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Original Research

Efficacy of PD-1–based immunotherapy after radiologic progression on targeted therapy in stage IV melanoma

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Abstract ***Objectives:*** Targeted therapy (TT) is an effective treatment for advanced BRAFV600-mutated melanoma, but most patients eventually acquire resistance and progress. Here, we evaluated the outcome of second-line immune checkpoint blockade (ICB) after progression on dual BRAF and MEK inhibition.
Methods: Patients with metastatic melanoma progressing on combined BRAF + MEK inhibition and receiving second-line ICB between 2015 and 2019 in 9 tertiary referral centres were enrolled. Demographic and clinical data and blood counts of all patients were collected retrospectively.
Results: We identified 99 patients with stage IV melanoma receiving ICB (nivolumab, pembrolizumab [n = 39] or ipilimumab plus nivolumab [n = 60]) after progression on combined TT.

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The median progression-free survival was similar in the PD-1 and ipilimumab plus nivolumab group (2.6 months [95% confidence interval {CI}, 2.0–3.1] vs. 2.0 [95% CI, 1.4–2.6], $p = 0.15$). The objective response rate was 18.0% in the PD-1 and 15.0% in the ipilimumab plus nivolumab group ($p = 0.70$). The disease control rate was 25.7% for monotherapy and 18.3% for combined ICB ($p = 0.39$). The median overall survival was 8.4 months (95% CI, 5.1–11.7) for patients receiving PD-1 monotherapy and 7.2 months (95% CI, 5.2–9.1) for patients receiving ipilimumab plus nivolumab ($p = 0.86$). The latter was associated with a higher rate of treatment-related adverse events (AEs). No significant association of laboratory values or clinicopathological characteristics with response to second-line ICB was observed.

Conclusions: PD-1 monotherapy and combined ipilimumab plus nivolumab show similar activity and outcome in patients with melanoma resistant to BRAF + MEK inhibition. However, combined ipilimumab plus nivolumab was associated with a higher rate of treatment-related AEs compared with monotherapy.

1. Introduction

Targeted therapies (TTs) using dual inhibition of the MAPK pathway (MAPKi) and immune checkpoint blockade (ICB) inhibiting programmed death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) can prolong survival in patients with metastatic melanoma harbouring mutated BRAF (V600 E/K) [1]. Although dual inhibition of the MAPK pathway leads to disease control in the vast majority of patients, acquired resistance evidenced by tumour progression is very frequent, especially in patients with poor prognostic features [2]. To date, it remains unknown whether a specific sequence of TT and ICB provides greater benefit or whether the combination of ICB and TT is superior to sequential administration. With prospective clinical trials still ongoing, data from clinical practice might provide assistance to answer these questions.

Immunotherapy is a standard of care in the first-line treatment of advanced melanoma, based on the result of a number of pivotal trials [3–6]. Combination ICB (ipilimumab plus nivolumab) is associated with a higher objective response rate (ORR) and modest improvement in progression-free survival (PFS) and overall survival (OS) compared with single-agent PD-1 inhibition but at the expense of significantly higher toxicity [5,6]. However, data on the efficacy and survival of patients receiving regimes containing PD-1–blocking agents after failure of dual MAPKi are limited [7,8]. In particular, data on combined ipilimumab plus nivolumab in patients with MAPKi resistance are lacking but are urgently needed for clinical decision-making. To this end, we conducted a retrospective, multicentre study to explore the outcome of patients with melanoma receiving second-line PD-1–based ICB regimes after radiologic progression on TT.

2. Materials and methods

2.1. Patient cohort

The databases of all participating sites were searched for patients with melanoma with unresectable stage III/IV disease (American Joint Committee on Cancer 2017) who received dual BRAFi + MEKi as first-line therapy and a subsequent ICB with either nivolumab, pembrolizumab or the combination of ipilimumab plus nivolumab. All but one site enrolled consecutive patients. From one site, only patients with primary resistance were enrolled (n = 4). Only data of patients who experienced radiologic progression on TT and received PD-1–based ICB as second-line therapy were collected. Patients who switched treatment because of side-effects or switched before occurrence of resistance, as well as patients with uveal or mucosal melanoma, were excluded.

Demographic and clinical data were collected from all patients. White blood cell and serum lactate dehydrogenase (LDH) levels were measured 0–31 days before the first dose of TT (t1) and immunotherapy (t2). If data from multiple time points were available, those closest to the start of therapy were used. A scheme illustrating the study design can be found in Fig. 1. The study was conducted according to the Declaration of Helsinki. An ethical approval was waived by the central ethical review board of the medical faculty of the University of Würzburg because of its retrospective nature.

2.2. Definition of end-points and data acquisition

The end-points were best overall response (BOR; RECIST 1.1), ORR, disease control rate (DCR), PFS and OS. OS was calculated from initiation of TT

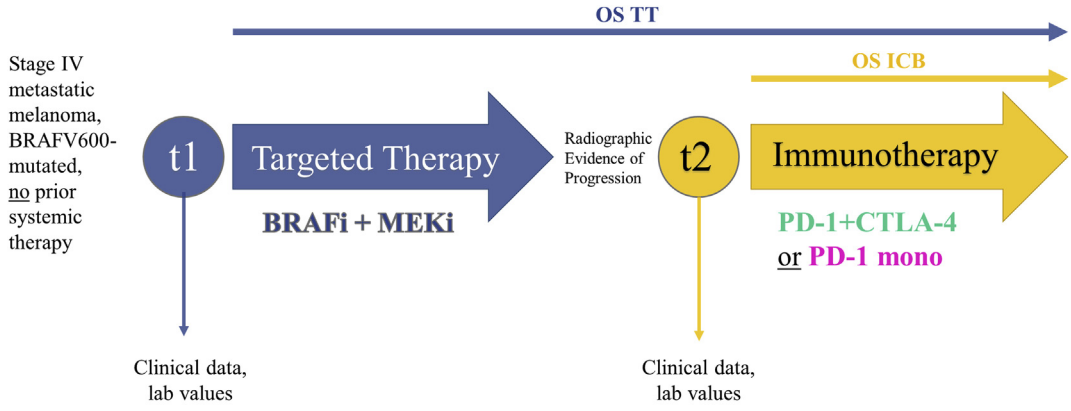

Fig. 1. Flow chart showing the inclusion criteria and time points of assessment. ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ICB, immune checkpoint blockade; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1.

until the date of death (OS TT) and from initiation of ICB until the date of death. Patients not reaching these end-points were censored at the last documented follow-up. The ORR was calculated by dividing the sum of patients achieving a complete response (CR) or partial response (PR; BOR according to RECIST 1.1) by all patients assessed. The DCR was calculated by dividing the sum of patients achieving a CR or PR or stable disease (SD; RECIST 1.1) by all patients. Treatment-related adverse events (AEs) were categorised according to the common toxicity criteria for adverse events (CTCAE).

2.3. Statistical analysis

Statistical analysis was performed by applying Fisher's exact, the McNemar–Bowker and the Mann–Whitney U test as appropriate using SPSS (IBM, version 25.0). Survival analysis was conducted using the Kaplan–Meier method; the log-rank test was used for curve comparison. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1. Study population

In total, 99 patients with stage IV melanoma from 9 sites were enrolled into the study. In our cohort, 55.6% ($n = 55$) were men; 82.8% ($n = 82$) had a cutaneous primary, 17.2 (n = 17) had an unknown primary, 66.7% ($n = 66$) harboured a V600E mutation, 17.2% had a V600K mutation ($n = 17$) and 16.1% had activating V600 mutations not further specified ($n = 16$).

When commencing TT, 30.3% (n = 30) had brain metastases, and further 23.2% (n = 23) developed intracranial disease during TT, resulting in a significant shift of the M category from t1 to t2 according to the AJCC classification 2017 (M1d 30.3% vs 53.5%, $p = 0.00$ Supp. Table 1). LDH and Eastern Cooperative Oncology Group (ECOG) remained similar when comparing these time points.

All 99 patients started first-line treatment with BRAFi + MEKi (dabrafenib + trametinib [$n = 85$], vemurafenib + cobimetinib [$n = 6$], encorafenib + binimetinib [$n = 8$]). After discontinuation of TT, 39 patients (39.4%) were switched to PD-1 inhibition (pembrolizumab $n = 27$, nivolumab $n = 12$), and 60 patients (60.6%) received ipilimumab plus nivolumab. The median time between discontinuing TT and first dose of ICB was 8 days (range, 1–102). After stopping second-line ICB, 28 patients received other treatments (13 patients of the PD-1 and 15 patients of the ipilimumab plus nivolumab group). Most of them received one line ($n = 22$) and 6 patients had 2-4 lines of subsequent treatment. Re-exposure to TT was most common ($n = 20$). Other treatments included chemotherapy ($n = 5$), clinical trials ($n = 2$) and immunotherapy ($n = 6$).

3.2. Response rate and OS stratified by second-line treatment

The median duration of BRAFi + MEKi treatment was 6.5 months (95% confidence interval [CI], 1.8–38.3), and the median PFS was 5.8 months (95% CI, 5.0–6.6) (Table 1). The ORR and DCR of TT were 46.4% and 59.6%, respectively. The median PFS from the start of ICB was 2.6 months (95% CI, 2.0–3.1) for PD-1 blockade and 2.0 months (95% CI 1.4–2.6) for combination ICB blockade (Fig. 2A). The OS was 8.4 months (95% CI, 5.1–11.7) and 7.2 months (95% CI 5.2–9.1)

Table 1
Treatment characteristics.

Parameter	Targeted therapy (n = 99)	PD-1 (n = 39)	PD-1 + CTLA-4 (n = 60)	p
	Median (95% CI)	Median (95% CI)	Median (95% CI)	
Duration (months) [range]	6.5 [1.8–38.3]			
Cycles (n) [range]		4.0 [1–42]	3.0 [1–27]	**0.02**^
PFS (months)	5.8 (5.0–6.6)	2.6 (2.0–3.1)	2.0 (1.4–2.6)	0.15§
OS (months) from start of therapy	19.8 (16.4–23.2)	8.4 (5.1–11.7)	7.2 (5.2–9.1)	0.86§
Time to ICB (days) [range]		9 [1–62]	8 [1–102]	0.57^
	n (%)	n (%)	n (%)	**p**
BOR				
CR	2 (2.0)	1 (2.6)	1 (1.7)	0.37#
PR	44 (44.4)	6 (15.4)	8 (13.3)	
SD	13 (13.1)	3 (7.7)	2 (3.3)	
PD	37 (37.4)	22 (56.4)	44 (73.3)	
Unknown	3 (3.0)	7 (18.0)	5 (8.3)	
BOR with brain metastases*				
CR	0 (0)	0 (0)	0 (0)	0.82#
PR	16 (53.3)	2 (10.0)	3 (9.1)	
SD	5 (16.7)	1 (5.0)	1 (3.0)	
PD	8 (26.7)	13 (65.0)	25 (75.8)	
Unknown	1 (3.3)	4 (20.0)	4 (12.1)	
BOR without brain metastases				
CR	2 (2.9)	1 (5.3)	1 (3.7)	0.44#
PR	28 (40.6)	4 (21.1)	5 (18.5)	
SD	8 (11.6)	2 (10.5)	1 (3.7)	
PD	29 (42.0)	9 (47.4)	19 (70.4)	
Unknown	2 (2.9)	3 (15.8)	1 (3.7)	

CI, confidence interval; PFS, progression-free survival; OS, overall survival; ICB, immune checkpoint blockade; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TT, targeted therapy; PD-1, programmed death 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery.
Exact p-values, those <0.05 are shown in bold.
Fisher's exact test comparing PD-1 and PD-1+CTLA-4.
§ Log-rank test comparing PD-1 and PD-1+CTLA-4.
^ Mann–Whitney U test comparing PD-1 and PD-1+CTLA-4.
* Concurrent radiotherapy TT: WBRT n = 3, stereotactic radio surgery (SRS) n = 7; PD-1: WBRT n = 9, SRS n = 3; PD-1+CTLA-4: WBRT n = 5, SRS n = 2.

for monotherapy and combination ICB, respectively (p = 0.86) (Fig. 2B). The OS from the start of ICB correlated significantly with OS TT (p < 0.00, Suppl. Figure 1).

An objective response was achieved in 18.0% (n = 7) patients receiving PD-1 monotherapy and 15.0% (n = 9) receiving combination ICB (p = 0.70). Disease control was observed in 25.7% (n = 10) monotherapy and 18.3% (n = 11) combination ICB patients (p = 0.39). Patients without pre-treatment brain metastases (n = 46) had improved response to immunotherapy. The ORR was 26.4% (5/19) for PD-1 inhibition and 22.2% (6/27) for combination ICB. In patients with pre-treatment brain metastases (n = 53), ORR was 10.0% (2/20) for monotherapy and 9.1% (3/33) for combination ICB. No responses to second-line ICB were observed in patients with brain metastases and an elevated LDH or an ECOG >0. No correlation of PFS TT and ICB was found (Supp. Figure 1).

Patients responding to ICB had a better OS (Fig. 2C). In the Kaplan–Meier estimate, median OS was not reached in responders (n = 16), whereas the median OS in patients progressing on ICB (n = 66) was 6.8 months (95% CI, 4.3–9.3) (p = 0.00). The efficacy of treatment for subgroups stratified by second-line regimes and presence of intracranial disease is summarised in Table 1. The median number of doses of treatment was 4 (range, 1–42) for PD-1 monotherapy and 3 (range, 1–27) for combined ICB.

Prognostic factors before ICB were balanced between both groups, as shown in Table 2. In particular, no significant difference was evident for M category and serum LDH. At the start of the therapy, patients receiving combined ipilimumab plus nivolumab were significantly younger than patients receiving PD-1 monotherapy (p = 0.01). In both groups, 5 patients received >10 mg prednisolone or equivalent per day within 14 days before starting ICB (p = 0.17, Fisher's exact test). One response was noted in each of these 5 patients, and steroid use was not associated with shorter OS after ICB (data not shown).

3.3. Adverse events

As shown in Table 2, treatment-related AEs of any grade were reported in 10 patients treated with PD-1 blockade (25.6%) and 36 patients treated with combination ICB (60.0%). Grade 3/4 toxicities according to the CTCAE occurred in 1 patient (2.6%) of the PD-1 cohort and in 28 patients (46.7%) of the combination cohort. The most common treatment-related grade 3 or 4 toxicities were colitis and hepatitis. Discontinuation of ICB due to treatment-related AEs was noted in 2 (5.1%) patients receiving monotherapy and 12 (20.0%) patients exposed to combinational ICB. There were no treatment-related deaths reported. No association of AEs and BOR was observed (data not shown).

3.4. Biomarker-based subgroup analyses of response to ICB

To identify patients more likely to respond to subsequent ICB after failure of TT, the patients were stratified into responders (PR or CR as BOR to ICB) and non-responders (progressive disease [PD]). When comparing categoric and continuous biomarkers previously reported, we found no significant associations of any clinical characteristic or laboratory value with either outcome. There was a trend for a higher absolute eosinophil count and a more favourable M category in responders (p = 0.07 and p = 0.09, respectively) (Supp.

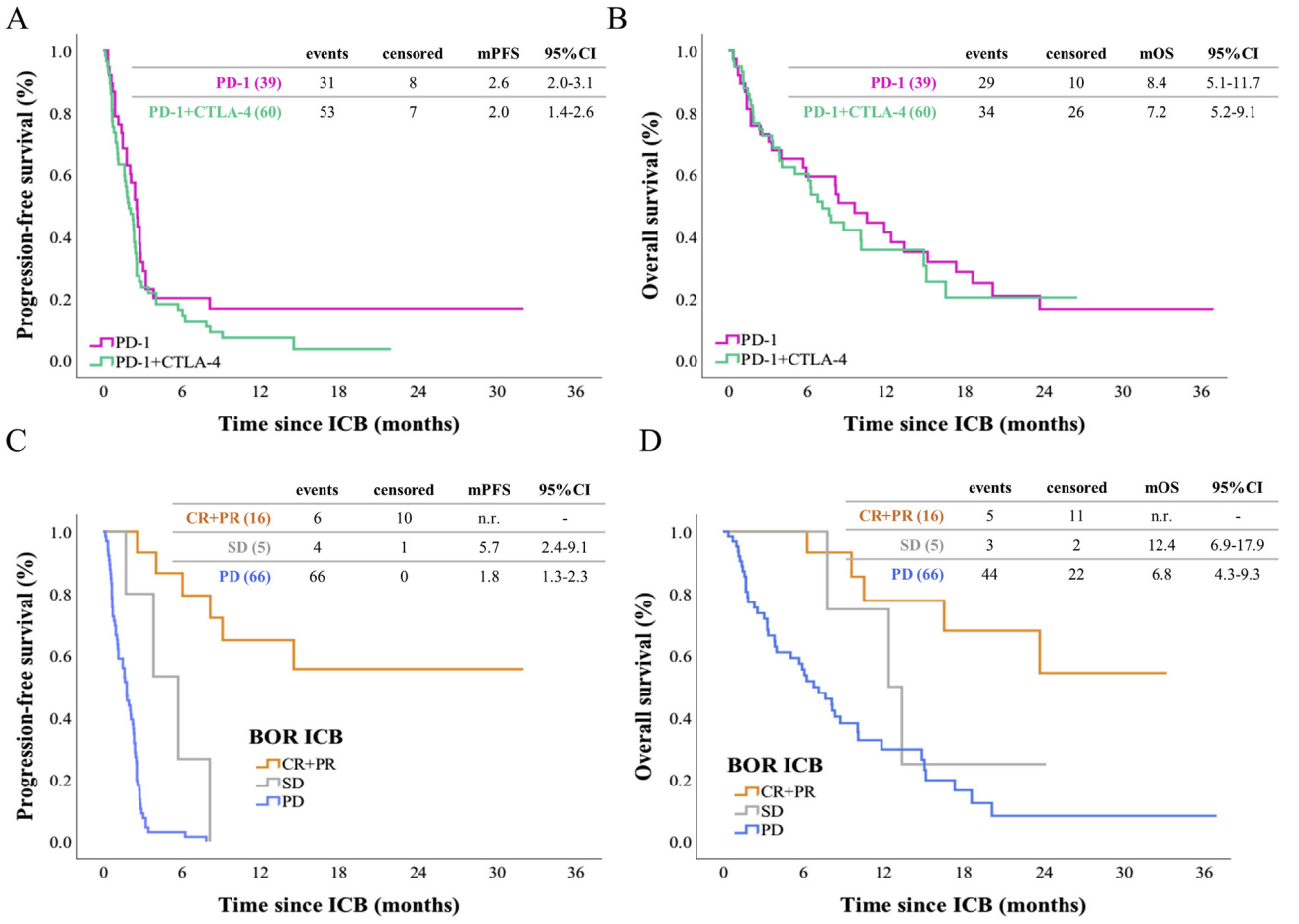

Fig. 2. Comparison of PD-1 and combined PD-1 plus CTLA-4 blockade: (A and B) Kaplan–Meier estimates of progression-free and overall survival in 99 patients with advanced melanoma who received either PD-1 or PD-1+CTLA-4 immune checkpoint inhibition after progression to TT. (C and D) Kaplan–Meier estimates of progression-free and overall survival in 87 patients stratified based on the response (complete response and partial response [CR + PR] vs. Stable disease [SD] vs progressive disease [PD]) to second-line ICB. Patients with unknown response data were excluded. TT, targeted therapy; ICB, immune checkpoint blockade; CI, confidence interval; PD-1, programmed death 1; CTLA-4, cytotoxic T-lymphocyte antigen 4.

Figure 2 and Table 3). Overall, there was no association of any leucocyte subgroup to BOR to TT and ICB (Supp. Figure 2). Interestingly, among patients responding to ICB, 31.3% (n = 5) had PD as BOR to TT, indicating that primary resistance against TT does not rule out response to PD-1–based immunotherapy.

4. Discussion

Here, we present the largest cohort of patients with metastatic melanoma receiving subsequent PD-1–based ICB after failure of dual BRAF + MEK inhibition. In this retrospective data set, we found that outcome of second-line ICB is strikingly poor, with no clear difference between single-agent PD-1 inhibition (nivolumab, pembrolizumab) and combination therapy (ipilimumab + nivolumab). The ORR, PFS and OS were similar in both groups. The combination of PD-1 inhibition and ipilimumab, however, is as in treatment-naive patients, associated with a higher rate of immune-related adverse events (irAEs). These data suggest that the addition of ipilimumab to PD-1 inhibition does not improve ORR or OS in patients failing dual MAPK inhibition but bears a higher risk of irAEs.

Although the retrospective nature of our observation does not allow exclusion of a selection bias, our cohort indicates that TT is preferentially used as first-line therapy in patients with poor prognostic features who need a fast-acting treatment in real-world practice [9,10]. At baseline, 30.3% had intracranial disease, 48.5% showed elevated LDH and 62.2% had ≥3 metastatic sites when commencing TT, explaining the short PFS of 5.8 months and ORR of 46.4% to TT. While this is shorter than the median PFS reported in the phase III COMBI-d trial [11], it resembles data from COMBI-MB [12] and the association of elevated LDH with disease progression during TT [2,13]. Patients enrolled in randomised clinical trials generally show less advanced disease with lower tumour burden and no or a limited number of brain metastases.

Table 2
Comparison of patients receiving PD-1 and PD-1 plus CTLA-4 blockade.

Parameter	PD-1	PD-1 + CTLA-4	*p*
Individual patients	*N* = 39 (%)	*n* = 60 (%)	
Gender			
Male	19 (48.7)	36 (60.0)	0.31#
Female	20 (51.3)	24 (40.0)	
Age at start ICB			
Median (range)	63 [25–85]	53 [19–78]	**0.01**^
M category			
M1a	2 (5.1)	3 (5.0)	1.00#
M1b	2 (5.1)	3 (5.0)	
M1c	14 (35.9)	22 (36.7)	
M1d	21 (53.8)	32 (53.3)	
ECOG			
0	23 (59.0)	41 (68.3)	0.13#
1	9 (23.1)	16 (26.7)	
≥2	5 (12.9)	1 (1.7)	
Missing	2 (5.1)	2 (3.3)	
LDH			
<1xULN	17 (43.6)	23 (38.3)	0.92#
1-2xULN	13 (33.3)	24 (40.0)	
≥2xULN	8 (20.5)	11 (18.3)	
Missing	1 (2.6)	2 (3.3)	
Number of metastatic sites			
Median [range]	3 [1–6]	3 [1–9]	0.64^
Toxicity			
Any AEs	15 AEs in 10 patients (25.6)	72 AEs in 36 patients (60.0)	**0.00**#
Grade 3/4	1 (2.6)	28 (46.7)	
Colitis	0 (0)	12 (20.0)	
Hepatitis	0 (0)	9 (15.0)	

ICB, immune checkpoint blockade; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; AEs, adverse events; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1; ULN, upper limit of normal.
Exact p-values, those <0.05 are shown in bold.
Fisher's exact test used for comparison.
^ Mann–Whitney U test used for comparison.

Data on the outcome of patients receiving PD-1–based ICB after showing radiologic progression on TT are limited. In one study conducted by Simeone *et al.*, a short PFS on pembrolizumab was observed for 16 patients with melanoma who had previously been treated with BRAFi monotherapy (median PFS, 3 months [95% CI, 2.3–3.7]) [14]. The ORR was 12.5%, and DCR was 18.6%. These patients, however, received ipilimumab between both treatments. The phase Ib KEYNOTE 001 study found an ORR of 23.7% (n = 23/97) to pembrolizumab after BRAF ± MEK inhibition without specification on how many had BRAFi monotherapy or dual treatment [15]. More than half of these patients had prior CTLA-4 blockade, further limiting comparability to our study. The lack of efficacy of PD-1 blockade was also identified in a study by Amini-Adle *et al.* [7] reporting 41 patients failing TT (BRAFi n = 15; BRAFi + MEKi n = 26) who were treated subsequently with PD-1 inhibitor monotherapy. The median PFS was 2 months (95% CI, 1.6–2.4), and the median OS was 7 months (95% CI, 4.0–10.0). The ORR was 12.2%, and the DCR was 24.4%. Another retrospective study investigating the same treatment sequence in a smaller subset (n = 17) showed similar results. The ORR to PD-1 inhibition was 17.7%, and the DCR was 23.5% [8]. These data indicate limited knowledge derived from heterogenous cohorts of patients on the efficacy of second-line PD-1–based ICB. For combined ipilimumab and nivolumab, the ABC trial reported a poor outcome after intracranial progression on BRAFi ± MEKi (n = 8 in cohort A) [16]. However, comparison with our study is limited because no explicit subgroup analysis of patients progressing on BRAFi + MEKi and receiving second-line combination ICB is available. The report indicates that there was only 1 response in those 8 patients. The observation that combined ICB yields a similar outcome as PD-1 monotherapy is supported by studies that have investigated ipilimumab in patients with melanoma resistant to TT. No objective response was observed for ipilimumab monotherapy applied after progression on BRAF monotherapy [17] or BRAFi ± MEKi [18]. The biological explanation for the lack of efficacy of ipilimumab, not augmenting the effect of PD-1 inhibition, remains elusive and to be determined.

In our cohort, we could not identify any biomarker previously reported [10,19] predicting response or resistance to second-line ICB. This could be related to the cohort size [19] or differences in the investigated treatment line [10]. Because progression on second-line ICB was associated with inferior survival, treatment beyond progression or clinical trials instead of PD-1–based ICB could be other options to be considered as second-line treatment [20]. No responses to second-line ICB were observed in patients with brain metastases and an elevated LDH or an ECOG >0. In translational studies, possible mechanisms have been proposed mediating ICB resistance in patients with prior MAPKi including the possibility of cross-resistance [21]. Interestingly, we observed responses to PD-1–based ICB in patients with primary resistance to TT. This indicates that both cross-resistance and specific mechanisms mediating resistance to either therapeutic strategy might exist. Identification of such specific mechanisms and biomarkers could help guide treatment decisions in patients with metastatic BRAFV600-mutated melanoma but will have to be validated in prospective clinical trials.

Data on the safety and tolerability of PD-1–based ICB in patients with melanoma failing TT are limited. Among the 41 TT patients with pre-treated melanoma enrolled in the study by Amini-Adle *et al.*, immune-mediated toxicities to anti–PD-1 monotherapy were observed in 9.8% (n = 4) patients. Those included colitis (n = 2), hypophysitis (n = 1), pneumonitis (n = 1), vitiligo (n = 2) and other significant toxicities (n = 1). For combined ipilimumab plus nivolumab, no safety data in MAPKi-resistant patients have been

Table 3
Clinicopathological characteristics of patients with (CR or PR) or without response (PD) to second-line ICB.

Individual patients	CR + PR	PD	$p^{\#}$
	n = 16 (%)	n = 66 (%)	
Gender			
Male	8 (50.0)	41 (62.1)	0.41
Female	8 (50.0)	25 (37.9)	
M stage t			
M1a	2 (12.5)	1 (1.5)	0.09
M1b	1 (6.3)	2 (3.0)	
M1c	7 (43.8)	26 (39.4)	
M1d	6 (37.5)	37 (56.1)	
ECOG t2			
0	13 (81.3)	44 (66.7)	0.37
≥1	3 (18.8)	22 (33.3)	
LDH t2			
<1xULN	7 (43.8)	28 (42.4)	0.44
1-2xULN	8 (50.0)	22 (33.3)	
≥2xULN	1 (6.3)	14 (21.2)	
Missing	0 (0)	2 (3.0)	
Number of metSites t2			
<3	6 (37.5)	20 (30.3)	0.77
≥3	10 (62.5)	44 (66.7)	
Missing	0 (0)	2 (3.0)	
ICB regime			
PD-1 monotherapy	7 (43.8)	22 (33.3)	0.56
PD-1+CTLA-4	9 (56.3)	44 (66.7)	

CR, complete response; PR, partial response; PD, progressive disease; ICB, immune checkpoint blockade; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1; ULN, upper limit of normal.
[#] Fisher's exact test.

reported yet. In our cohort, no unexpected irAE or treatment-related deaths were found. As expected, the number of grade 3 or 4 toxicities was significantly higher in the combination therapy than in the PD-1 subgroup. Related to ipilimumab plus nivolumab, 28 patients developed grade 3 or 4 toxicity according to the CTCAE, with only 5 of them achieving an objective response and 2 achieving more SD. Compared with first-line data [5], the risk–benefit ratio seems less favourable in patients receiving combinational ICB after failing TT. If our findings are confirmed in prospective clinical trials such as NCT02224781, the use of combination ICB might not be reasonable in MAPKi-resistant metastatic melanoma with poor prognostic features. The low response rates of ICB after dual MAPKi support first-line therapy with ICB in patients with metastatic melanoma harbouring a BRAFV600 mutation [10]. However, prospective clinical trials evaluating the sequence of TT and ICB in these patients are ongoing, but results have not been reported yet. These trials address questions regarding sequencing TT and ICB (NCT02224781), time of switching (NCT02631447, NCT02902029) and priming by TT for ICB (NCT03235245). Although the retrospective nature of our observation does not allow exclusion of a selection bias or underreporting of irAE outside a clinical trial, these data reflect clinical decisions in an unselected population and thus might be useful as guidance in real-life settings until prospective clinical trials are reported.

In this study, we provide the largest cohort of patients treated with PD-1–based ICB after radiologic progression on dual MAPKi, representing a contemporary clinical situation in standard-of-care treatment of metastatic melanoma. Response rate and survival were similar in patients receiving combined ipilimumab plus nivolumab compared with PD-1 blockade alone, when applied after MAPKi failure in patients with poor prognostic factors. Combined ICB was associated with a higher rate of severe irAE. Prospective clinical trials are needed to validate our findings. Until then, our data indicate that PD-1 monotherapy might be preferred over combined ICB as second-line treatment after radiologic progression on TT in advanced BRAFV600 mutant melanoma.

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Conflict of interest statement

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Appendix A. Supplementary data

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