Switch to checkpoint inhibition (CPI) after targeted therapy (TT) at time of progression or during ongoing response: A retrospective analysis of patients with advanced BRAF mutated melanoma

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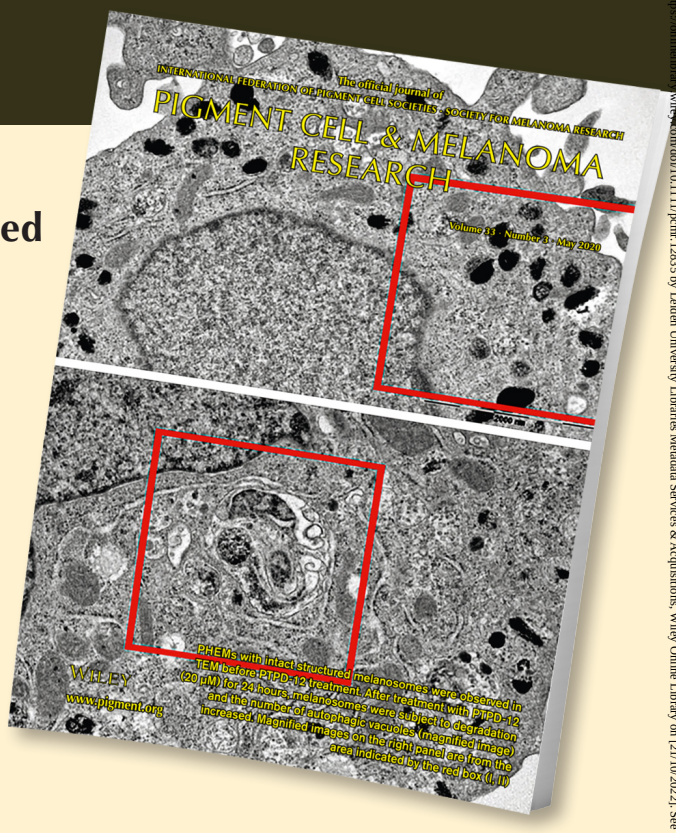

Switch to checkpoint inhibition after targeted therapy at time of progression or during ongoing response: A retrospective single-centre experience in patients with BRAF-mutated melanoma

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Switch to checkpoint inhibition after targeted therapy at time of progression or during ongoing response: A retrospective single-centre experience in patients with BRAF-mutated melanoma

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Abstract

BRAF + MEK inhibition is preferentially applied as first-line therapy in *BRAF* V600-mutated melanoma patients with unfavourable prognostic features, due to the ability of targeted therapy (TT) to induce rapid symptom control, decrease tumour burden and normalize lactate dehydrogenase (LDH) levels. In addition, short-term TT transiently increases tumour antigen presentation and tumour influx of T cells. Therefore, it might be favourable to switch TT to checkpoint inhibition (CPI) before progression (PD). We retrospectively analysed melanoma patients treated first line with TT (TT1) and who subsequently switched to CPI during response to TT (sDR group) or at progression upon TT (sPD group). We identified 74 patients (n = 37 sDR group and n = 37 sPD group). ORR to CPI was 27.0% in the sDR group versus 24.3% in the sPD group (p = .790). Median was PFS 2.5 months versus 1.2 months (p = .145), and median OS was 30.6 versus 14.1 months (p = .007). After adjusting for baseline differences and known prognostic factors, hazard ratios (HRs) favouring sDR were 0.89 for PFS upon CPI (p = .956) and 0.48 for OS (p = .055). Thus, patients switching to CPI during ongoing clinical benefit from TT do not have an inferior outcome. Due to baseline imbalances and small patient population, a favourable trend for the sDR group can be hypothesized only.

KEYWORDS

anti-CTLA-4, anti-PD-1, BRAF inhibition, *BRAF* mutation, checkpoint inhibition, MEK inhibition, melanoma, targeted therapy

1 | INTRODUCTION

The introduction of (dual) targeted therapy (TT) inhibiting the MAPK pathway and checkpoint inhibition (CPI) dramatically improved the survival of melanoma patients harbouring a *BRAF* V600 mutation (Rozeman, Dekker, Haanen, & Blank, 2018). Currently, these patients are treated with either first-line CPI (anti-PD1, nivolumab or pembrolizumab, or the combination nivolumab + anti-CTLA-4, ipilimumab) or combined BRAF and MEK inhibition (vemurafenib + cobimetinib, dabrafenib + trametinib, or encorafenib + binimetinib; Coit et al., 2016; Dummer, Hauschild, Lindenblatt, Pentheroudakis, & Keilholz, 2015).

The decision on first-line treatment in *BRAF*-mutated advanced melanoma remains complex due to the absence of prospective data

Reijers and Rozeman contributed equally.

directly comparing first-line TT versus CPI, and biomarkers clearly favouring one.

Melanoma patients responding to CPI often experience long-term benefit, as the majority of complete and partial responses are durable (Wolchok et al., 2017), and continue even after stop of treatment (Jansen et al., 2017; Robert et al., 2017). However, the time to onset of response to CPI often is variable, and patients with high tumour burden, bad performance status (PS), and/or elevated baseline lactate dehydrogenase (LDH) levels are less likely to respond (Rosner et al., 2018; Weide et al., 2016). TT can induce rapid clinical benefit and induces high response rates (Ascierto et al., 2016; Long et al., 2017), even in patients with high LDH levels (Long et al., 2016). However, the majority of patients will develop treatment resistance (Ascierto et al., 2016; Long et al., 2017). Hence, TT is frequently used as first-line treatment in *BRAF*-mutated metastatic melanoma patients with high tumour burden, high LDH levels, fast progressive (symptomatic) disease, and/or brain metastases (Ascierto et al., 2018), whereas first-line CPI is often favoured in asymptomatic patients with low tumour burden and normal LDH levels (Schilling et al., 2019).

To further increase patient outcome, treatment strategies with combined or sequential TT and CPI are currently explored in several clinical trials (Atkins & Larkin, 2016). It is hypothesized that pretreatment with TT might improve CPI effectiveness by decreasing tumour burden and normalization of LDH, both are known unfavourable prognostic factors for response upon CPI. Additionally, preclinical data suggest that TT might enhance tumour susceptibility to CPI by modulating the tumour microenvironment (Boni et al., 2010; Bradley et al., 2015; Callahan et al., 2014; Frederick et al., 2013; Wilmott et al., 2012). However, these immune-modulating effects appear to be transient and decrease at disease progression (Frederick et al., 2013; Wilmott et al., 2012), or even during TT (beyond ≥15 days after start of therapy) in the absence of disease progression (Deken et al., 2016). Based on these observations, one could hypothesize that pretreatment with TT is more effective in improving efficacy of subsequent CPI when patients switch prior to progression upon TT. However, currently, it remains unclear whether melanoma patients treated with TT should switch to CPI at time of progressive disease (PD) or during an ongoing response on TT.

This single-centre retrospective study investigates whether *BRAF* V600 metastatic melanoma patients switching early during an ongoing response or at progression on TT to CPI derive most benefit in terms of OS.

Significance

The introduction of checkpoint inhibition (CPI) and targeted therapy (TT) has dramatically improved the prognosis of *BRAF* V600-mutated melanoma. The optimal sequence of targeted therapy and checkpoint inhibition is not known. We observed no inferior outcome and a trend to better survival and longer duration of response for patients who switched to checkpoint inhibition during ongoing response upon targeted therapy compared to patients who switched at progressive disease. This observation has yet to be confirmed in randomized prospective trials.

2 | MATERIALS AND METHODS

2.1 | Study design and patient cohort

Advanced melanoma patients treated with BRAF inhibition ± MEK inhibition (TT) followed by subsequent anti-PD1 ± anti-CTLA-4 (CPI) at the Netherlands Cancer Institute were retrospectively identified. The patients were divided into two groups: patients who switched to CPI during ongoing benefit from TT (sDR group) and patients who switched to CPI at progressive disease (sPD group). Patients receiving second-line ipilimumab monotherapy, with no initial benefit upon TT treatment, with treatment-free periods TT->CPI > 15 days, or with a history of TT or anti-PD1 therapy prior to start of the identified TT->CPI schedule, were excluded [CONSORT diagram, Figure S1].

2.2 | Endpoints

Objective response rate (ORR) upon CPI (ORR CPI), progression-free survival (PFS) of CPI (PFS CPI), overall survival (OS), ORR and treatment duration of TT re-challenge after CPI failure (ORR TT2, TD TT2), and total treatment duration of targeted therapy (TD TT1 + TT2) were analysed. A schematic illustration of treatment lines and corresponding outcome measures is shown in Figure S2.

Radiological responses for both intracranial and extracranial metastases were scored according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. If lesions were irradiated, they were considered as not evaluable (NE). Patients were regarded progressive if they qualified as PD according to RECIST v1.1, or if they showed signs of deterioration (biochemical or clinical parameters, and no scans were performed anymore). Prognostic factors analysed for the outcomes included progression status (Y/N) on targeted therapy, baseline AJCC stage (8th Edition), number of metastatic sites scored as previously described (Schadendorf et al., 2017), baseline WHO PS, LDH, and switch to CPI monotherapy or combination therapy. The last date of follow-up was defined as date of death or, in case of patients still living, the date of last follow-up with a data freeze on 1 May 2018.

2.3 | Statistical analysis

Differences in patient baseline characteristics were analysed using the chi-square test and the Mann–Whitney *U* test. PFS and OS curves were estimated with the Kaplan–Meier method and compared using a log-rank test. Univariate hazard ratios (HRs) of progression and survival status were calculated using the Cox regression method. In the multivariate Cox regression models, analysis was corrected for known prognostic factors and differences in baseline characteristics.

TABLE 1 Baseline Characteristics

Characteristic	Switch groups, *n* (%)		
	sDR group	sPD group	
	n = 37	*n* = 37	*p*-value
Median age, years (range)	57 (50)	53 (43)	.619[a]
Sex			
Male	22 (62.2)	19 (51.4)	.348[b]
Female	14 (37.8)	18 (48.6)	
BRAF mutation			
V600E	33 (89.2)	36 (97.3)	.482[b]
V600K	2 (5.4)	1 (2.7)	
Other[c]	2 (5.4)	0 (0.0)	
Baseline AJCC statusd			
IIIc, M1a, M1b	4 (10.8)	6 (16.2)	.109[b]
M1[c]	21 (56.8)	12 (32.4)	
M1[d]	12 (32.4)	19 (51.4)	
Liver metastases	10 (27.0)	15 (40.5)	.291[b]
Skeletal metastases	16 (43.2)	15 (40.5)	.814[b]
Symptomatic brain metastases	5 (13.5)	11 (29.7)	.090[b]
Baseline WHO PS			
0	18 (48.6)	13 (35.1)	.214[b]
1	16 (43.2)	16 (43.2)	
2 + 3	3 (8.1)	8 (21.6)	
Number of metastatic sites			
<3	13 (35.1)	9 (24.3)	.309[b]
3 or more	24 (64.9)	28 (75.7)	
Baseline serum LDH			
<ULN	18 (48.6)	15 (40.5)	.87[b]
ULN < LDH <2 ULN	11 (29.7)	12 (32.4)	
>2 ULN	4 (10.8)	6 (16.2)	
Baseline s100: median (range)	0.25 (6.72)	0.64 (80.31)	.028[a]
Baseline Leucocytes: median (range)	9.2 (15.3)	10.9 (34.6)	.055[a]
Baseline NLR: median (range)	4.34 (17.86)	6.29 (22.46)	.483[a]
TT as # line of therapy			
1st line	30 (81.1)	33 (89.2)	.327[b]
2nd line	7 (18.9)	4 (10.8)	
Targeted therapy agent			
BRAFi	21 (56.8)	11 (29.7)	.019[b]
BRAFi + MEKi	16 (43.2)	26 (70.3)	
Checkpoint inhibition agent			
anti-PD1	23 (62.2)	17 (45.9)	.162[b]
anti-PD1 + anti-CTLA4	14 (37.8)	20 (54.1)	

Abbreviations: BRAFi, BRAF inhibitor; LDH, lactate dehydrogenase; MEKi, MEK inhibitor; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; sDR, switch during response; sPD, switch at progressive disease; TT, targeted therapy; ULN, upper limit of normal.

[a]Mann–Whitney *U* test.

[b]Chi-square test.

[c]One patient with V600R mutation and one patient with K601E and L584F mutation.

[d]According to AJCC 8th Edition Cancer Staging System.

Significance tests were all two-sided, in which *P*-values of <.05 were considered as significant. All statistical analyses were performed using SPSS (IBM, version 22).

3 | RESULTS

Between 12 October 2012 and 5 September 2017, 118 patients with BRAF-mutated metastatic melanoma received TT followed by CPI at the Netherlands Cancer Institute and 74 patients were eligible for the analysis [CONSORT diagram, Figure S1]. Thirty-seven patients switched to CPI at PD upon TT (sPD group), and 37 patients switched to CPI during ongoing response upon TT (sDR group).

Baseline characteristics were balanced between both groups, except for significant differences regarding AJCC stages (more frequent M1c in sDR group), S100 level (higher on sPD group) and BRAFi monotherapy versus BRAFi + MEKi treatment (more often doublet in sPD group; Table 1). Moreover, patients in the sPD group had a worse PS and more frequent brain metastases including symptomatic brain metastasis, although these did not reach statistical significance.

Median treatment duration of frontline targeted therapy (TD TT1) was 3.2 months (range 1.0–8.9) in the sDR group and 4.5 months (range 2.3–43.7) in the sPD group, with an ORR TT1 of 91.9% versus 75.7%, respectively. In the sDR group, 14 patients (37.8%) were treated with subsequent anti-PD-1 + anti-CTLA4, compared to 20 patients (54.1%) in the sPD group. sPD patients had a higher LDH, worse PS and more frequent brain metastases at switch to CPI compared to sDR patients (Table S1), reflecting the disease progression. At time of the data cut-off, in both groups 31 patients (83.8%) had progressed upon CPI (Figure 1). Fourteen patients (37.8%) had died in the sDR group compared to 25 patients (67.6%) in the sPD group (Figure 1). Median follow-up was 28.2 in the sDR group versus 35.8 months in the sPD group, with a minimal follow-up of 7.8 and 11.8 months of patients alive.

Objective responses upon CPI were reported in 10 patients (27.0%) in the sDR group and nine patients (24.3%) in the sPD group (Table 2). An additional seven patients in both groups achieved stable disease as BOR, resulting in a disease control rate of 45.9% in the sDR group and 43.2% in the sPD group. Of note, despite similar ORR, there were more complete responses in the sDR group (six vs. two patients). Duration of response to CPI was longer in the sDR group with a median of 30.7 months (95% confidence interval [CI] 0.0–61.9) compared to 14.4 months (95% CI 0.0–29.3) in the sPD group (p = .084). Median PFS upon CPI (PFS CPI) was 2.5 months (95% CI 2.4–2.7) in the sDR group and 1.2 months (95% CI 0.0–2.7) in the sPD group (p = .145; Figure 2a) with an univariable HR of 0.69 (p = .151) for PFS of CPI (Tables S2 and 3).

After progressing on CPI, 29 patients (78.4%) in the sDR group and 20 patients (54.1%) in the sPD group received subsequent systemic therapy or radiotherapy (Figure S1). Forty patients were re-challenged with TT after progression on CPI (TT2), 25 in the sDR group and 15 in the sPD group. Objective response rates of TT2 were 56.0% in the sDR group versus 33.3% in the sPD group (Table 2).

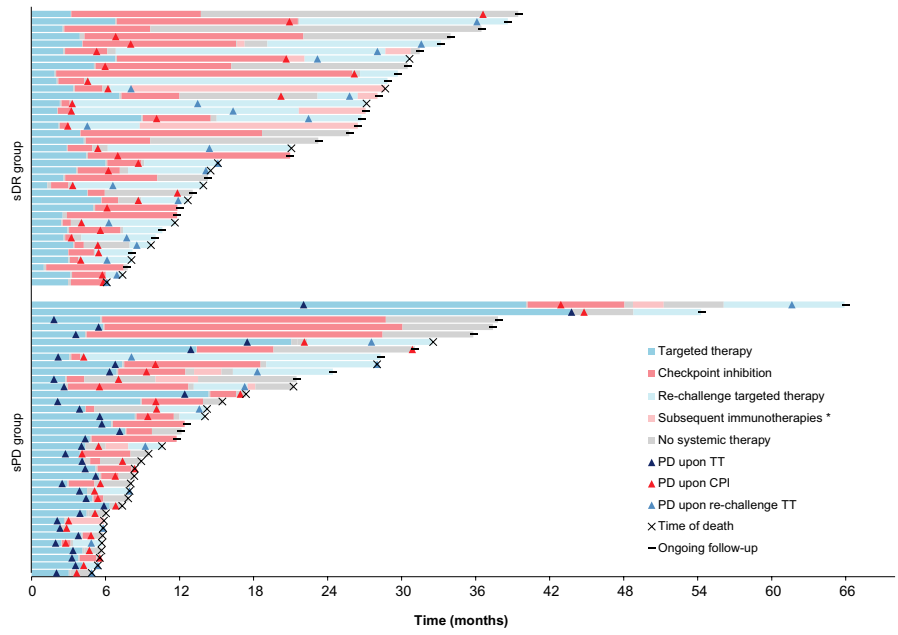

FIGURE 1 The swimmer plot illustrates a retrospective overview of the treatment history, response duration and survival of patients in the sDR group (upper part) and sPD group (lower part) treated with targeted therapy (blue line, progression marked as dark blue triangle), checkpoint inhibition (red line, progression marked as red triangle) and in some patients followed by re-challenge with targeted therapy (light blue line, progression marked as blue triangle) and/or subsequent immunotherapy (pink line). *Subsequent immunotherapies include anti-CTLA4, anti-PD1, anti-CTLA4/anti-PD1 and tumour-infiltrating lymphocytes (n = 1). Abbreviations: CPI, checkpoint inhibition; PD, progressive disease; sDR, switch during response; sPD, switch at progressive disease; TT, targeted therapy

The median treatment duration of TT2 was numerically in favour of the sDR group (6.0 months vs. 3.2 months, p = .104; Figure 2b). The median total TT treatment duration of all patients (TT1 + TT2) was 11.2 months in the sDR group and 6.7 months in the sPD group (p = .400; Figure 2c).

Median OS was 30.8 months in the sDR group versus 14.1 months in the sPD group (95% CI 6.7–21.4, p = .007; Figure 2d). All patients with CR on CPI were still alive at time of data cut-off. Median OS in patients with PR or *SD* was not reached and was 12.7 months (95% CI 7.1–18.2) in PD patients and 8.1 months (95% CI 7.9–8.3) in NE patients (Figure 2e). The univariable Cox regression method revealed a significant benefit in OS for patients in the sDR group (hazard ratio [HR] 0.42, p = .009; Tables S2 and 3).

Exploratory analyses demonstrated a trend for survival benefit across several sDR subgroups (Figure S3). Notably, OS benefit for the sDR group was also observed for patients with brain metastases (unadjusted HR 0.19, p = .009; Table S3).

To address the influence of the baseline imbalances between the two groups, a multivariable analysis was performed correcting for number of metastatic sites, brain metastases, baseline PS, baseline LDH, prior treatment with ipilimumab and response on TT. HRs were 0.48 for total OS (p = .055) favouring the sDR group and 0.89 for PFS CPI (p = .956; Tables S2 and 3). In a multivariable analysis of the subgroup of patients with brain metastases, the survival benefit for the sDR group did not reach statistical significance anymore (HR 0.28, p = .071; Table S3). Excluding all patients diagnosed with brain metastasis and WHO performance status 2/3 resulted in more balanced baseline characteristics and showed comparable results with a trend in favour of the sDR group (univariable HR 0.76, p = .476 for PFS; and HR 0.58, p = .208, for OS; Tables S4-S6 and Figure S4).

4 | DISCUSSION

Our retrospective analysis suggests that BRAF-mutated advanced melanoma patients switching from TT to CPI during an ongoing response to TT do not have an inferior outcome and might derive survival benefit compared to patients that switch at the moment of PD. The higher

TABLE 2 Responses to checkpoint inhibition and re-challenge with targeted therapy

	Responses to TT1, *n* (%)			Responses to CPI, *n* (%)			Responses to TT2, *n* (%)		
	sDR group	sPD group		sDR group	sPD group		sDR group	sPD group	
	n = 37	*n* = 37	*p*-value	*n* = 37	*n* = 37	*p*-value	*n* = 25	*n* = 15	*p*-value
Best overall response			.108[c]			.564[c]			.014[c]
Complete response	0 (0.0)	1 (2.7)		6 (16.2)	2 (5.4)		2 (8.0)	0 (0.0)	
Partial response	34 (91.9)	27 (73.0)		4 (10.8)	7 (18.9)		12 (48.0)	5 (33.3)	
Stable disease	2 (5.4)[a]	7 (18.9)		7 (18.9)	7 (18.9)		1 (4.0)	5 (33.3)	
Progressive disease	0 (0.0)	2 (5.4)[d]		17 (45.9)	17 (45.9)		9 (36.0)	1 (6.7)	
Not evaluated[e]	1 (2.7)[b]	0 (0.0)		3 (8.1)	4 (10.8)		1 (4.0)	4 (2.7)	
Response rates									
Objective response rate[f]	34 (91.9)	28 (75.7)	.058[c]	10 (27.0)	9 (24.3)	.790[c]	14 (56.0)	5 (33.3)	.165 [c]
Disease control rate[g]	36 (97.3)	35 (94.6)	.556[c]	17 (45.9)	16 (43.2)	.815[c]	15 (60.0)	10 (66.7)	.673 [c]
Median duration of response (95% CI)—mo.	-- --	-- --	--	30.7 (0.0–61.9)	14.4 (0.0–29.3)	.084[h]	-- --	-- --	--

Abbreviations: CPI, checkpoint inhibition; sDR, switch during response; sPD, switch at progressive disease; TT2, re-challenge with TT.

[a]Two patients achieved an intracranial partial response and peripheral stable disease, resulting in an overall response assessed as stable disease.

[b]One patient switched to immunotherapy before radiological evaluation due to toxicities on targeted therapy. This patient had a clear clinical response on targeted therapy.

[c]Chi-square test.

[d]One patient with clinical response before radiological evaluation showing PD and one patient with extracranial response but one new cerebral lesion.

[e]Switch before radiological evaluation during clinical response.

[f]Patients with best response of CR or PR.

[g]Patients with best overall response of CR, PR or *SD*.

[h]Log-rank test.

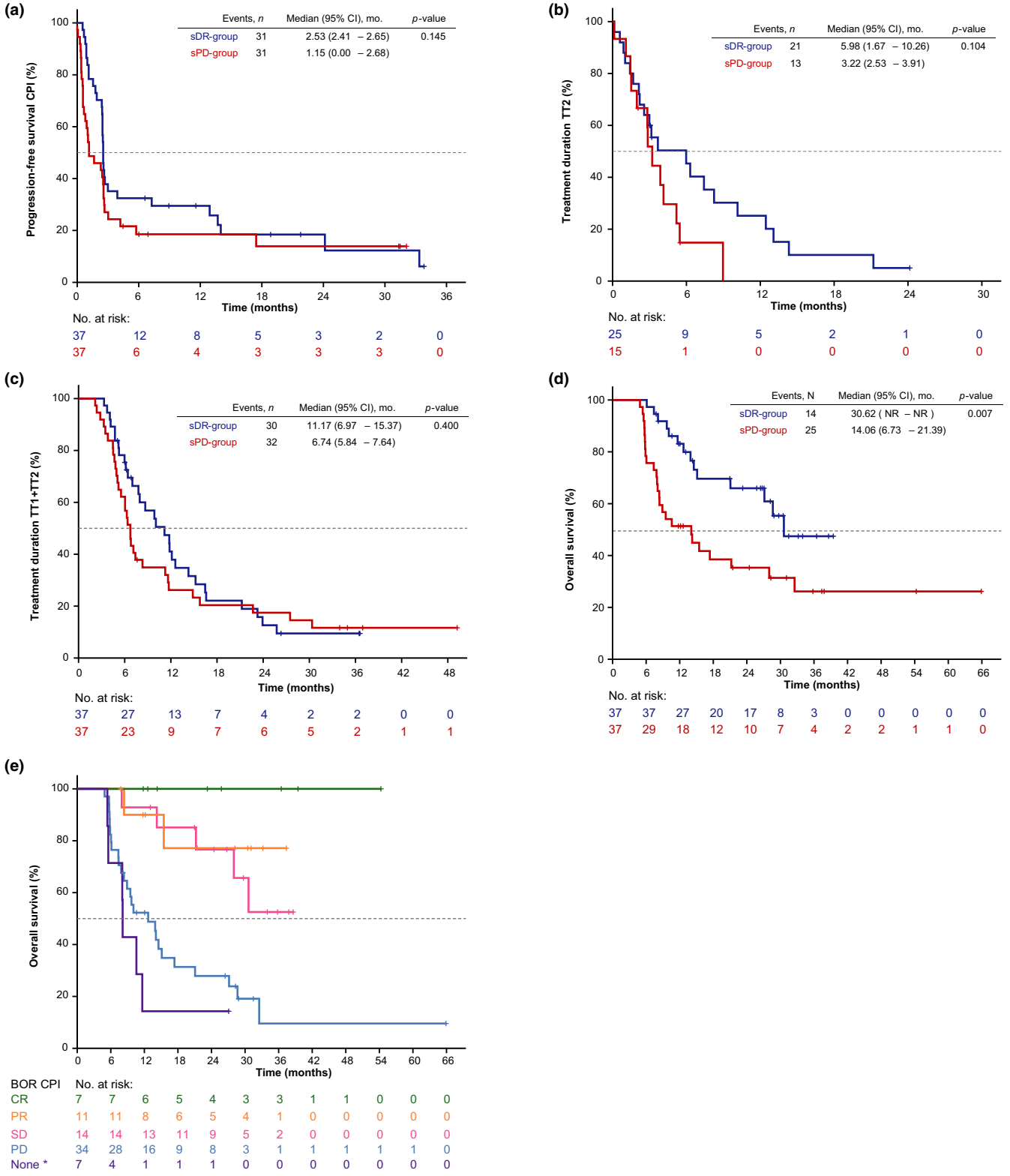

FIGURE 2 A-D, Kaplan–Meier curves comparing the sDR group (blue) and sPD group (red) regarding the (A) progression-free survival of CPI, (B) treatment duration of re-challenge with TT (TT2), (C) total treatment duration of TT (TT1 + TT2) and (D) overall survival from start TT. E, Kaplan–Meier curves of the association between best overall response (BOR) to CPI and overall survival. Abbreviations: CPI, checkpoint inhibition; sDR, switch during response; sPD, switch at progressive disease; TT, targeted therapy

TABLE 3 Hazard ratios of sDR group versus sPD group

	Univariable analysis			Multivariable analysis[a]		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
PFS CPI	0.692	0.418–1.145	.151	0.892	0.450 – 1.85	.956
OS	0.418	0.217–0.805	.009	0.478	0.225 – 1.015	.055
TD TT2	0.540	0.254–1.149	.110	0.651	0.231 – 1.836	.418
TD TT1 + TT2	0.807	0.488–1.332	.401	0.937	0.524 – 1.674	.826

Abbreviations: CPI, checkpoint inhibition; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; sDR, switch during response; sPD, switch at progressive disease; TD, treatment duration; TT1, targeted therapy; TT2, re-challenge with targeted therapy.
[a]Corrected for: number of metastatic sites, brain metastases, baseline PS, baseline LDH, line of therapy and best response on targeted therapy.

frequency of CRs to CPI, the numerically longer duration of response to CPI, and the significant longer OS in the sDR group may result from the baseline imbalances in the cohort, but could also reflect improved tumour susceptibility for CPI, when switching before deterioration upon first-line TT. To address this caveat, we tried to correct for markers known to be associated with unfavourable outcome upon CPI. In doing so, we still observed favourable outcomes for the sDR group, yet not significant anymore (likely to the low patient numbers in the subgroups).

Preclinical studies imply that short-term BRAF inhibition induces a more favourable tumour microenvironment, but also demonstrated that T-cell infiltration is diminished at progressive disease (Frederick et al., 2013; Wilmott et al., 2012) or even early during treatment (Deken et al., 2016), arguing indeed for an early switch to CPI after initiation of TT. While patients with an early switch experienced significant OS benefit and a superior duration of response to CPI, this is not supported by a difference in PFS. This might be explained by the fact that more patients in the sDR group achieved a CR upon CPI (Figure 2e) and more patients in the sDR group were, after failure to CPI, still in a performance status to receive a subsequent third line of therapy.

Sequential treatment strategies in patients with BRAF-mutated melanoma are currently extensively tested, considering the fact that concurrent use of TT and CPI is associated with high toxicity rates. For example, in the randomized phase II KEYNOTE-022 trial [NCT02130466], testing dabrafenib and trametinib plus pembrolizumab or placebo, triplet therapy demonstrated a numerically higher PFS, but at cost of substantial higher toxicity rates (57% vs. 27% grade 3–4 AEs; Ribas et al., 2017).

Published results on the efficacy of sequential TT and CPI are rare. Some retrospective studies have shown that anti-CTLA4 or anti-PD1 treatment following progression on BRAF ± MEK inhibitors results in poorer outcomes than what is expected from first-line CPI (Ackerman et al., 2014; Ascierto et al., 2012; Johnson et al., 2017; Simeone et al., 2017). These studies suggest that TT resistance may be accompanied by selection for more aggressive disease and an immune-suppressed tumour microenvironment (Frederick et al., 2013). Our results corroborate these findings with substantial inferior outcomes compared to the first-line phase III trials (Schachter et al., 2017; Wolchok et al., 2017).

However, the outcomes upon CPI are not only poorer for the sPD group but also for the sDR group, reflecting the worse patient characteristics in this real-world cohort analysed here. The median treatment duration of TT1 in the sPD group was also substantially shorter compared to the phase III trials testing frontline BRAF inhibitors or combined BRAF and MEK inhibitors (Ascierto et al., 2016; Dummer et al., 2018; Long et al., 2017). In these trials, patient characteristics were generally better and patients with brain metastases were excluded if their disease was not stable and asymptomatic. The COMBI-MB study testing solely patients with brain metastases treated with dabrafenib plus trametinib demonstrated lower PFS rates that are more in line with our results (Davies et al., 2017). Moreover, a pooled analysis of patients treated with BRAFi + MEKi in the randomized trials designates elevated LDH, >3 metastatic sites and ECOG PS ≥ 1 as bad prognostic factors (Long et al., 2016).

Previously, we have shown that end-of-line TT (even beyond PD) can have OS benefit for patients (Scholtens et al., 2015). The ORR of the re-challenge of TT in our cohort was similar to that found in other studies (Schreuer et al., 2017; Valpione et al., 2018). This confirms that resistance mechanisms upon TT can be reversible in a relevant number of patients. The total time of TT treatment was numerically longer in patients who switched during response; however, this may be biased by the difference in baseline characteristics.

Our study has a number of limitations. First, inherent to the retrospective character of our analysis, the groups were not balanced well at baseline. After correcting in multivariable analysis and by performing subgroup analysis, there were no significant differences between the groups anymore, likely partly due to small numbers, which makes our observations only hypothesis-generating. Second, patients were not homogeneously treated, as single-agent and combination therapy were applied for both TT and CPI. However, monotherapies were more often given in the sDR group biasing the results against the favourable outcome of the sDR group. We did not observe a difference in clinical outcome when comparing patients treated with the monotherapy anti-PD-1 or the combination, which is in line with a recently published study analysing the efficacy of anti-PD-1-based therapies after progression on TT (Kreft et al., 2019). Given the fact that the immune-modulating effects predominantly seem to be caused by BRAF inhibitors (Boni et al., 2010; Bradley et al., 2015; Callahan et al., 2014; Frederick et al., 2013; Wilmott et al., 2012), one can assume that the baseline imbalances between single-agent versus

combination TT might not have biased our observations. Third, the treatment duration of TT1 in the sDR group strongly varied due to the lack of standardization of switch time point. Finally, there was no homogeneous timing and frequency of response assessments, making PFS data less solid, while OS is likely less influenced.

Given the above-discussed limitations, our data need to be interpreted with caution. Nevertheless, and to our knowledge, this is the first study that attempts to analyse the best moment of switch from TT to CPI in a real-world clinical setting. Definitive answers, however, can only come from prospective randomized trials that are currently underway but will not be presented before 2020 (ImmunoCobiVem, NCT02902029; SECOMBIT, NCT02631447; EORTC 1612).

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CONFLICT OF INTEREST

No author has received support for the work in this manuscript. EAR reports to have received travel support from NanoString and MSD. JVT reports to have received travel support from Roche and has served as a consultant adviser for Pfizer and Novartis, for which the institution (NKI) received funding. JBAGH has served as a consultant advisor for BMS, MSD, Pfizer, AZ/MedImmune, Roche/Genentech, Ipsen, Bayer, Immunocore, Novartis, Seattle Genetics, Neon Therapeutics, Celsius Therapeutics, Gadet and GSK for which the institution (NKI) received funding, and has received grant support from BMS, MSD, Novartis and Neon Therapeutics. CUB reports personal fees as a consultant advisor for BMS, MSD, Roche, Novartis, Lilly, Pfizer, GSK, GenMab and Pierre Fabre and has received research grants from BMS, Novartis and NanoString all paid to the institution (NKI). ILMR and SW have nothing to disclose.

ETHICAL APPROVAL

The study protocol is approved by the Local Ethical Committee and complies with the guidelines of the responsible governmental agency.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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