11 (64.7 %)	29 (56.9 %)
Best response				
Complete response	1 (7.7 %)	3 (18.8 %)	4 (23.5 %)	9 (17.6 %)
Partial response	2 (15.4 %)	3 (18.8 %)	5 (29.4 %)	10 (19.6 %)
Mixed response	1 (7.7 %)			1 (2.0 %)
Stable disease	3 (23.1 %)	3 (18.8 %)	2 (11.8 %)	10 (19.6 %)
Progressive disease	6 (46.2 %)	6 (37.5 %)	4 (23.5 %)	18 (35.3 %)
Missing	-	1 (6.3 %)	2 (11.8 %)	3 (5.9 %)
Median FU (95 % CI)	26.7 (12.9-NR)	16.6 (9.3–21.1)	14.0 (9.3–24.0)	14.5 (12.3–21.1)
Survival (95 % CI)**				
Median PFS	2.6 (1.9–9.1)	10.1 (2.9-NR)	8.3 (3.8–15.5)	7.4 (2.3-NR)
Median OS	13.9 (3.5-NR)	NR (9.5-NR)	NR (13.1-NR)	24.2 (16.7-NR)
Median ToT	6.9 (1.4–10.0)	6.8 (2.8-NR)	6.1 (1.6–12.8)	6.1 (3.0–8.4)

N, number of patients; ORR, overall response rate; DCR, disease control rate; FU, follow-up; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; NR, not reached, CI, confidence interval.

* 5 patients ended adjuvant therapy due to investigators decision/patient's wish/other.

** Survival from start of non-adjuvant pembro treatment.

3.2.2. Outcome in later lines

23 patients in later line cohort received intervening therapies prior to pembro retreatment. Most were treated with combined ICI as ipi/nivo (n=15; 20.3 %), BRAF/MEKi (n=7; 9.5 %) or both inhibitor agents (n=4; 5.4 %). A small number of patients (n=5; 6.7 %) were treated with chemotherapy and other agents.

Patients in the later line group were younger (median age: 59.0 [37.0–83.0] years), had a higher melanoma stage IV M1c/d (73.9 %), more metastatic sites (60.9 % ≥ 3), and a higher rate of elevated serum LDH (60.9 %) compared to the 1 L group (Tables 1 and 2).

Comparison of the outcomes of patients treated with pembro in 1 L with those who received intervening therapies show that only two responses (ORR: 8.7 %) were seen with pembro in later line, none of them following failure from BRAF/MEKi or combined ICI in intermittent lines (Table 4). Accordingly, a low PFS (95 % CI) of 1.8 (0.9–4.8) months compared to 7.4 (2.3-NR) months for 1 L patients. OS (95 % CI) was 7.6 (4.3–17.9) months in later lines compared to 24.2 (16.7-NR) in 1 L (Table 3).

4. Discussion

This real-world study demonstrates the potential of pembro in advanced melanoma settings following adjuvant anti-PD1 treatment failure. We report the efficacy outcome of 74 patients who failed adjuvant anti-PD1 therapy and received pembro either as 1 L treatment or as a salvage option after other treatments, most importantly ipi/nivo and

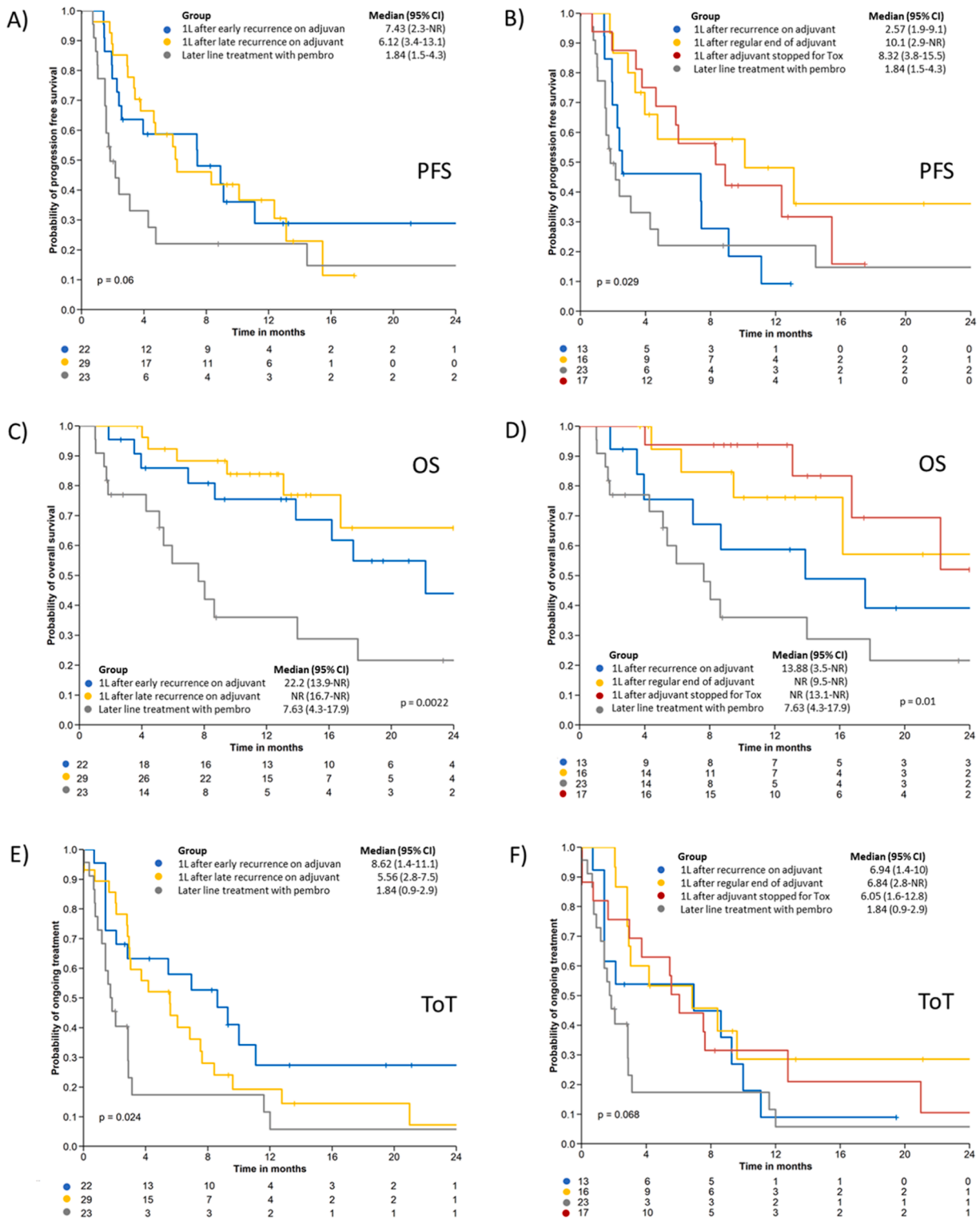

Fig. 1. : Kaplan-Meier curves of (A,B) PFS, (C,D) OS, and (E,F) ToT outcome in patients stratified by (A,C,E) timing of recurrence (1 L after early recurrence on adjuvant, 1 L after late recurrence on adjuvant, and later line treatment with pembro) to adjuvant anti-PD1 and by (B,D,F) reason for end of treatment of adjuvant treatment (1 L after recurrence on adjuvant, 1 L after treatment completed, 1 L after adjuvant stopped for Tox, and later line treatment with pembro). PFS, progression-free survival; OS, overall survival; ToT, time on treatment; CI, confidence interval; NR, not reached.

BRAF/MEKi. [9] For the 1 L advanced setting, the response rate of 37.3 % for pembro that we observed is comparable to ORR for pembro single-agent reported from other real-world studies in melanoma patients without adjuvant pre-treatment ranging from 24.9 % to 49.0 %. [10-12] This is also in line with the approx. 34 % ORR reported for pembro in the Keynote-006 trial, which included both 1 L and 2nd line (2 L) patients after a 1 L BRAFi or chemotherapy. [13]

Comparable data on anti-PD1 retreatment after failure from adjuvant anti-PD1 are sparse. Two studies indicated that retreatment with anti-PD1 monotherapy may provide additional benefit and new anti-

Table 4
Outcome of non-adjuvant pembro treatment by intermittent therapies.

Outcome	Pembro in 1 L	Pembro in later line*	
	(N=51)	Pembro after Anti-PD1/CTLA4 (N=15)	Pembro after BRAF/MEKi (N=7)
ORR	19 (37.3 %)	0	0
DCR	29 (56.9 %)	3 (20.0 %)	0
Best response			
Complete response	9 (17.6 %)	0	0
Partial response	10 (19.6 %)	0	0
Mixed response	1 (2.0 %)	1 (6.7 %)	0
Stable disease	10 (19.6 %)	2 (13.3 %)	0
Progressive disease	18 (35.3 %)	10 (66.7 %)	4 (57.1 %)
Missing	3 (5.9 %)	2 (13.4 %)	3 (42.9 %)
Median FU (95 % CI)	14.5 (12.3–21.1)	23.3 (2.8-NR)	NR
Survival ** **(95 % CI)**			
Median PFS	7.4 (3.8–11.1)	1.7 (1.0–2.4)	1.5 (0.8–2.2)
Median OS	13.9 (3.5-NR)	7.6 (1.8–14.0)	1.7 (1.0–6.0)
Median ToT	6.1 (3.0–8.4)	1.7 (0.7–2.9)	0.8 (0.4–1.7)

N, number of patients; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; NR, not reached; CI, confidence interval.

* 4 of 23 patients in the pembro later line received both anti-PD1/anti-CTLA4 and BRAF/MEK inhibition. 5 of 23 patients in the pembrolater line received treatment other than anti-PD1/anti-CTLA4 and BRAF/MEK inhibition.

** Survival from start of non-adjuvant pembro treatment.

tumour activity for patients with advanced melanoma that responded to a first course of anti-PD1 independent if the patient was in CR, partial response (PR), stable disease (SD) or progressive disease (PD) after the first course of anti-PD1 treatment [14,15]. Eggermont et al. reported results in the 'rechallenge' part of the Keynote-054 study. Out of 47 patients who had a recurrence > 6 months after completing 1-year adjuvant pembro therapy 20 patients were retreated with pembro for up to 2 years. Among 9 patients with evaluable response to pembro in the metastatic setting, one reached CR, 3 patients were considered SD and 5 as PD. Compared to our study, the median PFS (4.1 months) and ORR (11 %) were lower. [16]

Owen et al. investigated retreatment of stage III/IV melanoma patients who relapsed during or after adjuvant anti-PD1 therapy and compared ipi (±PD1), BRAF/MEKi, and anti-PD1 monotherapy. While none out of 9 patients recurring on anti-PD1 adjuvant therapy responded to a rechallenge with anti-PD1, there were two responses with anti-PD1 out of 5 patients who recurred at least 1 month after end of adjuvant treatment. [17]

In contrast, our study demonstrates that also patients with early recurrence may respond to retreatment with pembro in the 1 L setting. In accordance with the SITC (Society for Immunotherapy of Cancer) definitions we defined the upper interval limit of 12 weeks after the last infusion for early recurrence. [18] On note, many of the patients with early recurrence were not immediately retreated but have had non-medical management such as surgery and radiotherapy of their recurrence in the first place and a non-adjuvant pembro retreatment only after further progression of disease at a later time point. It might therefore well be that immediate retreatment with anti-PD1 for early recurrences on adjuvant treatment is not useful because of ICI resistance, while delayed rechallenge might work again and reflect reconstitution of immunoreactivity over time.

A major part of the research on anti-PD1 resistance and its impact on later lines of therapy stems from studies in the advanced metastatic or non-resectable situation. When anti-PD1 antibodies were first registered, a salvage therapy with anti-CTLA4 was the major option available after progression to anti-PD1, in particular in BRAF V600 wildtype melanoma showing a potential for objective response. [19] In more recent time, combined ICI with ipi/nivo has become a frequent option after anti-PD1 failure with a durable PFS of around 5 months and OS of about 25 months. [20-22] A recent clinical trial comparing ipi with or without nivo showed a favorable hazard ratio for PFS in the combination arm. [23]

Although at least the study by Owen et al. suggests a similar role for anti-PD1/CTLA4 for recurrences while on adjuvant anti-PD1 [17], patients not suitable for the potential toxicity of combined ICI may still benefit from delayed anti-PD1 rechallenge.

In real-world evidence studies, ORR of pembro varied for 1 L treatments between 25 % and 49 %, and for all treatment lines between 24 % and 42 %. [10-12] In contrast to a retreatment with pembro in the 1 L advanced situation, rechallenge at a later line did not show to be beneficial in our study. In particular, pre-treatment with anti-PD1/CTLA4 or with BRAF/MEKi was not associated with meaningful responses to further pembro retreatment. For pre-treatment with BRAF/MEKi this is well in concordance with the results on sequencing ICI and targeted treatment in the metastatic situation, as it had been shown that ICI lose efficacy if given after BRAF/MEKi in the 2 L setting. [24-27]

In patients progressing on combined anti-PD1/CTLA4 there is no established treatment option available despite using BRAF/MEKi in BRAF V600 mutated melanoma, and new treatment options for these patients are urgently needed. In addition, patients retreated in later lines of treatment more frequently had elevated serum LDH level and stage M1c/d, and a higher burden of disease shown by the rate of ≥ 3 metastatic sites compared to those in 1 L. In accordance with the literature these all are prognostic factors for poorer outcome in patients with metastatic melanoma [28].

Finally, a similar situation may occur in the future for the emerging case of upcoming neoadjuvant treatments with ICI in resectable stage III melanoma, where re-treatment options need to be explored for those patients who recur after neoadjuvant pembro or ipi/nivo. [29,30]

Our study has several limitations, first its observational setting may be prone to several sources of statistical bias. The analyzed sample size of 74 cases can be considered small and the study population is not representative for patients recurring from adjuvant anti-PD1, since patients receiving pembro instead of e.g. combined ICI may have very different clinical characteristics leading to biased results. Still, so far and to our knowledge it is the largest population of pembro retreatment after adjuvant anti-PD1 failure. The observed survival outcomes of patients who relapsed on adjuvant anti-PD1 therapy are comparable to other studies, although our results differ slightly from those in the literature. The patient characteristics and risk profiles in this study differed from other similar studies, which may also contribute to the numerically higher responses and survival outcomes of patients in this study. Differences of real-world treatment strategies, baseline demographics and patient risk profiles, could also be reasons for discrepancies.

This real-world data analysis demonstrates that retreatment of patients who have failed adjuvant anti-PD1 therapy with pembro can be an effective option in the metastatic situation. A meaningful treatment response can be expected for delayed retreatments, while for immediate retreatments it might depend on factors that need to be explored in further due to the limited sample size in our study.

Ethics approval and consent to participate

This study is a retrospective database analysis. Submission of this study to an Institutional Review Board/Independent Ethics Committee was not required.

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CRediT authorship contribution statement

Helen Gogas: Writing – review & editing. **Friedegund Meier:** Writing – review & editing. **Lidija Kandolf:** Writing – review & editing. **Ulrike Leiter:** Writing – review & editing. **Iva Gavrilova:** Writing – review & editing. **Paolo Antonio Ascierto:** Writing – review & editing. **Inge Marie Svane:** Writing – review & editing. **Shan Jiang:** Writing – review & editing, Supervision, Conceptualization. **Michael Weichenthal:** Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Marc Bender:** Visualization, Validation, Software, Methodology, Formal analysis. **Jose Luis Manzano:** Writing – review & editing. **Pablo Cerezuela-Fuentes:** Writing – review & editing. **Eva Ellebaek:** Writing – review & editing. **Reinhard Dummer:** Writing – review & editing. **Dirk Schadendorf:** Writing – review & editing, Conceptualization. **Dimitrios Ziogas:** Writing – review & editing. **Peter Mohr:** Writing – review & editing, Conceptualization. **Christine Ruhlmann:** Writing – review & editing. **Johanna Mangana:** Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MW: consulting/advisory roles: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers and Squibb, Sun Pharma, Sanofi, Pierre Fabre. Honoraria: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers and Squibb, Sanofi. Research funding: institutional funding from Merck Sharp & Dohme, Bristol Myers and Squibb, Novartis, 4SC, Innate Pharma.

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