Efficacy of pembrolizumab in metastatic melanoma patients following adjuvant anti-PD1 treatment

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Background

The development of immune checkpoint inhibitors (ICI) and targeted therapy with BRAF and MEK inhibitors, has improved the treatment of unresectable and metastatic melanoma dramatically in recent years. Postoperative treatment of patients with either anti-PD1 antibodies or BRAF and MEK inhibitors in the adjuvant setting results in better recurrence free survival rates and has therefore become the standard of care for the majority of resected stage III melanoma, particularly stage IIIB/IID. Currently, there is insufficient evidence regarding efficacy of anti-PD1 antibodies in patients who need systemic treatment after failure of adjuvant ICI.

From the European Melanoma Treatment Registry (EUMelaReg) we have identified 74 patients, who were eligible for this analysis and evaluated the clinical characteristics outcome of patients who underwent non-adjuvant anti-PD1 treatment with pembrolizumab after failure of adjuvant anti-PD1 therapy.

Methods and Study Objectives

Adult (age ≥18 years) patients with non-resectable stage III or stage IV melanoma who were treated with non-adjuvant pembrolizumab after failure from adjuvant anti-PD1 treatment were selected from the EUMelaReg database. Patients treated with non-adjuvant pembrolizumab at 1st line or later line were stratified by timing of recurrence (early recurrence [recurrence occurred under treatment or within 12 weeks after end of treatment] and late recurrence [recurrence within >12 weeks after end of treatment]) and by reason for end of treatment in the adjuvant setting.

Primary outcomes of interest were (1) to describe the demographic features, clinical characteristics, and treatment history, (2) to describe time on treatment (TOT), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), among patients treated with pembrolizumab under real-world conditions after adjuvant anti-PD1 therapy, (3) to describe TOT, recurrence free interval, reasons for discontinuation of adjuvant treatment, and location of recurrence with anti-PD1 adjuvant therapy. Secondary objectives included TOT, ORR, PFS, and OS for included patients by reason for discontinuation in the adjuvant setting.

Results

We could analyze 74 cases with a pembrolizumab retreatment after failure from adjuvant anti-PD1 treatment, 51 of whom were treated in the 1st line setting after recurrence. Stratification by timing of recurrence show that patients with early recurrence (n=22) more often had an elevated serum LDH level (31.8% vs. 20.7%) and a higher metastatic stage M1c/d (40.9% vs. 24.1%) as compared to those with a late recurrence (n=29). Still, the overall response rates were not significantly different and accordingly, PFS and OS were similar in these groups (Fig.1)

Stratification by reason for end of adjuvant treatment showed that patients who ended treatment due to toxicity presented with lower melanoma stage IV M1c/d (29.4%) at recurrence than patients with regular treatment end (37.5%) or patients with disease progression (38.5%). Outcome stratified by reason for end of adjuvant treatment showed lower PFS for patients who progressed on adjuvant treatment (2.57 [1.94-9.11] months) compared to patients who ended treatment regularly (10.1 [2.93-NR] months) or due to toxicity (8.32 [3.78-15.4] months). Also, overall survival after recurrence was better in patients who had stopped adjuvant treatment regularly or due to side effects than in patients who had stopped for recurrence.

Patients treated with pembrolizumab in later line were younger (median age: 59 years) and had a higher metastatic stage M1c/d (73.9%) compared to patients who received pembrolizumab in 1st line (31.4% M1c/d). These patients showed a lower ORR (17.4%), lower PFS (5.53 [2.3-7.63] months) and lower ToT (1.89 [1.15-3.0] months) compared to patients treated with pembrolizumab in 1st line (ORR: 37.3%; PFS: early recurrence: 7.43 months, late recurrence: 6.12 months; ToT: early recurrence: 8.62 months, late recurrence: 5.56 months). Looking for the type of intermittent non-adjuvant treatments, patients pretreated with combined anti PD1/CTLA-4 (n=15) and/or BRAF-/MEK inhibitors (n=7) show no meaningful responses to pembrolizumab in a later line (Tab.3).

Table 1: Patient demographics and clinical characteristics

Characteristics	Pembrolizumab in 1st line treatment					Pembrolizumab in later line treatment	Total
	Early vs. late recurrence in adjuvant treatment N=51		Reason for end of adjuvant treatment N=46*				
	Early recurrence** (N=22)	Late recurrence*** (N=29)	Disease Progression (N=13)	Regularly Ended (N=16)	Toxicity (N=17)	(N=23)	(N=74)
Age at 1st line							
Mean (SD)	69.4 (16.8)	66.5 (16.8)	65.2 (19.2)	67.4 (11.1)	72.7 (16.3)	60.7 (14.1)	65.6 (16.2)
Median (Range)	77.0 (27.0-85.0)	71.0 (20.0-87.0)	73.0 (27.0-82.0)	65.0 (53.0-85.0)	78.0 (20.0-87.0)	59.0 (37.0- 83.0)	68.5 (20.0- 87.0)
AJCC staging v8							
Stage III	6 (27.3%)	6 (20.7%)	4 (30.8%)	2 (12.5%)	3 (17.6%)	2 (8.7%)	14 (18.9%)
Stage IV						1 (4.3%)	1 (1.4%)
Stage IV-M1a	5 (22.7%)	7 (24.1%)	3 (23.1%)	5 (31.3%)	4 (23.5%)	2 (8.7%)	14 (18.9%)
Stage IV-M1b	2 (9.1%)	9 (31.0%)	1 (7.7%)	3 (18.8%)	5 (29.4%)	1 (4.3%)	12 (16.2%)
Stage IV-M1c	8 (36.4%)	7 (24.1%)	4 (30.8%)	6 (37.5%)	5 (29.4%)	10 (43.5%)	25 (33.8%)
Stage IV-M1d	1 (4.5%)		1 (7.7%)			7 (30.4%)	8 (10.8%)
ECOG							
0	12 (54.5%)	18 (62.1%)	8 (61.5%)	10 (62.5%)	8 (47.1%)	10 (43.5%)	40 (54.1%)
1	6 (27.3%)	8 (27.6%)	3 (23.1%)	5 (31.3%)	6 (35.3%)	8 (34.8%)	22 (29.7%)
>=2	1 (4.5%)	1 (3.4%)	1 (7.7%)		1 (5.9%)	2 (8.7%)	4 (5.4%)
Unknown	3 (13.6%)	2 (6.9%)	1 (7.7%)	1 (6.3%)	2 (11.8%)	3 (13.0%)	8 (10.8%)
LDH							
Normal	11 (50.0%)	20 (69.0%)	6 (46.2%)	13 (81.3%)	10 (58.8%)	6 (26.1%)	37 (50.0%)
Elevated	7 (31.8%)	6 (20.7%)	5 (38.5%)	1 (6.3%)	6 (35.3%)	14 (60.9%)	27 (36.5%)
Missing	4 (18.2%)	3 (10.3%)	2 (15.4%)	2 (12.5%)	1 (5.9%)	3 (13.0%)	10 (13.5%)
Number of sites							
1	10 (45.5%)	17 (58.6%)	6 (46.2%)	7 (43.8%)	10 (58.8%)	5 (21.7%)	32 (43.2%)
2	8 (36.4%)	8 (27.6%)	6 (46.2%)	6 (37.5%)	3 (17.6%)	5 (21.7%)	21 (28.4%)
>=3	4 (18.2%)	4 (13.8%)	1 (7.7%)	3 (18.8%)	4 (23.5%)	13 (56.5%)	21 (28.4%)

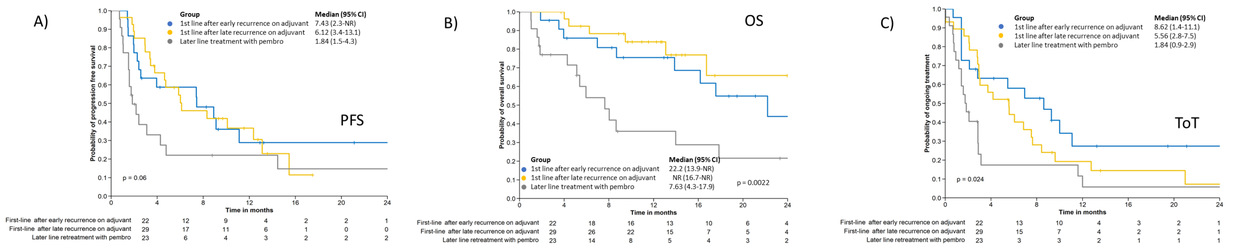
Abbreviations: N, number of patients; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase. *5 of 74 patients ended adjuvant therapy due to investigators decision/patient´s wish/other; **Early recurrence: recurrence occurred under treatment or within 12 weeks after end of treatment. ***Late recurrence: recurrence within >12 weeks after end of treatment

Table 2: Clinical outcomes and responses

Outcome	Pembrolizumab in 1st line treatment					Pembrolizumab in later line treatment	Total
	Early vs. late recurrence in adjuvant treatment N=51		Reason for end of adjuvant treatment N=46*				
	Early recurrence** (N=22)	Late recurrence*** (N=29)	Disease Progression (N=13)	Regularly Ended (N=16)	Toxicity (N=17)	(N=23)	(N=74)
ORR	9 (40.9%)	10 (34.5%)	3 (23.1%)	6 (37.5%)	9 (52.9%)	2 (8.7%)	21 (28.4%)
DCR	13 (59.1%)	16 (55.2%)	6 (46.2%)	9 (56.3%)	11 (64.7%)	6 (26.1%)	35 (47.3%)
Best response							
Complete response	3 (13.6%)	6 (20.7%)	1 (7.7%)	3 (18.8%)	4 (23.5%)	2 (8.7%)	11 (14.9%)
Partial response	6 (27.3%)	4 (13.8%)	2 (15.4%)	3 (18.8%)	5 (29.4%)		10 (13.5%)
Mixed response	1 (4.5%)		1 (7.7%)			1 (4.3%)	3 (4.1%)
Stable disease	4 (18.2%)	6 (20.7%)	3 (23.1%)	3 (18.8%)	2 (11.8%)	3 (13.0%)	2 (2.7%)
Progressive disease	8 (36.4%)	10 (34.5%)	6 (46.2%)	6 (37.5%)	4 (23.5%)	11 (47.8%)	13 (17.6%)
Missing		3 (10.3%)		1 (6.3%)	2 (11.8%)	6 (26.1%)	9 (12.2.2%)
Survival** (95% CI)**							
Median PFS	7.43 (2.3-NR)	6.12 (3.4-13.1)	2.57 (1.9-9.1)	10.10 (2.9-NR)	8.32 (3.8-15.5)	1.84 (1.51-4.28)	4.74 (3.0-8.3)
Median OS	22.20 (13.88-NR)	NR	13.88 (3.5-NR)	NR	NR	7.63 (4.28-17.86)	17.86 (13.9-NR)
Median ToT	8.62 (1.4-11.1)	5.56 (2.8-7.5)	6.94 (1.4-10)	6.84 (2.8-NR)	6.05 (1.6-12.8)	1.84 (0.92-2.86)	3.03 (2.8-6.8)

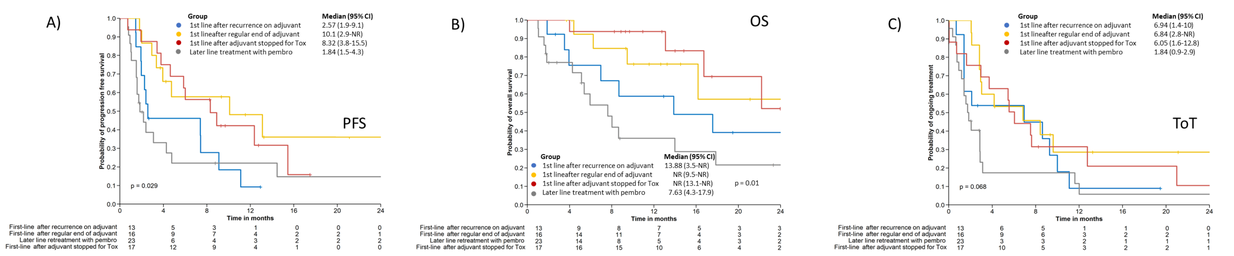
Abbreviations: N, number of patients; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; NR, not reached, CI, confidence interval. *5 of 74 patients ended adjuvant therapy due to investigators decision/patient´s wish/other; **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 pembrolizumab treatment

Figure 1: Survival outcomes stratified by timing of recurrence



Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS) and (C) time on treatment (ToT) at start of non-adjuvant pembrolizumab stratified by timing of recurrence (early and late recurrence) to adjuvant pembrolizumab treatment, CI, confidence interval; NR, not reached; pts, patients.

Figure 2: Survival outcomes stratified by reason for end of adjuvant treatment



Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS) and (C) time on treatment (ToT) at start of non-adjuvant pembrolizumab stratified by reason for end of treatment of adjuvant treatment (disease progression, regularly ended and toxicity) at adjuvant setting, CI: confidence interval, NR: not reached.

Table 3: Clinical outcomes and responses stratified by intermittent therapies

Outcome	Pembrolizumab in 1st line	Pembrolizumab in later line	
	Pembrolizumab as 1st line (N=51)	Pembrolizumab after Anti-PD1/CTLA-4 (N=15)	Pembrolizumab after BRAF/MEKi (N=7)
ORR	19 (37.3%)		
DCR	29 (56.9%)	3 (20.0%)	
Best response			
Complete response	9 (17.6%)		
Partial response	10 (19.6%)		
Mixed response	1 (2.0%)	1 (6.7%)	
Stable disease	10 (19.6%)	2 (13.3%)	
Progressive disease	18 (35.3%)	10 (66.7%)	4 (57.1%)
Missing	3 (5.9%)	2 (13.4%)	3 (42.9%)
Survival* (95% CI)			
Median PFS	7.40 (3.8-11.1)	1.74 (1.0-2.4)	1.51 (0.8-2.2)
Median OS	13.88 (3.5-NR)	7.63 (1.8-14.0)	1.74 (1.0-6.0)
Median ToT	6.05 (3.0-8.4)	1.74 (0.7-2.9)	0.76 (0.4-1.7)

Abbreviations: 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. *Survival from start of non-adjuvant pembrolizumab treatment

Conclusions

This study demonstrates the real-world potential of pembrolizumab treatment in advanced melanoma settings following adjuvant anti-PD1 treatment failure.

In 1st line, retreatment with pembrolizumab resulted in a response rate of 37.3% in the advanced setting, which compared well to the approximately 33% response rates reported for pembrolizumab in treatment naive patients in the KEYNOTE-006 study. Furthermore, patients who had stopped adjuvant treatment regularly or for side effects, showed a favorable response rate and survival on re-treatment with pembrolizumab.

In contrast, pembrolizumab in later line, in particular following failure of either combined anti-PD1/CTLA-4 or BRAF/MEKi could not achieve meaningful benefit.

This real-world study demonstrates that retreatment of patients with pembrolizumab who have failed adjuvant anti-PD1 therapy is a valuable treatment option in first-line, particularly if recurrences occur after end of adjuvant treatment.

Additional Information

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