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ORIGINAL ARTICLE

Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma

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Background: Programmed cell death protein 1 (PD-1) blocking monoclonal antibodies improve the overall survival of patients with advanced melanoma but the optimal duration of treatment has not been established.

Patients and Methods: This academic real-world cohort study investigated the outcome of 185 advanced melanoma patients who electively discontinued anti-PD-1 therapy with pembrolizumab ($N = 167$) or nivolumab ($N = 18$) in the absence of disease progression (PD) or treatment limiting toxicity (TLT) at 14 medical centres across Europe and Australia.

Results: Median time on treatment was 12 months (range 0.7–43). The best objective tumour response at the time of treatment discontinuation was complete response (CR) in 117 (63%) patients, partial response (PR) in 44 (24%) patients and stable disease (SD) in 16 (9%) patients; 8 (4%) patients had no evaluable disease (NE). After a median follow-up of 18 months (range 0.7–48) after treatment discontinuation, 78% of patients remained free of progression. Median time to progression was 12 months (range 2–23). PD was less frequent in patients with CR (14%) compared with patients with PR (32%) and SD (50%). Six out of 19 (32%) patients who were retreated with an anti-PD-1 at the time of PD obtained a new antitumour response.

Conclusions: In this real-world cohort of advanced melanoma patients discontinuing anti-PD-1 therapy in the absence of TLT or PD, the duration of anti-PD-1 therapy was shorter when compared with clinical trials. In patients obtaining a CR, and being treated for >6 months, the risk of relapse after treatment discontinuation was low. Patients achieving a PR or SD as best tumour response were at higher risk for progression after discontinuing therapy, and defining optimal treatment duration in such patients deserves further study. Retreatment with an anti-PD-1 at the time of progression may lead to renewed antitumour activity in some patients.

Clinical trial registration: NCT02673970 (https://clinicaltrials.gov/ct2/show/NCT02673970?cond=melanoma&cntry=BE&city=Jette&rank=3)

Key words: melanoma, anti-PD-1 therapy, duration of treatment, immunotherapy

Introduction

Blockade of the programmed cell death protein 1 (PD-1) cell surface receptor relicenses antitumour T-cell activity in a tumour microenvironment with expression of the programmed death-ligand 1 (PD-L1) on tumour and/or other tumour infiltrating cells [1, 2]. The PD-1 blocking monoclonal antibodies pembrolizumab and nivolumab demonstrated overall survival (OS) benefit when compared with ipilimumab or dacarbazine in patients with advanced melanoma [3–5]. One- and two-year survival rates were in the order of 70% (68%–74%) and 57% (55%–59%), respectively [3, 6].

Optimal duration of anti-PD-1 therapy has not been established. Within most clinical trials, patients could continue therapy until progressive disease (PD) or treatment limiting toxicity (TLT). In an early phase I trial with nivolumab, 12 (71%) of 17 patients experienced ongoing antitumour responses after treatment cessation for reasons other than PD [7]. In the subgroup of 67 patients who stopped pembrolizumab treatment after obtaining a complete response (CR) in the KEYNOTE-001 trial, the 24-month disease-free survival from time of CR was 89.9% [8]. In the phase III KEYNOTE-006 trial, 103 patients discontinued pembrolizumab after the foreseen maximum duration of 24 months of which, 19 (18%) patients developed PD after a median follow-up of 20 months [9]. Notably, four (50%) responses were observed among eight patients retreated with anti-PD-1 therapy.

Previously we reported the outcome of advanced melanoma patients treated with PD-1 therapy outside of an interventional clinical trial [10]. In this cohort, a subgroup of patients electively stopped therapy in the absence of PD or TLT. We expanded this cohort with additional patients from sites in Switzerland and Australia and reported the pooled analysis of their characteristics and clinical outcome.

Methods

Study design

Clinical data from 803 unselected patients (cohort 1) with advanced melanoma treated with anti-PD-1 monotherapy in 12 sites across Europe and Australia were collected and pooled for analysis. Patients received pembrolizumab or nivolumab in an expanded access programme or according to the label after approval. Out of this cohort all patients that discontinued therapy upon a joint-decision by the patient and the treating physician in the absence of PD or TLT (=elective discontinuation) were identified. An additional cohort (cohort 2) of patients that electively stopped anti-PD-1 at two additional sites in Australia and Switzerland was included in this analysis. Baseline characteristics, treatment disposition, tumour responses (according to immune related response criteria [irRC]), progression-free survival (PFS) and OS were collected based on the assessments made by the investigators.

In part, data were collected prospectively following written informed consent of an institutional medical ethics committee approved form (UZ Brussels and MIA) or by retrospective collection of data following approval of the institutional MEC (all other centres).

Statistical analysis

Descriptive statistics were used to report the baseline characteristics of the study population. Logistic regression analysis and chi-square test were used to identify potential predictive biomarkers for treatment discontinuation.

Time on treatment was calculated as the time between the date of the first administration of anti-PD-1 therapy and the date of the last administration. Follow-up and PFS after elective treatment discontinuation were calculated from the date of the last cycle to the date of PD or last follow-up. OS was calculated from start of anti-PD-1 therapy to date of death or last follow-up. PFS and OS for the whole population and subgroups (according to best objective response [BOR] and duration of therapy) were estimated using the Kaplan–Meier method and compared using log-rank tests. Cox proportional hazard regression models were applied to analyse associations between clinical characteristics and risks for PD. Analyses were carried out using SPSS 25 (IBM).

Results

Baseline patient characteristics

We identified 185 advanced melanoma patients (cohort 1: 150 patients [supplementary Figure S1, available at *Annals of Oncology* online] and cohort 2: 35 patients) who electively stopped anti-PD-1 therapy (pembrolizumab [$N = 167$] or nivolumab [$N = 18$]) (supplementary Table S1, available at *Annals of Oncology* online) in the absence of PD or TLT. Anti-PD-1 therapy was initiated between February 2013 and October 2016. Baseline characteristics at treatment initiation are summarised in Table 1. Anti-PD-1 therapy was administered as a first-line therapy in 80 (43%) patients. Prior therapies consisted of ipilimumab (91 [49%] patients) and BRAF-inhibitor (27 [15%] patients). Ninety-eight (53%) patients were diagnosed with AJCC seventh edition stage IV-M1c disease, 25 (13%) patients with brain metastases, the majority had an ECOG performance status ≤ 1 (179 [97%] patients) and serum lactate dehydrogenase (LDH) was elevated in 43 (23%) of the tested patients.

Treatment disposition and tumour response

At the data cut-off date on 10 May 2018, median follow-up after treatment initiation was 32 months (range 3–60). BOR by irRC on CT was CR in 117 (63%) patients, PR in 44 (24%) patients and SD in 16 (9%) patients. Eight (4%) patients were non-evaluable (NE, due to non-measurable disease according to irRC). Median duration of anti-PD-1 therapy was 12 months (range 0.7–43); only 26 (14%) patients were treated for <6 months. Patients with CR, PR and SD as best response to anti-PD1 were treated respectively for a median duration of 11 months (range 2–36), 15 months (range 2–43) and 14 months (range 5–24) (Table 2).

Outcome after elective discontinuation of anti-PD-1 treatment

After a median follow-up of 18 months (range 0.7–48) after treatment discontinuation, 40 (22%) patients had progressed (Table 2, Figure 1 and supplementary Figure S2, available at *Annals of Oncology* online). Median PFS after discontinuation has not been reached (Figure 1A). Median time to progression was 12 months (range 2–23). The estimated 1-year and 2-year PFS-rates after discontinuation were 90% (95% CI 85–94) and 71% (95% CI 63–79), respectively. BOR during initial anti-PD-1

Table 1. Baseline characteristics of patients who discontinued anti-PD-1 treatment in the absence of PD or TLT

Patient	All patients
Characteristics	*N* (%)
Median follow-up (months; range)	32 (3–60)
Anti-PD-1 mAb	
Pembrolizumab	167 (90)
Nivolumab	18 (10)
Age, years	
Median (range)	64 (27–93)
Gender	
Female	70 (38)
Male	113 (61)
Unknown	2 (1)
Primary	
Skin	155 (84)
Mucosal	1 (0.5)
Occult primary	1 (0.5)
Unknown	28 (15)
Disease stage	
Stage IIIc	10 (5)
Stage IV M1a	38 (21)
Stage IV M1b	37 (20)
Stage IV M1c	98 (53)
Unknown	2 (1)
Brain metastases	
Yes	25 (13)
No	153 (83)
Unknown	7 (4)
BRAF V600 mutation	
Yes	52 (28)
No	127 (69)
Unknown	6 (3)
Prior treatment with ipilimumab	
Yes	91 (49)
No	92 (50)
Unknown	2 (1)
Prior BRAF- ± MEK-inhibitor	
Yes	27 (15)
No	156 (84)
Unknown	2 (1)
Prior dacarbazine	
Yes	12 (7)
No	171 (92)
Unknown	2 (1)
Line of therapy for anti-PD-1 mAb	
First-line	80 (43)
Second-line or higher	103 (56)
Unknown	2 (1)
ECOG PS	
0	151 (82)
1	28 (15)
≥2	4 (2)
Unknown	2 (1)
CRP	
Normal	53 (29)
>ULN—5× ULN	19 (10)
5× ULN—10× ULN	4 (2)
>10× ULN	4 (2)
Unknown	105 (57)
LDH	
Normal	134 (72)
>ULN—1, 5× ULN	37 (20)
1.5× ULN—2× ULN	2 (1)
>2× ULN	4 (2)
Unknown	8 (4)
ALC	
>2000/mm^3	48 (26)
1500–2000/mm^3	51 (28)
1000–1500/mm^3	43 (23)
500–1000/mm^3	30 (16)
<500/mm^3	2 (1)
Unknown	11 (6)
ANC	
<7500/mm^3	163 (88)
>7500/mm^3	13 (7)
Unknown	9 (5)

Data are presented as *N* (%) unless otherwise noted. According to AJCC seventh edition. Abbreviations: PD-1, programmed cell death protein 1; PD, disease progression; TLT, treatment limiting toxicity; mAb, monoclonal antibody; ECOG PS, Eastern cooperative oncology group performance status; CRP, C-reactive protein; ULN, upper limit of normal; LDH, lactate dehydrogenase; ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

therapy in patients that developed PD was a CR in 16 (14% of all patients with CR), PR in 14 (32% of all patients with PR), SD in 8 (50% of all patients with SD) and NE in 2 patients (25% of all patients who were NE) (Table 2; Figures 2 and 3). Patients obtaining a CR had a significant lower risk of PD compared with patients obtaining a PR ($P = 0.002$; HR 2.99, 95% CI 1.45–6.16) or maintaining SD ($P < 0.001$; HR 5.15, 95% CI 2.19–12.09) (supplementary Table S2, available at *Annals of Oncology* online). Estimated median PFS after discontinuation had not been reached in patients with a CR, PR or NE and was 16 months (range 13–18) in patients with SD (Figure 1B, supplementary Table S2, available at *Annals of Oncology* online). Median PFS after discontinuation was not reached in any of the subgroups stratified according to treatment duration and no significant difference in PFS was found between these groups (Figure 1C, supplementary Table S3, available at *Annals of Oncology* online).

Multivariable analysis including known prognostic clinical characteristic (e.g. stage of disease and prior therapies) demonstrated that patients with a CR had a lower risk of PD when compared with patients with PR and SD and revealed no significant association between risk of PD and treatment duration or clinical characteristics (supplementary Table S4, available at *Annals of Oncology* online). In the 117 patients with CR, patients who were treated for <6 months had a significant higher risk of progression (median PFS: 18.9 months [95% CI 15.8–22.3] versus not reached for patients treated for >6 months, $P < 0.05$). There was no difference in risk of PD between patients with CR treated for 6

Table 2. Treatment duration, follow-up and outcome according to BOR for patients who discontinued therapy with anti-PD-1 in the absence of PD or TLT

Best objective response	Number of patients		Patients diagnosed with PD		Median time of follow-up from start anti-PD-1		Median time on anti-PD-1 therapy		Median time of follow-up after discontinuation	
	N (%)		*N* (%)		months (range)		months (range)		months (range)	
All	185	(100)	40	(22)	32	(3–60)	12	(0.7–43)	18	(0.7–48)
Complete response	117	(63)	16	(14)	32	(3–60)	11	(2–36)	20	(0.7–48)
Partial response	44	(24)	14	(32)	34	(7–53)	15	(1–43)	16	(1–31)
Stable disease	16	(9)	8	(50)	32	(14–44)	14	(6–24)	16	(3–26)
Non-evaluable disease	8	(4)	2	(25)	27	(13–41)	7	(0.7–12)	17	(11–29)

Abbreviations: PD-1, programmed cell death protein 1; PD, disease progression; TLT, treatment limiting toxicity.

to 12, 12 to 18, 18 to 24 or >24 months (Figure 1D, supplementary Table S5, available at *Annals of Oncology* online).

Site of progression was known for 18 of the 40 (45%) progressing patients; 11 (65%) patients had new lesions and 7 (35%) patients progressed at a previously existing metastatic site. In 7 (35%) patients, the brain was the first site of progression (in 6 [86%] patients these were new lesions).

Outcome after retreatment with anti-PD-1 therapy and alternative treatment-options

Nineteen (48%) of the 40 patients with PD were re-challenged with pembrolizumab or nivolumab (Figures 2 and 3; Table 3). Initial BOR of these 19 patients was a CR in 9 patients, PR in 6 and maintaining SD in 4 patients. BOR following retreatment was CR in 2 (11%) patients (durable ongoing CR [10 and 21 months]), PR in 4 (21%) patients and SD in 5 (26%) patients. Six (32%) patients did not benefit from retreatment. One (5%) patient died before the first response evaluation and 1 (5%) patient has not yet been evaluated. Of the six objective responses (two CR's and two PR's) documented after retreatment of anti-PD-1 therapy, 5 (83%) responses were seen in patients obtaining CR during their first exposure to anti-PD1 therapy (Table 3).

Twelve (30%) of the 40 patients with PD were salvaged with loco-regional therapy (eight underwent surgery, three had radiotherapy and one received electro chemotherapy) (Figure 3). Most patients salvaged with surgery remained progression-free at data cut-off; obtaining CR in 4 (50%), PR in 1 (13%), PD in 1 (13%) and 2 (25%) patients were not yet evaluated. Three (8%) patients were treated with BRAF-targeted therapy. In 6 (15%) no additional treatment was started. One patient had a spontaneous decrease in the size of a brain lesion (4–2 mm) without active treatment. Six (15%) patients died after developing PD, of which 4 (10%) died due to melanoma.

Discussion

Anti-PD-1 therapy is the most effective single-agent immunotherapy for patients with advanced melanoma [2, 3, 6]. In prospective clinical trials, the duration of therapy has been arbitrarily defined as up to the time of PD, TLT (CheckMate-067) or a maximum of 2 years (KEYNOTE-006) [3, 6]. Ongoing disease control after cessation of anti-PD-1 therapy was observed in a substantial number of patients discontinuing therapy due to TLT [11]. Likewise, a number of observations from phase I and phase III clinical trials indicate that patients can experience ongoing benefit after discontinuing therapy in the absence of PD or TLT [7–9]. Furthermore, in melanoma patients treated with ipilimumab plus nivolumab, similar survival outcomes were reported for patients that discontinued due to TLT and those who did not [12]. Durable responses after short duration of therapy have also been observed for other immunotherapies, including ipilimumab mono-therapy, TIL therapy and high dose interleukin 2 [13, 14].

Our study is the first to report treatment duration and outcome (including outcome after retreatment with anti-PD-1) after elective treatment discontinuation in a large real-world cohort of 185 advanced melanoma patients. Treatment exposure was variable and with a median of 1 year on treatment, considerably shorter when compared with the maximum treatment duration in the KEYNOTE-006 trial (2 years) [3, 6]. The conditions for stopping anti-PD-1 therapy were not predefined or harmonised among centres and were made at the discretion of the treating physician in agreement with the patient, reflecting both the patient's desire and physician's acceptance to discontinue therapy.

Retrospectively, CR was a main driver for treatment discontinuation and this subgroup had the shortest treatment exposure. A significant number of patients stopped treatment despite persisting radiological evidence of disease. Objective parameters not captured during our study such as depth of response, durability of response and the metabolic responses on FDG-PET scans are likely to have contributed to the decision-making. The population of patients that electively stopped therapy was characterised by a lower frequency of *BRAF* V600 mutation, a better performance status, a lower tumour stage and incidence of brain metastases, and lower frequency of elevated CRP and LDH levels at baseline when compared with patients that did not discontinue before PD or TLT (supplementary Tables S6 and S7, available at *Annals of Oncology* online).

After a median follow-up of 18 months following treatment discontinuation, 40 (22%) patients had developed PD which is a comparable to the KEYNOTE-006 trial (18% progressed after a median follow-up of 20 months) [9]. Our cohort includes a higher number of patients (185 versus 103), and was characterised by a higher percentage of patients with a CR (63% versus 27%), but a lower percentage of patients receiving anti-PD-1 as first-line therapy (43% versus 66%). Notably 50% had prior ipilimumab, and 15% targeted therapy, however this did

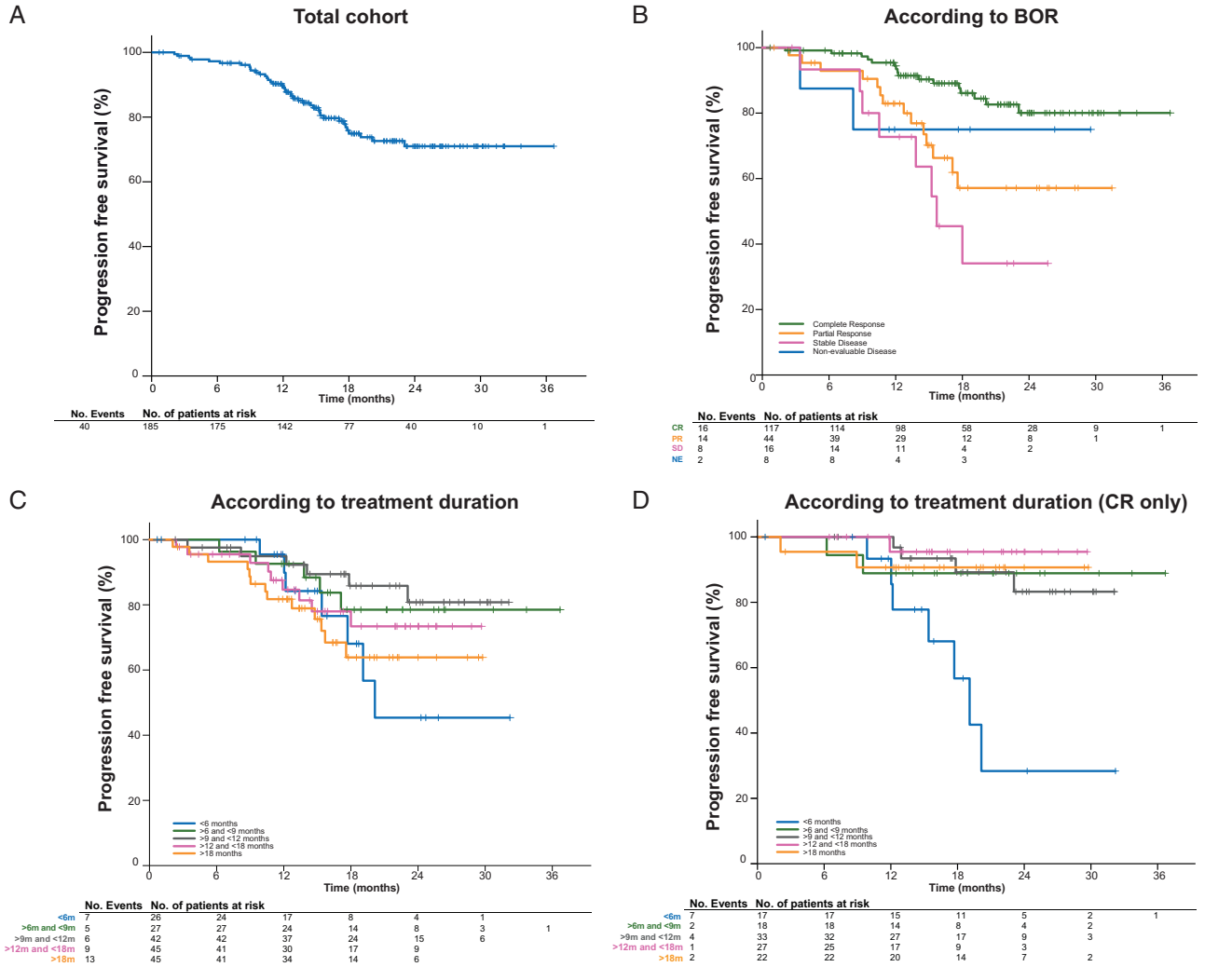

Figure 1. Kaplan–Meier probability curves for progression-free survival from discontinuation of anti-PD-1. Progression free survival from discontinuation of anti-PD-1 for the total cohort that discontinued in the absence of PD or TLT (A); according to best overall (B) and according to time on anti-PD-1 therapy for the whole cohort (C) and only for patients with a CR (D). The hash marks designate patients who were censored at that time point. Abbreviations: PD-1, programmed cell death protein 1; BOR, best overall response; PD, progressive disease; TLT, treatment limiting toxicity.

not affect the risk of disease progression. We observed that the risk of PD following treatment discontinuation was significantly associated with BOR, and significant lower in patients with a CR. Among patients with a CR, the risk of progression was significantly higher in the group treated for <6 months; however, this association was not seen for the whole population (including the smaller populations of patients with PR, SD or NE), and in patients with CR treated for >6 months, we did not find an association between risk of PD and duration of therapy.

In our real-world retrospective cohort, patients with a PR who discontinued anti-PD-1 therapy in the absence of TLT or PD seemed to be at higher risk for subsequent PD compared with those in the prospective KEYNOTE-006 study (32% versus 14%). While inevitably enriching for patients who would have progressed on-therapy when evaluating a population with a shorter exposure, and difference in baseline characteristics may be of influence, a negative effect of shorter treatment duration on PFS, and perhaps also on OS, cannot be ruled out.

The retrospective nature and the lack of central radiology review warrant a careful interpretation of our observations but they clearly indicate that defining the optimal duration of treatment with anti-PD-1 therapy deserves further investigation. Continuing therapy means that patients remain at risk of treatment related adverse events, which may affect quality of life. Secondly, unnecessary continuation of therapy is associated with a significant financial burden with drug costs, administration infrastructure and out-of-pocket expenses to patients.

Data from randomised trials are needed to establish guidelines for optimal treatment duration, especially in patients achieving a PR or SD as best tumour response. Recently, it was shown that a complete metabolic tumour response on FDG-PET/CT at 1-year following initiation of anti-PD-1 may have greater utility than CT response in predicting long-term PFS [15]. Other innovative measures addressing the kinetics and depth of tumour response (measurement of circulating tumour DNA [16]) as well as baseline and on-treatment molecular-genetic tumour characteristics

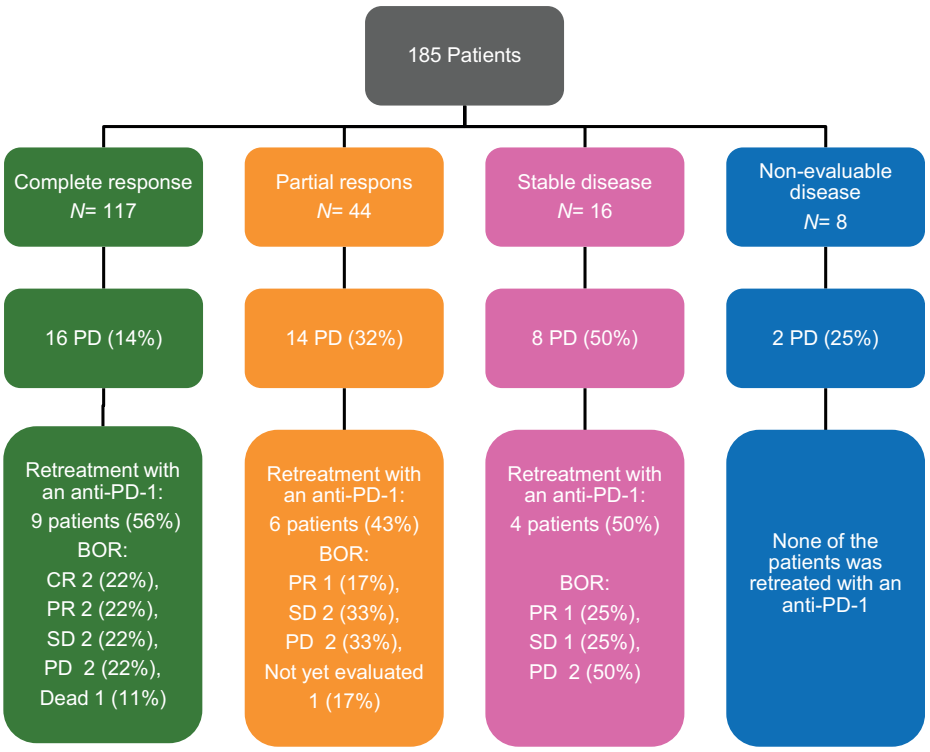

Figure 2. Outcome of 185 patients discontinuing treatment according to BOR and outcome after PD-1 reintroduction. Of the 185 patients who discontinued anti-PD-1, 40 patients experienced progressive disease. A PD-1 inhibitor was re-introduced in 19 patients leading to 6 renewed objective responses (32%, two patients with a CR [11%] and four patients with a PR [21%]). Abbreviations: PD-1, Programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; NE, non-evaluable disease; PD, progressive disease; BOR, best objective response.

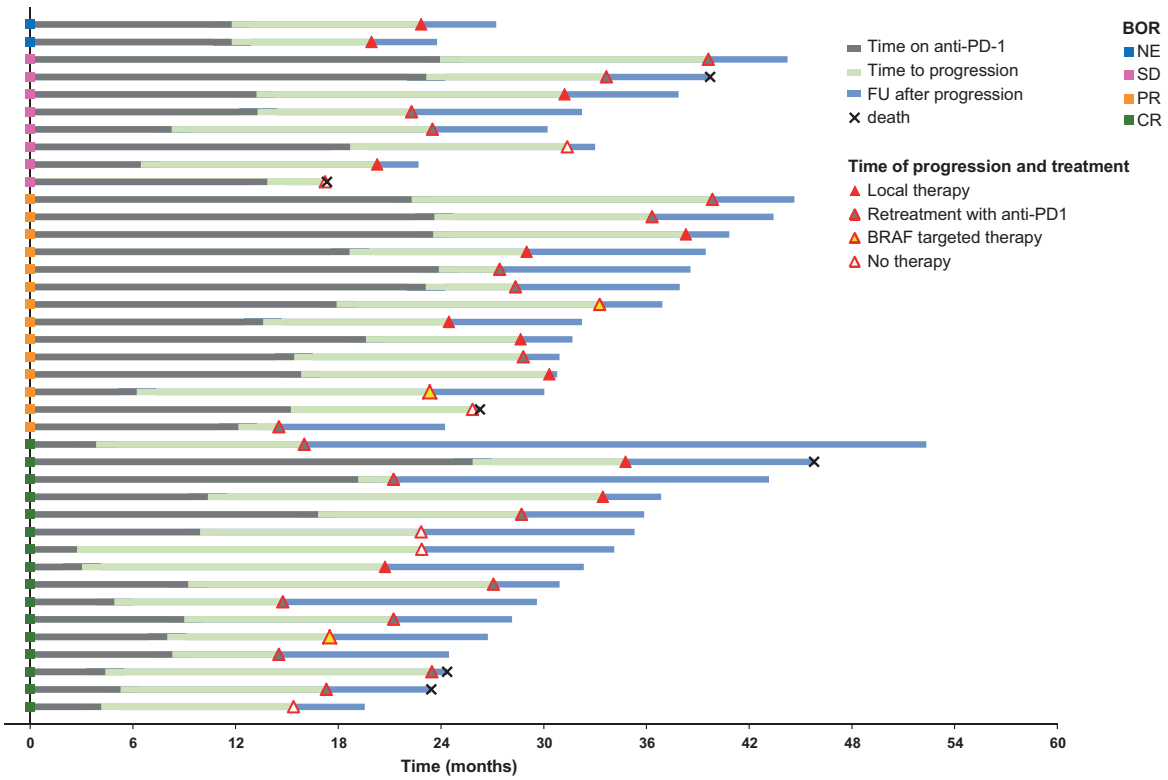

Figure 3. Swimmer plot indicating time on anti-PD-1 treatment, progression-free survival, and overall survival of patients with progression after discontinuation of anti-PD-1. Abbreviations: PD-1, Programmed cell death protein 1; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease, NE, non-evaluable disease.

Table 3. Outcome of patients after retreatment with anti-PD-1 therapy

Patient	Time on anti-PD-1 (months)	BOR 1st course anti-PD-1	Time to PD (months)	Therapy for PD	BOR 2nd course anti-PD-1	Disease status at time data cut-off
1	<6	CR	9.9	Pembrolizumab	CR	Ongoing CR[a]
2	>18	CR	2.1	Pembrolizumab	CR	Ongoing CR
3	<6	CR	12.2	Pembrolizumab	PR	PD
4	<6	CR	12.0	SRS + Pembrolizumab	PR	Ongoing PR
5	9–12	CR	17.8	SRS + nivolumab	PR	Ongoing PR
6	6–9	CR	19.2	Pembrolizumab	SD	Slow PD
7	9–12	CR	12.2	Pembrolizumab	PD	
8	12–18	CR	12.0	pembrolizumab	PD	
9	<6	CR	16.2	Pembrolizumab	died	
10	>18	PR	5.3	Pembrolizumab	PR	Ongoing PR
11	12–18	PR	2.3	Pembrolizumab	SD	Ongoing SD[b]
12	>18	PR	17.5	Pembrolizumab	SD	Ongoing SD
13	12–18	PR	13.4	Nivolumab	not yet	
14	>18	PR	12.7	Nivolumab	PD	
15	>18	PR	3.5	Pembrolizumab	PD	
16	6–9	SD	15.2	Pembrolizumab	SD	PD[c]
17	>18	SD	10.6	Pembrolizumab	SD	Ongoing SD
18	12–18	SD	9.0	Nivolumab	PD	
19	>18	SD	10.6	Pembrolizumab	PD	

Anti-PD-1 therapy was re-introduced in 19 patients leading to 6 renewed objective responses (32%, 2 patients with a CR [11%] and 4 patients with a PR [21%]). Abbreviations: PD-1, programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; NE, non-evaluable disease; PD, progressive disease; BOR, best objective response.

[a]Discontinued therapy after 9 cycles.

[b]Discontinued therapy after 4 cycles.

[c]Received chemotherapy for NHL.

e.g. gene expression signatures or mutational load [17], may be able to define optimised individualised treatment schedules in patients benefiting from anti-PD-1 therapy, especially in non-CR patients. Our data can help guide the design of future prospective clinical trials examining this important issue. Three investigator-led clinical trials have already been initiated (STOP-GAP trial, *NCT02821013*, SAFE-STOP *NTR7502* and DANTE, *EDURACT2017-002435-42*).

Although the number of patients being retreated at the time of progression is relatively small ($N = 19$), our case series indicates, in line with the data from the KEYNOTE-006 trial, that retreatment can lead to renewed antitumour activity in a subset of patients after a treatment break. Future prospective studies are needed to address the efficacy of retreatment with anti-PD-1 therapy.

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VA: Honoraria—BMS, MSD and Novartis; Consulting or advisory role—BMS, MSD, Merck Serono, Novartis, Pierre Fabre; Speaker Bureau—MSD, Novartis, BMS; Travel, Accommodation or Expenses—BMS, Novartis.
CUB: Consulting or Advisory Role—AstraZeneca (Inst), Bristol-Myers Squibb (Inst), GlaxoSmithKline (Inst), Lilly (Inst), MSD Oncology (Inst), Novartis (Inst), Pfizer (Inst), Roche/Genentech (Inst), GenMab (Inst), Pierre Fabre (Inst); Research Funding—Bristol-Myers Squibb (Inst), Novartis (Inst); Travel, Accommodations, Expenses—Pfizer, Roche.
BN: Honoraria—Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche; Consulting or Advisory Role—Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche; Speakers' Bureau—Novartis Travel, Accommodations; Expenses—Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche.
All remaining authors have declared no conflicts of interest.

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