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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma

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Abstract

Background Therapeutic chances for metastatic melanoma have consistently changed over the last years with the advent of antibodies targeting the programmed cell death protein-1 (PD-1). Onset of immune-related adverse events (irAEs) during treatment can be a source of concern, and the association with survival outcome is yet to be defined.

Patients and methods Data of consecutive patients treated with anti-PD1 (nivolumab or pembrolizumab) for metastatic melanoma between July 2013 and January 2018 were retrospectively reviewed. Baseline factors, together with onset of irAEs and vitiligo during treatment, were evaluated to identify predictors of progression-free (PFS) and overall (OS) survival. PFS and OS were assessed using Kaplan–Meier and Cox models.

Results Overall, 173 patients were included in the present analysis, and 102 patients (59%) experienced irAEs. Disease control rate was 51%. Median (interquartile range) PFS and OS were 4.9 (2.6–13.3) and 8.6 (3.5–18.3) months, respectively. At multivariate analysis, irAEs occurrence was independently associated with improved PFS [HR 0.47 (95% CI 0.26, 0.86); $p=0.016$], and correlated with better OS [HR 0.39 (95% CI 0.18, 0.81); $p=0.007$]. Among various irAEs, the occurrence of vitiligo was associated with a trend toward a non-significant improved OS in comparison with other irAEs ($p=0.061$). Median OS was undefined for patients experiencing vitiligo vs. 21.9 months for patients with other irAEs vs. 9.7 months for patients who had no irAEs ($p=0.003$).

Conclusions Our study underlines the association between irAEs and survival outcomes from anti-PD1 therapy. Careful management of treatment-related toxicity can lead to achieve maximum clinical benefit from this therapy.

Keywords Melanoma · Immunotherapy · Anti-PD1 · IrAEs · Vitiligo · Toxicity

Introduction

Immune checkpoint inhibitors (ICIs) have dramatically improved the prognosis of patients with melanoma over the past decade (Hodi et al. 2010; Weber et al. 2015; Ribas et al. 2015; Larkin et al. 2015). Monoclonal antibodies (Ab) acting as ICIs modulate the immune system through targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1). Recent phase III trials have demonstrated higher response rates and improved survival outcomes for ICIs compared with chemotherapy, leading to the approval of these drugs as mono- and combination therapies for metastatic melanoma (Hodi et al. 2010; Weber et al. 2015; Ribas et al. 2015; Larkin et al. 2015).

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To date, three ICIs have been approved for the treatment of metastatic melanoma: the anti-CTLA4 antibody ipilimumab, and the anti-PD1 antibodies nivolumab and pembrolizumab, while others are currently under study (i.e., the PD-L1 targeted mAb, atezolizumab; the PD-1 targeted mAb, spartalizumab). Anti-PD1 antibodies have also demonstrated their superiority in prolonging both progression-free (PFS) and overall (OS) survival if compared to anti-CTLA-4 drugs (Robert et al. 2015), and the combination of these two drugs seems to further improve outcomes (Larkin et al. 2015). However, only a subset of patients gain clinical benefit from these treatments, with disease response rates accounting for only ~ 20% of patients receiving ipilimumab, and 35–60% of patients receiving anti-PD-1-based immunotherapy (Hodi et al. 2010; Weber et al. 2015; Ribas et al. 2015). Moreover, ICIs are associated with a peculiar spectrum of immune-related adverse events (irAEs), which can virtually affect all body systems and range widely in their severity. Anti-PD1 antibodies have a safer toxicity profile, with an overall lower incidence of irAEs compared with ipilimumab (Hodi et al. 2010; Weber et al. 2015; Ribas et al. 2015; Larkin et al. 2015; Robert et al. 2015; Topalian et al. 2012). The combination of these two drugs has been characterized by a high (up to 50%) incidence of serious irAEs (Larkin et al. 2015). Moreover, even if rarely described, also fulminant and fatal toxic irAEs can possibly complicate these innovative therapies (Wang et al. 2018). At the basis of immune-related toxicity lies an aberrant autoimmune T-cell activation, suggesting a possible association between irAEs onset and derived clinical benefit from ICIs. However, to date, reports of patients developing irAEs during treatment with ICIs have been contradictory regarding the impact of toxicity on survival outcome, and a clear association between these two variables has not been found yet.

In this study, we aimed to identify factors related to response to anti-PD1 treatment in a population of patients with metastatic melanoma, and investigate the potential association of irAEs onset with survival outcomes.

Patients and methods

This study received the approval of our Institutional Review Board (IRB). We retrospectively analyzed patients with advanced/metastatic melanoma treated with anti-PD1 therapy at our institution from July 2013 to January 2018. Inclusion criteria were diagnosis of unresectable (stage III) or metastatic (stage IV) melanoma, treatment with at least three doses of anti-PD1 therapy, and available radiologic assessment for disease response. All patients gave their written informed consent for use of clinical data for scientific purposes. Patients were treated with intravenous pembrolizumab 2 mg/kg once every 21 days, or nivolumab 3 mg/kg once every 14 days. Treatment was administered for a total of 24 months, until disease progression, a report of unacceptable toxic effects, or patients' decision. Clinical assessments were performed according to the standard of care at our institution. Radiological disease assessment was made with whole body computed tomography (CT) scans performed at baseline and every 4–6 courses (every 3 months). Clinical response to treatment was categorized as either complete response (CR), partial response (PR), stable disease (SD) (meaning disease stability maintained over a period ≥ 6 months), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 criteria. Best overall response (BOR) was defined as the best achieved response from the start of anti-PD1.

Demographic and baseline patients' characteristics, together with data regarding previous systemic treatment were collected for the present study. *BRAF* mutation status was determined on primary or metastatic tumor tissue with polymerase chain reaction (PCR) amplification and direct sequencing (Thermo Fisher Scientific, Life Technologies, 3500 DX Genetic Analyzer). Performance status (PS) at the beginning of treatment was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale. Disease stage at anti-PD1 initiation was assessed according to the American Joint Committee on Cancer (AJCC) VIII edition staging system. Data regarding AEs were collected according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Differences in survival and response to anti-PD1 treatment were investigated according to clinical and biochemical variables: age, gender, ECOG PS, site of primary melanoma, presence of tumor-infiltrating lymphocytes (TIL) on primary tumor tissue, *BRAF* mutational status, disease stage and pattern of visceral tumor involvement, previous adjuvant treatment, previous systemic therapy, concomitant radiotherapy, baseline serum LDH levels and complete blood count (leukocyte count, absolute, and relative counts of lymphocytes, neutrophils, monocytes, eosinophils, and basophils). PFS was defined as the time from treatment start until the date of disease progression (local, regional, or distant metastasis) or diagnosis of new primary melanoma; OS was defined as the time from treatment start until the date of death from any cause. Patients were followed up for safety after treatment withdrawal, and data regarding irAEs incidence and features were collected. Treatment-related irAEs were managed following the recently published American Society of Clinical Oncology (ASCO) clinical practice guidelines for irAEs (Brahmer et al. 2018).

Statistical analysis

Data are summarized using basic descriptive statistics. Normality testing (D'Agostino and Pearson test) was performed

to determine whether data were sampled from a Gaussian distribution. Mann–Whitney *U* test was used to compare continuous nonparametric variables. Incidence of events among the groups was analyzed for statistical significance using the Fisher exact test. Odds ratio (OR) and 95% confidence intervals (CI) were calculated for each comparison. Survival outcomes were evaluated with both Kaplan–Meier and Cox models. Hazard ratio (HR) and 95% CI were calculated for each comparison. Univariate and multivariate analysis were performed when appropriate, using Cox proportional hazard model. All covariates with a p value less than 0.10, based on univariable analysis were included in the multivariable model. All p values were two-sided. p values < 0.05 were statistically significant.

Statistical analysis was performed with GraphPad Prism version 6.0 for Mac (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS (SPSS Statistics. International Business Machines Corporation IBM. 2013. Armonk, USA) version 20.0 for Mac.

Results

Patients and treatments

Overall, 229 patients were treated with anti-PD1 during the study period. After the exclusion of 56 patients who did not meet the inclusion criteria, 173 patients were included in the present analysis (107 males, 66 females). Figure 1 shows the flow of patients through the study design. The mean (SD) age was 60.8 (± 14.1) years. The primary site of melanoma was cutaneous in 130 patients (75%), uveal in 14 (8%) and mucosal in 11 (7%); 18 patients (10%) had unknown primary site melanoma. All patients had stage IV disease: 33 patients (19%) had M1a, 15 (9%) had M1b, 94 (54%) had M1c, and 31 (18%) had M1d disease. *BRAF* mutation status was wild type in 125 patients (72%) and mutated in 40 patients (23%); 8 patients with uveal melanoma (5%) were not tested for *BRAF* mutation status. ECOG PS was 0 in 120 patients (69%), 1 in 46 patients (27%) and 2 in 6 patients (4%). LDH levels were ≤ upper limit of normal (ULN) in 114 patients (66%), while 18 patients (10%) had LDH ≥ ULN and 11 (7%) had LDH ≥ 2 × ULN; for 30 patients (17%), data on serum LDH value was not available. Table 1 shows patients' baseline characteristics.

Fourteen patients (8%) received systemic treatment in the adjuvant setting, which consisted of immunotherapy [either with interferon (IFN), melanoma-associated antigen-A (MAGE-A) vaccine, pembrolizumab, or ipilimumab] for 13 patients, while one patient received adjuvant chemotherapy. Ninety-nine patients (57%) received at least one prior systemic treatment for metastatic disease; 82 patients (47%) received previous ipilimumab. Considering the *BRAF* mutant population, anti-PD1 was administered as first-line treatment in 5 patients (3%), while 27 patients (16%) had received prior BRAFi +/- MEKi therapy. Anti-PD1 treatment consisted of nivolumab in 105 patients (61%) and pembrolizumab in 68 (39%). Treatment was administered for a median time of 6 months (range 2–46). At the time of the present analysis, 56 patients (32%) are actively on treatment; 11 (6%) completed the 24 months of treatment, while 106 (61%) withdrew treatment for either PD (90 patients, 52%), or other reasons (irAEs, patients' decision, lost to follow-up).

Safety

Treatment-related irAEs (any grade) occurred in 102 patients (59%), and 55 of them experienced more than one AE. The most frequently reported irAEs were mild (i.e., G 1–2) and included fatigue (19%), AST and ALT increase (11%), hypothyroidism (8%), nausea (8%), skin rash (7%), pruritus (6%), arthralgias (6%), and diarrhea (6%). Eleven patients (6%) had severe (i.e., G 3–5) irAEs; one patient

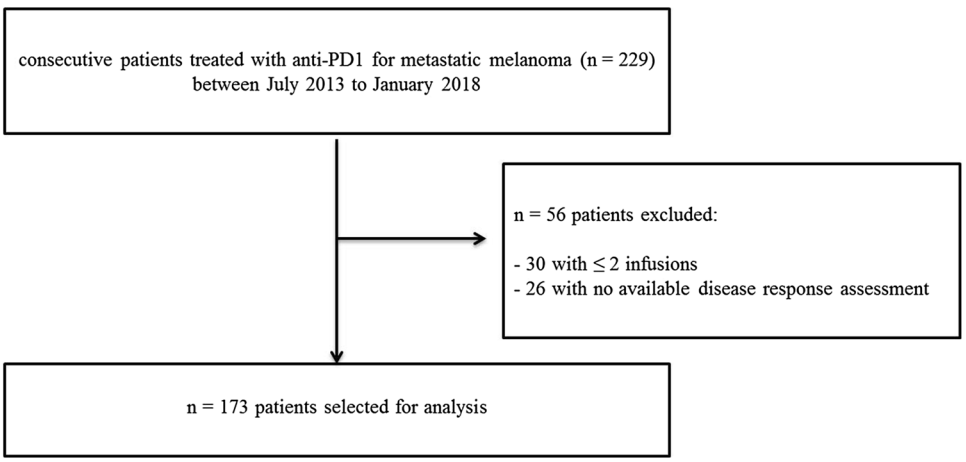

Fig. 1 Flow diagram of patients through the study design

Table 1 Main characteristics of the study population ($n = 173$)

Age, years (*N*%)	
< 65	76 (44%)
≥ 65	97(56%)
Mean (SD)	60.8 (± 14.1)
Median (range)	62 (18–85)
Gender, *N* (%)	
Male	107 (62%)
Female	66 (38%)
ECOG performance status, *N* (%)	
0	120 (69%)
1	46 (27%)
2	6 (4%)
Site of primary disease, *N* (%)	
Cutaneous	130 (75%)
Mucosal	11 (7%)
Uveal	14 (8%)
Unknown	18 (10%)
TILs, *N* (%)	
Brisk	5 (3%)
Non-brisk	17 (10%)
Absent	34 (20%)
Undetermined	117 (67%)
BRAF mutation status, *N* (%)	
Wild type	125 (72%)
Mutant	40 (23%)
Undetermined[a]	8 (5%)
Baseline LDH value, *N* (%)	
< ULN	114 (66%)
> ULN	18 (11%)
> 2× ULN	11 (6%)
Unknown	30 (17%)
M category, *N* (%)	
M1a	33 (19%)
M1b	15 (9%)
M1c	94 (54%)
M1d	31 (18%)
Number of metastatic sites, *N* (%)	
< 3	94 (54%)
≥ 3	79 (46%)
Line of treatment, *N* (%)	
First line	74 (43%)
Second line or later	99 (57%)
Previous ipilimumab, *N* (%)	
No	91 (53%)
Yes	82 (47%)
Duration of anti-PD1 therapy (months)	
Median (range)	6 (2–46)
Time interval to best response achieved (months)[b]	
Mean (SD)	9.0 (8.6)
Median (range)	6.0 (1, 46)
Response to anti-PD1, *N* (%)	
Complete response	11 (7%)
Partial response	30 (17%)
Stable disease	47 (27%)
Progressive disease	85 (49%)
Patients experiencing irAEs, *N* (%)	
Yes	102 (59%)
No	71 (41%)
Toxicity[c]	
AEs G1–2	118 (68%)
AEs G3–5	11 (6%)
Follow-up (months)	
Mean (SD)	12.8 (± 11.9)
Median (range)	9 (1–57)

[a]Undetermined BRAF status for patients with uveal melanoma

[b]Time interval to best response achieved in patients having stable disease and partial response

[c]Toxicity: 55 patients experienced more than one irAE

had a fatal irAE, consisting of an autoimmune myasthenia gravis overlapped with myositis. No baseline clinical and biochemical factors were found to predict for irAEs occurrence. Treatment discontinuation due to irAEs onset was reported in 13 patients (7%), with the most common being colitis and myasthenia gravis/myositis. At the time of the present analysis, all irAEs had completely resolved except for vitiligo, peripheric sensory neuropathy (3 patients), and endocrine irAEs requiring permanent hormone replacement therapy. Table 2 shows details of treatment-related toxicities. Overall, 40 (23%) patients required steroids as the treatment of irAEs: no differences in clinical outcomes were observed between patients receiving steroids for the management of irAEs and those who did not.

Response rate and survival

Overall response rate (ORR) was 24%: 11 patients (7%) had CR and 30 (17%) had PR. Disease control rate (DCR) was 51%, including 47 patients (28%) experiencing SD. After a median (range) follow-up of 9 (1–57) months, 85 patients (49%) experienced PD: 29 patients (17%) continued treatment beyond progression, 14 of them combined with local treatment at the site of disease progression when feasible (surgery, radiotherapy, trans-arterial chemoembolization). At the time of this analysis, 83 patients (48%) had died. The most commonly reported cause of death was disease progression (80 patients, 46%). One death was attributed to anti-PD1 toxicity (autoimmune myasthenia gravis overlapped with myositis). Median (interquartile range) PFS and OS were 4.9 (2.6–13.3) and 8.6 (3.5–18.3) months, respectively

Table 2 Treatment-related toxicity, *N* (%)

	G 1–2	G 3–5
Cutaneous		
Rash	12 (7)	0
Pruritus	11 (6)	0
Lichen	1 (< 1%)	0
Vitiligo	8 (4%)	–
General disorders		
Fatigue	33 (19)	1 (< 1)
Fever	4 (2%)	0
Infusion-related reaction	2 (1%)	0
Decreased appetite	6 (3%)	0
Gastrointestinal		
Dysgeusia	2 (1)	–
Dry mouth	2 (1)	–
Oral mucositis	2 (1)	0
Nausea	13 (7%)	0
Vomiting	0	1 (< 1)
Gastritis	2 (1)	0
Colitis	0	1 (< 1)
Diarrhea	10 (6)	0
Hepatic		
AST, ALT increase	18 (10)	1 (< 1)
γGT increase	1 (< 1)	0
Pancreatic		
Amylase increased	2 (1)	0
Lipase increased	3 (2)	0
Hyperglycemia	1 (< 1)	0
Renal		
Serum creatinine increase	2 (1)	0
Acute renal failure	1 (< 1)	0
Pulmonary		
Cough	5 (3)	0
Interstitial pneumonitis	1 (< 1)	1 (< 1)
Rheumatologic		
Arthralgias	11 (6)	1 (< 1)
Endocrine		
Hypothyroidism	14 (8)	0
Hypophysitis	1 (< 1)	1 (< 1)
Hematologic		
Anemia	6 (3)	0
Thrombocytopenia	3 (2)	1 (< 1)
Neurologic		
Myasthenia with myositis	0	1 (< 1)
Headache	2 (1)	0
Paresthesia	2 (1)	0
Peripheric sensory neuropathy	6 (3)	2 (1)
Peripheric motor neuropathy	1 (< 1)	
Eye disorders		
Uveitis	1 (< 1)	0
Conjunctivitis	1 (< 1)	0
Photophobia	2 (1)	0

(Fig. 2). Supplemental table 1 outlines baseline clinical and biochemical characteristics of patients' population obtaining DCR with anti-PD1 treatment. There was a slight, non-significant association between irAEs occurrence and ORR [HR 1.95 (95% CI 0.91, 4.15); $p < 0.082$], while the occurrence of irAEs correlated with DCR [HR 1.98 (95% CI 1.07, 3.67); $p < 0.029$]. Considering the subgroup of patients who completed the 24-month treatment, BOR was CR in 5, PR in 3 and SD in 3 patients, respectively. All these patients were alive and disease-free after a median (range) follow-up of 34.7 (24.8–57.3) months.

Looking at factors predicting PFS, via univariate analysis, patients' baseline clinical and disease characteristics, as well as blood tests, influenced PFS. In particular, our analysis underlined an association between PFS and age [HR 0.98 (95% CI 0.72, 0.99) per 10-year increase; $p = 0.034$], site of primary melanoma [HR 2.03 (95% CI 1.24, 3.34) per non-cutaneous vs. cutaneous melanoma; $p = 0.005$], presence of ≥ 3 metastatic site [HR 1.93 (95%: 1.29, 2.89); $p = 0.001$], neutrophil to lymphocyte ratio (NLR) [HR 1.07 (95% CI 1.03, 1.11); $p < 0.001$], lymphocyte to monocyte ratio (LMR) [HR 0.89 (95% CI 0.80, 1.01; $p = 0.075$], relative lymphocyte count (RLC) [HR 0.95 (95% CI 0.92, 0.98); $p = 0.002$] and LDH level > ULN [HR 2.59 (95% CI 1.55, 4.32); $p < 0.001$). Additionally, the occurrence of irAEs correlated with improved DFS [HR 0.54 (95% CI 0.36, 0.81); $p = 0.003$]. Figure 3 displays the association between clinical and biochemical factors with PFS.

Using multivariate analysis, only the presence of ≥ 3 metastatic sites [HR 1.83 (95% CI 1.007, 3.43); $p = 0.048$] and LDH level > ULN [HR 2.11 (95% CI 1.02, 4.38); $p = 0.043$] correlated with worse PFS; NLR increase [HR 1.06 (0.99, 1.13); $p = 0.066$] was also associated with a non-statistically significant trend toward worse PFS. The only factor that was independently associated with improved PFS was the occurrence of irAEs [HR 0.47 (95% CI 0.26, 0.86); $p = 0.016$]. Table 3 reports factors associated with PFS at univariate and multivariate analyses.

Considering factors influencing OS, via univariate analysis we observed that site of primary melanoma [HR 1.94 (95% CI 0.12, 3.39) per non-cutaneous vs. cutaneous melanoma; $p = 0.018$], presence of ≥ 3 metastatic sites [HR 1.70 (95% CI 1.10, 2.64); $p = 0.017$], NLR [HR 1.09 (95% CI 1.05, 1.14); $p < 0.001$], LMR [HR 0.81 (95% CI 0.71, 0.92); $p = 0.002$], RLC [HR 0.96 (95% CI 0.95, 0.98); $p < 0.001$], relative monocyte count [HR 1.10 (95% CI 0.98, 1.24); $p = 0.077$] and LDH level > ULN [HR 3.32 (95% CI 1.94, 5.67); $p = 0.001$] were associated with OS. The occurrence of irAEs correlated with improved OS [HR 0.57 (95% CI 0.36, 0.89); $p = 0.014$]. Figure 4 displays the association between clinical as well as biochemical factors with OS. Among various irAEs, the occurrence of vitiligo was associated with better OS. Patients experiencing vitiligo had

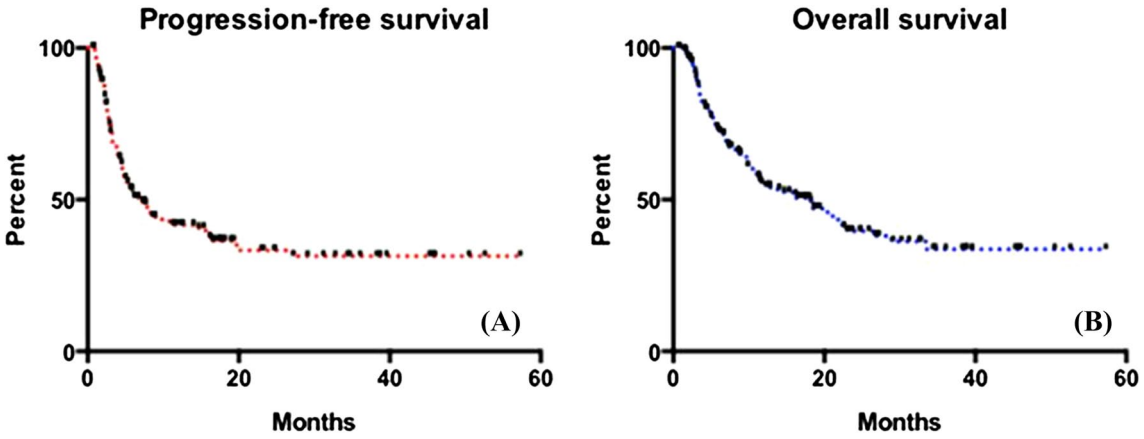

Fig. 2 Mean PFS (**a**) and OS (**b**) of the study population

a slightly improved OS in comparison with other irAEs ($p=0.061$, log-rank test). This comparison was more evident when we compared those groups with patients who had no irAEs ($p=0.003$): median OS was undefined for patients experiencing vitiligo vs. 21.9 months for patients with other irAEs vs. 9.7 months for patients who had no irAEs (Fig. 5).

Via multivariate analysis, the site of primary melanoma [HR 2.34 (95% CI 0.93, 5.84) per non-cutaneous vs. cutaneous melanoma; $p=0.068$] was associated with a non-statistically significant trend toward worse OS. Biochemical factors that correlated with OS were NLR [HR 1.08 (95% CI 1.01, 1.15); $p=0.028$] and LDH level > ULN [HR 2.85 (95% CI 1.26, 6.42); $p=0.012$]. As observed for PFS, the occurrence of irAEs correlated with better OS [HR 0.39 (95% CI 0.18, 0.81); $p=0.007$]. Table 4 shows factors predicting for OS at univariate and multivariate analysis.

Discussion

The present study evaluated how the onset of irAEs during anti-PD1 treatment reflects disease response and clinical benefit in patients with metastatic melanoma, thus suggesting a number of noteworthy findings. First, our results show a correlation between both clinical (site of primary melanoma, metastases burden, ECOG PS) and biochemical factors (baseline LDH and RLC values), and response to therapy. Second, we confirmed the relatively high prevalence of irAEs during anti-PD1 therapy. Third, the onset of irAEs during treatment appears to be strongly associated with better PFS and OS. Fourth, among various irAEs, the occurrence of vitiligo was associated with better OS.

ICIs have changed therapeutic chances and prognosis of patients with metastatic melanoma, at the expense of immune-related toxicity. There is evidence for an association between the onset of autoimmune phenomena and clinical activity of immunotherapy (e.g., dendritic cell vaccination (Boudewijns et al. 2016), anti-CTLA4) (Downey et al. 2007; Bouwhuis et al. 2011; Hu et al. 2014) in patients with melanoma. Exposure to higher doses of ipilimumab has correlation with increased tumor response, longer survival, and higher rates of irAEs (Feng et al. 2013). Regarding anti-PD1, it is still not clear whether development of irAEs reflects response to treatment and translates into better survival outcomes. Data on patients with non-small cell lung cancer (NSCLC) treated with nivolumab showed that ORR and PFS were significantly better in patients who developed irAEs than in patients who did not develop irAEs (Toi et al. 2018). There are only few studies in literature that specifically addressed this point in melanoma patients. A retrospective analysis of patients receiving nivolumab for resected and unresectable metastatic melanoma showed a strong association with survival only for cutaneous irAEs (including vitiligo), while there was no significant survival difference in patients experiencing other irAEs (i.e., endocrinopathies, colitis, or pneumonitis) (Freeman-Keller et al. 2016). Vitiligo, on the other hand, has been associated with favorable outcomes in patients receiving high dose adjuvant interferon (Gogas et al. 2006) and high dose interleukin-2 (Boasberg et al. 2006) for unresectable melanoma, and there is also evidence for this association with both anti-CTLA4 (Teulings et al. 2015) and anti-PD1 therapy (Freeman-Keller et al. 2016; Hua et al. 2016; Nakamura et al. 2017).

The main weaknesses of the present study include the inherent biases of the retrospective, single centre study design. The main strength of the present investigation is that it reports data from a heterogeneous population of non-selected patients, including a subset of patients with non-cutaneous melanomas, highlighting the association between irAEs onset (all kinds) and outcome of anti-PD1 therapy. In our series, well-recognized clinical (i.e., site of primary melanoma, metastases burden, and ECOG PS) and biochemical

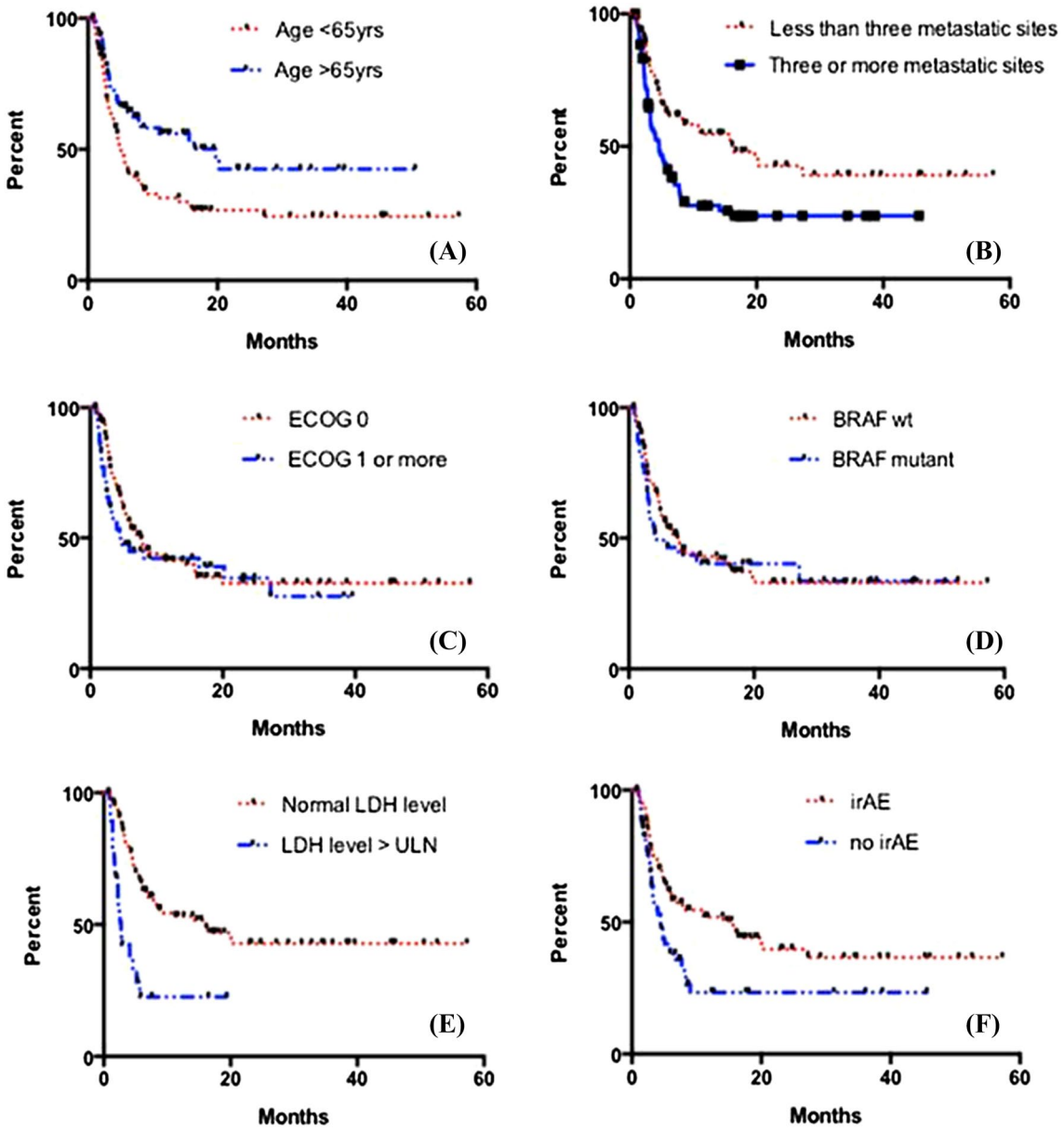

Fig. 3 PFS according to age (**a**), number of metastatic sites (**b**), ECOG PS (**c**), BRAF status (**d**), LDH value (**e**), irAEs onset (**f**)

(baseline LDH value, and RLC) factors confirmed to be related with better treatment outcomes (Weide et al. 2016; Nosrati et al. 2017; Nakamura et al. 2016; Heidelberger et al. 2017). Additionally, our investigation underlines the importance of irAEs in predicting survival outcomes. The overall toxicity profile observed in our population was consistent with prior studies of anti-PD1 treatment (Weber et al. 2015, 2017b; Ribas et al. 2015; Robert et al. 2015): the most common irAEs were mild (i.e., G1–2) and transient, and involved the skin and the endocrine system. A consistent proportion of patients experienced fatigue, which is frequently reported during treatment with ICIs and seems to occur cumulatively with therapy (Ku et al. 2010). Vitiligo was quite uncommon (7% of patients) but strongly correlated with better OS. Serious (i.e., G 3–5) adverse events were infrequent, and responded well to anti-PD1 temporary withdrawal and steroid administration. One patient died of treatment-related toxicity (autoimmune myasthenia gravis overlapped with myositis).

This report from our experience stress the need for careful patients' monitoring and prompt intervention, always bearing in mind that immune-related toxicities can be difficult to predict and diagnose, and possibly fatal in their outcome (Wang et al. 2018). This is particularly important considering the spreading use of these therapies, both as maintenance treatments and in the adjuvant setting (Weber et al. 2017a; Eggermont et al. 2018). The evidence of an association between

Table 3 Factors predicting PFS in patients with metastatic melanoma undergoing anti-PD-1 therapy

Characteristic	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Age (years)*	0.98 (0.72, 0.99)	**0.034**	0.98 (0.96, 1.004)	0.108
ECOG PS		0.592		–
0	Reference		–	
≥ 1	1.09 (0.78, 1.54)		–	
Sex		0.940		–
Female	Reference		–	
Male	0.98 (0.65, 1.47)		–	
Site of primary melanoma		**0.005**		0.141
Cutaneous	Reference		Reference	
Non-cutaneous	2.03 (1.24, 3.34)		1.81 (0.82, 4.07)	
Uveal melanoma		0.123		–
No	Reference		–	
Yes	1.65 (0.87, 3.11)		–	
TIL		0.729		–
Absent	Reference		–	
Present	0.87 (0.40, 1.88)		–	
Metastatic disease at diagnosis		0.491		–
No	Reference		–	
Yes	1.21 (0.69, 2.10)		–	
Adjuvant treatment		0.214		–
No	Reference		–	
Yes	0.61 (0.28, 1.32)		–	
BRAF mutation		0.567		–
No	Reference		–	
Yes	1.14 (0.71, 1.82)		–	
Previous systemic therapy		0.101		–
No	Reference		–	
Yes	1.43 (0.93, 2.19)		–	
Number of metastatic sites		**0.001**		**0.048**
< 3	Reference		Reference	
≥ 3	1.93 (1.29, 2.89)		1.83 (1.007, 3.43)	
Visceral involvement		0.491		–
No	Reference			
Yes	1.15 (0.76, 1.72)		–	
CNS involvement		0.222	–	–
No	Reference		–	
Yes	1.37 (0.82, 2.34)		–	
NLR*	1.07 (1.03, 1.11)	**< 0.001**	1.06 (0.99, 1.13)	0.066
LMR*	0.89 (0.80, 1.01)	**0.075**	0.97 (0.79, 1.20)	0.834
Neutrophils %	1.03 (1.01, 1.06)	0.003	–	–
Lymphocytes %	0.95 (0.92, 0.98)	**0.002**	0.98 (0.92, 1.04)	0.577
Monocytes %	1.04 (0.93, 1.15)	0.448	–	–
Eosinophils %	0.91 (0.78, 1.05)	0.210	–	–
LDH level > ULN		**< 0.001**		**0.043**
No	Reference		Reference	
Yes	2.59 (1.55, 4.32)		2.11 (1.02, 4.38)	
irAEs		**0.003**		**0.016**
No	Reference		Reference	
Yes	0.54 (0.36, 0.81)		0.47 (0.26, 0.86)	
Concomitant RT		0.827		**–**
No	Reference		**–**	
Yes	0.94 (0.55, 1.59)		**–**	

*Hazard ratio per 10-year increase in age, and 1-unit increase in NLR and LMR. Variables characterized by *p* value < 0.10 are presented in bold characters

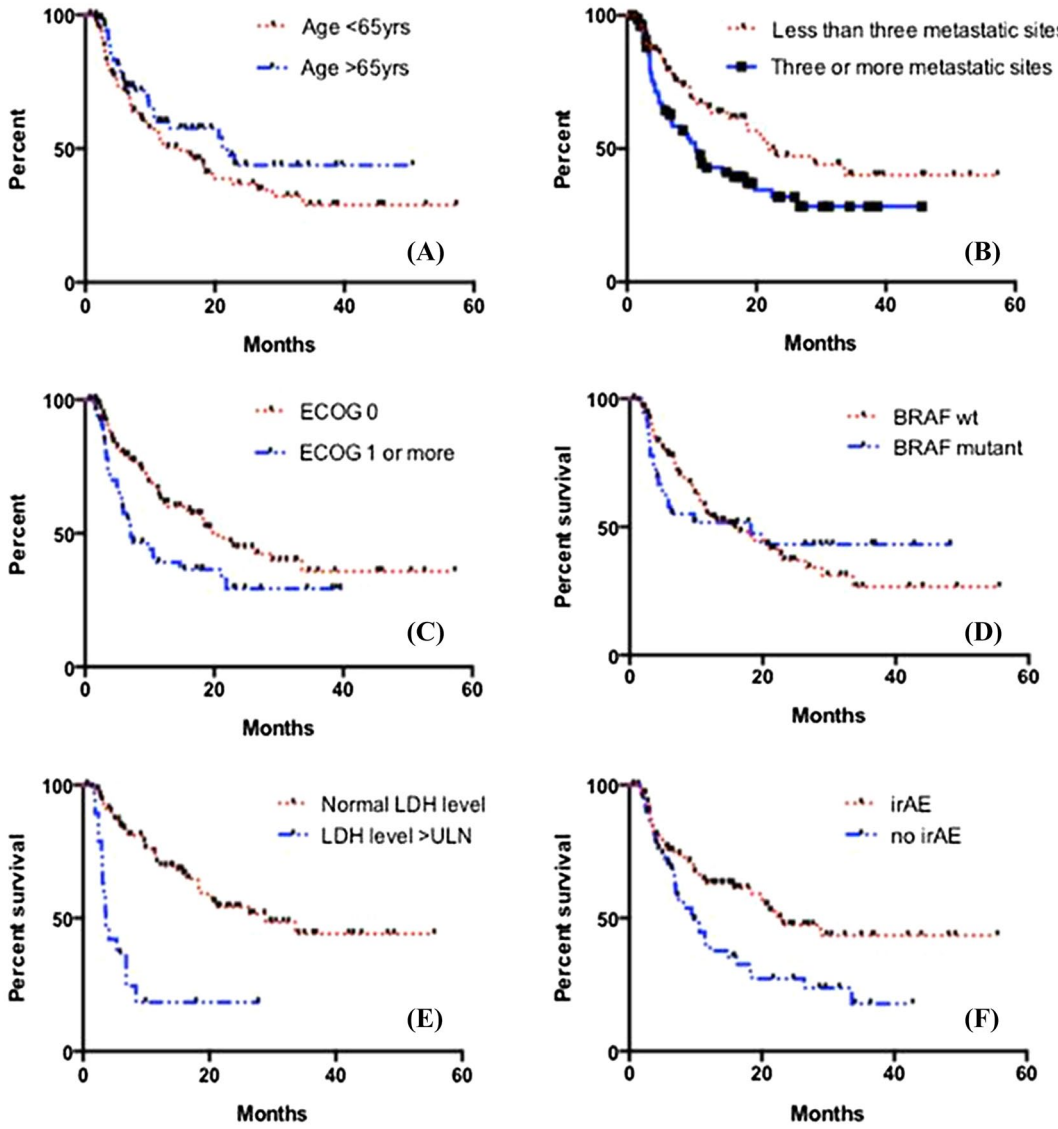

Fig. 4 OS according to age (**a**), number of metastatic sites (**b**), ECOG PS (**c**), BRAF status (**d**), LDH value (**e**), irAEs onset (**f**)

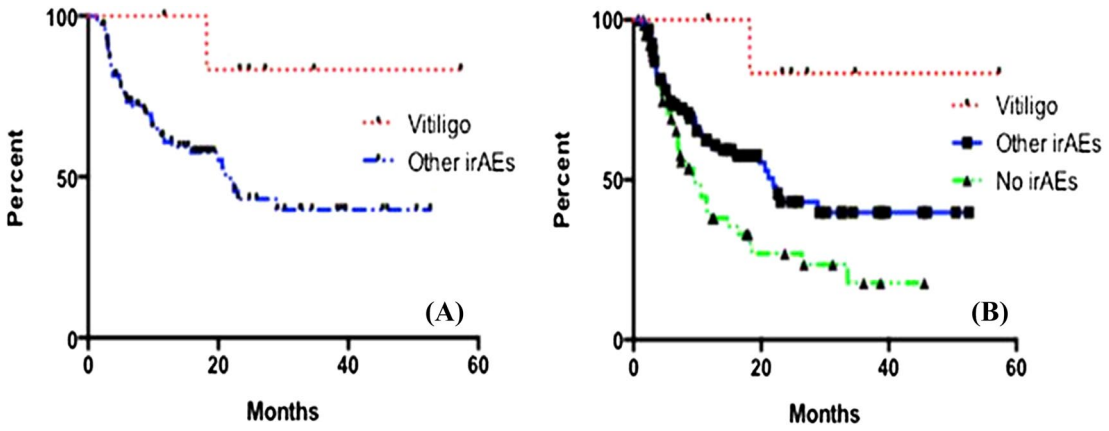

Fig. 5 OS for patients experiencing vitiligo vs. other irAEs (**a**); median OS for patients experiencing vitiligo vs. patients with other irAEs vs. patients with no irAEs (**b**)

Table 4 Factors predicting OS in patients with metastatic melanoma undergoing anti-PD-1 therapy

Characteristic	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Age (years)*	0.95 (0.81, 1.11)	0.548	–	–
ECOG PS		0.105		–
0	Reference		–	
≥ 1	1.33 (0.94, 1.90)		–	
Sex		0.341		–
Female	Reference		–	
Male	1.24 (0.79, 1.97)		–	
Site of melanoma		**0.018**		0.068
Cutaneous	Reference		Reference	
Non-cutaneous	1.94 (0.12, 3.39)		2.34 (0.93, 5.84)	
Uveal melanoma		0.256		–
No	Reference		–	
Yes	1.50 (0.74, 3.03)		–	
TIL		0.928		
Absent	Reference			
Present	0.96 (0.40, 2.26)			
Metastatic disease at diagnosis		0.685		–
No	Reference		–	
Yes	1.13 (0.61, 2.01)		–	
Adjuvant treatment		0.655		–
No	Reference		–	
Yes	0.82 (0.35, 1.91)		–	
BRAF mutation		0.908		–
No	Reference		–	
Yes	1.03 (0.61, 1.73)		–	
Previous systemic therapy		0.642		–
No	Reference		–	
Yes	1.12 (0.69, 1.81)		–	
Number of metastatic sites		**0.017**		0.882
< 3	Reference		Reference	
≥ 3	1.70 (1.10, 2.64)		1.05 (0.52, 2.01)	
Visceral involvement		0.297		–
No	Reference			
Yes	1.26 (0.81, 1.98)		–	
CNS involvement		0.366	–	–
No	Reference		–	
Yes	1.34 (0.73, 2.32)		–	
NLR*	1.09 (1.05, 1.14)	**< 0.001**	1.08 (1.01, 1.15)	**0.028**
LMR*	0.81 (0.71, 0.92)	**0.002**	0.99 (0.76, 1.28)	0.969
Neutrophils %	0.99 (0.99, 1.004)	0.380	–	–
Lymphocytes %	0.96 (0.95, 0.98)	**< 0.001**	0.94 (0.87, 1.04)	0.111
Monocytes %	1.10 (0.98, 1.24)	**0.077**	1.11 (0.95, 1.34)	0.181
Eosinophils %	0.91 (0.72, 1.15)	0.446	–	–
LDH > ULN		**0.001**		**0.012**
No	Reference		Reference	
Yes	3.32 (1.94, 5.67)		2.85 (1.26, 6.42)	
irAEs		**0.014**		**0.007**
No	Reference		Reference	
Yes	0.57 (0.36, 0.89)		0.39 (0.18, 0.81)	
Concomitant radiotherapy		0.765		–
No	Reference		–	
Yes	0.87 (0.65, 1.89)		–	

*Hazard ratio per 10-year increase in age, and 1-unit increase in NLR and LMR. Variables characterized by *p* value < 0.10 are presented in bold characters

safety and treatment efficacy might eventually be integrated in decision making for patients experiencing irAEs, to define the best management strategy on the basis of irAEs kind and severity, but also considering disease response.

In conclusion, our study underlines the association between irAEs and survival outcomes during treatment with anti-PD1, suggesting that a careful management of treatment-related toxicity can lead to achieving maximum clinical benefit from this therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human rights and animal participants This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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