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MELANOMA (DB JOHNSON, SECTION EDITOR)

Anti-PD-1: When to Stop Treatment

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Abstract

Purpose of Review Emerging data indicate that immune checkpoint blockade (ICB) in patients with metastatic melanoma can be stopped electively or at the time of toxicity with an acceptable risk for progression. However, the optimal treatment duration remains to be defined. We review published data on treatment duration, outcome after treatment discontinuation, and treatment re-introduction in patients with metastatic melanoma.

Recent Findings Published studies indicate that disease control can be maintained after discontinuation of ICB therapy. Discontinuation of therapy in responders decreases the risk for treatment-related adverse events and lowers the financial burden of ICB.

Summary With the limitation of the limited and heterogenous available published data, elective treatment discontinuation after 1 year of treatment appears safe with an acceptable risk of disease progression. The depth of response is currently the best predictor of prolonged response. The metabolic response on 18F-FDG-PET/CT is expected to gain importance, especially for partial responders.

Keywords Immunotherapy · Treatment duration · Anti-PD-1 · Metastatic melanoma

Introduction

Before the introduction of immune checkpoint blockade (ICB) and targeted therapy, the historical 10-year overall survival (OS) rates in patients with advanced melanoma was disappointingly low. The CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) blocking monoclonal antibody (mAb) ipilimumab, improved long-term OS in about 10–15% of advanced melanoma patients and changed the paradigm of melanoma being an "untreatable" malignancy [1, 2]. It did not take long before a new generation of ICB, the anti PD-1 antibodies pembrolizumab and nivolumab, entered the clinical arena.

The KEYNOTE 001, KEYNOTE 002, and KEYNOTE 006 and the CHECKMATE 037, CHECKMATE 067, and CHECKMATE O69 were the pivotal trials for pembrolizumab and nivolumab respectively [3–11]. No head-to-head comparison has been performed but due to their similar working mechanism and obtained comparable results, it is accepted to consider them equally effective. Objective response rates (ORR) on anti-PD-1 antibodies in the advanced melanoma population range between 27 and 45%, and these responses are durable with median duration of responses not reached at 5 years [3–5, 12, 13].

In the current era, anti-PD-1 antibodies (± anti-CTLA-4 antibodies) have become the standard first line treatment for patients with advanced unresectable melanoma [5, 14–16]. Following the introduction of anti-PD-1 ICB, two "new" patient populations emerged: patients discontinuing ICB treatment due to adverse events (most often grade 3/4 toxicity, or any "treatment-limiting toxicity [TLT]"), and

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patients discontinuing ICB in the absence of progressive disease (PD) or TLT (=elective discontinuation of ICB). Whether these two new patient populations share comparable outcomes (: same risk of disease recurrence and the same response to treatment rechallenge) remains unknown [5, 12–14, 16–21]. In this review, we will discuss the discontinuation of ICB "on an elective basis" or due to TLT separately.

Methods

Search Strategy

We searched PubMed and Embase, using a combination of broad terms related to melanoma and immunotherapy: melanoma, Keytruda, Opdivo, and treatment duration. References in recovered studies and relevant reviews were also screened. Databases were searched from their inception until October 2021. No language restrictions were applied.

Study Selection and Data Extraction

Two reviewers independently searched databases (YJ, BN) and assessed eligibility of studies based on abstracts and full texts, resolving disagreements by consensus. Eligible studies were randomized-controlled trials, case series, retrospective trials, or real-world trials describing outcomes of interest in a minimum of 15 metastatic melanoma patients. Studies with insufficient follow-up ($\leq$6 months) were excluded. Case reports and trials evaluating less than 15 metastatic melanoma patients were excluded.

Outcomes of Interest and Statistical Analysis

Overall survival (OS), progression-free survival (PFS), median follow-up, number of patients with progressive disease and best objective response were collected from all included trials. We adhered to the definition of progression, BOR, and discontinuation criteria used by each trial.

Results

The first data on treatment discontinuation originates from the KEYNOTE trials (KEYNOTE 001 and 006) with, respectively, 67 and 103 patients discontinuing treatment in the absence of PD or TLT [5, 12, 13, 16, 19]. While no foreseen discontinuation of nivolumab was included in the CHECKMATE trials, the 5-year follow-up data indicate that treatment was discontinued mostly for PD but in 11% of the patients, treatment was discontinued upon the patients' request and in 8% due to maximum clinical benefit (CR in 16 patients) [15].

We identified sixteen studies evaluating the outcome of patients that discontinue anti-PD-1 therapy in the absence of PD. A detailed overview is provided in Table 1. Eight trials focused on elective treatment discontinuation of which one prospective trial where patient discontinued treatment per protocol after 6 months independent of best objective response (BOR) [22–29]. Five trials evaluated the outcome of treatment discontinuation after TLT [23, 24, 26, 27, 30]. Three retrospective trials, by Asher et al., Warner et al. and Schank et al., discuss both discontinuation for TLT and elective discontinuation and do not provide exact relapse numbers per cohort [18, 31, 32]. The trials by Asher et al., Schank et al., and Gibney et al. included the patients treated with the combination of anti-CTLA-4 antibodies and anti-PD-1 antibodies [26, 31, 32].

Comparing data across all the different trials is difficult due to the heterogeneity of the included patient cohorts, lack of predefined and conformity on BOR classification, difference in time evaluation (time from BOR versus time from treatment discontinuation), unclear definition of reason for discontinuation and more. Below, we provide an overview of all available data.

Treatment-Limiting Toxicity

Most immune-mediated adverse events on anti-PD-1 antibodies occur within 16 weeks of treatment, but a small proportion of patients can still develop grade 3–4 immune-related adverse events thereafter. A recent landmark analysis of the KEYNOTE 001, 002, and 006 trials on the long-term safety of pembrolizumab demonstrated similar ORR-median time to response, -median duration of response, -median PFS and OS between the overall population and the population discontinuing due to TLT. This indicates that the survival of patients discontinuing due to TLT is aligned with the general anti-PD-1-treated population [14].

Five trials evaluated the outcome of treatment discontinuation after TLT [23, 24, 26, 27, 30]. The largest cohort by Van Zeijl et al. evaluated 89 patients (PR 47%), whereas the cohorts described by Swami et al., Valentin et al., Schvartsman et al., and Gibney et al. are small with 16, 28, 34, and 28 patients, respectively. Treatment duration was short (range median duration of treatment 3.5–7.2 months) and recurrence of disease after treatment discontinuation was low around 20%. Follow-up across these five trials ranges from 16 to 30 months.

A comparison between discontinuation for TLT and elective treatment discontinuation is scarce. Most articles focus on elective discontinuation, discontinuation due to TLT, or combine the two cohorts. The largest study

Table 1 Overview of trials evaluating outcome after treatment discontinuation of anti-PD-1 in patients with metastatic melanoma

Reference	Trial design	Studied therapy	Reason for discontinuation	BOR	Number of patients	Median FU (months) after discontinuation	Median treatment duration (months)	Number of relapses	TT PD after discontinuation (months)
Keynote (001)[$]	Prospective clinical trial exploratory analysis	Single agent anti-PD-1	Elective discontinuation	CR 67 PR 5	72	22	24	6 1	18
Keynote (006)	Prospective clinical trial exploratory analysis	Single agent anti-PD-1	Elective discontinuation*	CR 21 PR 69 SD 13	103	N.A	N.A	5 16 6	33
Jansen (2019)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD NE	185 117 44 16 8	18 20 16 16 17	12 11 15 14 17	40 16 14 8 2	N.A
Van Zeijl (2021)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD	180 67 98 15	18	12 12 13 11	87	N.A
Valentin (2021)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR/SD	37 25 12	15.7	14.1 16.8 21.2	5 3 2	9.3 11.9
Schvartsman (2018)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL (CR 56%)	41	16	19.5	3	
Pokorny (2020)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD	52 13 28 11	20.5	11.1	13	3.9
Gibney (2021)	Retrospective analysis	Single-agent anti-PD-1 ($n=10$) Anti-PD-1 + anti-CTLA-4 ($n=14$)	Elective discontinuation	CR***	24	N.A	12.1	2	N.A
Ladwa (2016)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	CR	29	8	12.5/24/9[$$]	3	N.A
Makela (2020)	Prospective trial	Single agent anti-PD-1	Per protocol 6 months**	ALL CR PR SD PD	17 4 7 4 2	N.A	6	14	N.A
Warner (2019)*	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation ($n=72$) TLT ($n=24$)	CR	102	21.1	9.4	23	
Asher (2021)	Retrospective analysis	Single-agent anti–PD-1 ($n=86$) Anti-PD-1 + anti-CTLA-4 ($n=20$)	Elective discontinuation (CR: $n=32$, PR: $n=14$) TLT ($n=60$)	ALL CR PR SD	106 80 22 4	20.8	15.2	34	8.5

Table 1 (continued)

Reference	Trial design	Studied therapy	Reason for discontinuation	BOR	Number of patients	Median FU (months) after discontinuation	Median treatment duration (months)	Number of relapses	TT PD after discontinuation (months)
Schank (2021)	Retrospective analysis	Single agent anti-PD-1 ($n=31$) Single agent ipilimumab ($n=4$) Anti-PD-1 + anti-CTLA-4 ($n=10$)	Elective discontinuation ($n=27$) TLT ($n=16$)	All CMR Non-CMR	45 32 13	34	21	9 3 6	N.A
Swami (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL	16	30.3	4.7	9	15,3
Van Zeijl (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL CR PR SD	89 7 61 21	N.A	6.9 7.2 3.5	N.A	N.A
Valentin (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL CR PR/SD	28 25 24	N.A	7.2	7 0 7	7.1
Schvartsman (2018)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL (CR 56%)	34	N.A	6.5	5	N.A
Gibney (2021)	Retrospective analysis	Single-agent anti–PD-1 ($n=7$) Anti-PD-1 + anti-CTLA-4 ($n=21$)	TLT	All CR PR SD	28 5 22 1	N.A	3.7	2	N.A

N.A. data not available in the published manuscript, *m* months, *pts* patients, *NR* not reached, *CR* complete response, *PR* partial response, *SD* stable disease, *TLT*,…

[$] Keynote 001: patients who received pembrolizumab for ≥ 6 months and at least two treatments beyond confirmed CR could discontinue therapy

[$$] Twenty-nine patients (20 named patient program, 3 nivolumab monotherapy, and 6 reimbursed pembrolizumab) ceased anti-PD-1 therapy after CR for observation. Median time on treatment was, respectively, 12.5 months, 24 months, and 9 months

[*] Warner et al. (2021) described the long-term outcome of single agent anti-PD-1, for the purpose of this table and this review; only data on CR are shown. All 102 patients classified as CR by the author are included in the table. Median time to progression and OS is calculated from CR to event. Median time after treatment discontinuation in CR patients was 0 months. **Per protocol discontinuation is considered: all the patients discontinuing treatment after a pre-defined period; this includes both patients in prospective trials as the patients stopped following hospital instated guidelines. *** CR is defined as no sign of active disease. BOR on CT was CR in 8/24 patients, PR 15/24 patients, and SD in 1/24 patients. PET CT confirmed no active disease in 14 patients with CMR and 6 non-CMR had biopsy proven non-active disease

comparing the discontinuation after TLT or after elective discontinuation is by Van Zeijl et al. and included 89 patients and 180 patients, respectively. The authors concluded that BOR was a major determinant for the different outcome of the two cohorts. The patients obtaining a CR or SD do equally well after discontinuation for both reasons, whereas the cohort obtaining a PR do better after elective discontinuation. Overall treatment duration was shorter in patients discontinuing due to TLT (compared to elective discontinuation) [23]. This is confirmed by the data of Warner et al. and Asher et al. [18, 31]. Van Zeijl et al. suggest that the shorter treatment duration in patients with TLT could be linked to the worse prognosis [23]. In the trial by Giberny, 24 patients electively discontinued treatment in the absence of PD, and 28 patients discontinued due to TLT. No difference in PFS after treatment discontinuation was identified; however, more events occurred in the TLT cohort (2/24 versus 6/28, $p=0.160$) [26].

Elective Treatment Discontinuation

The term elective treatment discontinuation refers to the discontinuation of treatment by a shared decision between the patient and the treating medical team, in the absence of PD or TLT. Data for the exact reason of discontinuation is lacking in most studies.

Overall, follow- up across the seven retrospective studies is comparable (range 8–22 months). The median time on treatment is also comparable (range 11.1–14.1 months) [22–28]. Real-world data confirm that a response is usually seen after a median of 3 months [23, 27].

In the KEYNOTE 001 and 006 trials, outcome after treatment discontinuation, appeared to be driven by depth of response [18, 31, 32]. Real world data confirms this correlation [18, 22–29, 31, 32]. The patients who obtained an objective response perform better than the patients with a BOR of SD (recurrences in patients with SD in 50% Jansen et al. [22] and 43% Van Zeijl et al. [33]). The patients with a CR tend to do better with a low risk of PD (< 15%) [18, 22]. The two largest cohorts, Jansen et al. and Van Zeijl et al., evaluated 185 patients and 180 patients, respectively [22, 33]. These patient populations differ mostly in BOR (Jansen et al. CR in 117 [63%] patients versus Van Zeijl PR 98 [54%] patients). Valentin et al., Schvartsman et al., Pokorny et al., and Gibney et al. are smaller retrospective, real-world studies evaluating respectively 38, 41, 52, and 25 patients discontinuing treatment in the absence of PD or TLT [24, 25, 27]. However, data on relapses per BOR are limited in these trials, probably due to the low number of patients per cohort. The trial of Van Zeijl does not describe the absolute number of relapses between the patients in the TLT and elective discontinuation group. However, with an 18 months PFS and OS probability of 62% and 91% for PR patients and 18 months PFS and OS probability 77% of 94%, respectively for CR, they concluded that the patients with a PR who electively discontinue treatment have a comparable outcome as the patients who obtained a CR [23]. This is in contrast with the data by Jansen et al., where BOR was a major factor in determining outcome after treatment discontinuation [22]. Given the difference in distribution of PR/CR in these cohorts, this could be due to a difference in the method of determination of BOR. One of the major problems with retrospective, real-world data is the lack of consistency in the determination of BOR (by using different radiologic response criteria) and the lack of a central review committee. Especially in the patients with a near complete CR, classification is difficult due to the presence of non-viable sequalae of previous metastases, or 18-FDG PET (8-fluorodeoxyglucose positron emission tomography) negative residual disease on CT [26, 34–39]. The data by Warner et al. confirms this difficulty. Of the 76 patients who were considered to have a CR by the treating physician, 18 patients were downgraded to a PR according to the formal response evaluation criteria in solid tumors (RECIST) evaluation by a reference radiologist. However, no difference was found in the time to treatment failure, PFS or OS based on CR determination [18]. Data by Gibney et al. support the use of 18-FDG PET CT in the evaluation between CR and PR. All the patients with a CR on CT had a complete metabolic response (CMR) on 18-FDG PET CT; however, eight patients with a PR on CT and one patient with a SD demonstrated a CMR. Six additional patients with a PR on CT demonstrated a non-CMR on 18-FDG PET CT but had biopsy proven negative disease. The PFS in the cohort with a CMR appears comparable to that of the patients with a CR in the previous trials with a 2- and 3-year OS probability of 95% [26].

Real world data confirms that a rapid tumor response (time to PR/CR) is associated with a better outcome [18, 33]. However, the correlation between time on treatment and outcome is inconsistent across trials. The trial by Jansen et al. demonstrated a significant worse prognosis in patients with a CR and treatment for less than 6 months (median PFS 18.9 months versus not reached, p 0.05) [22]. This is supported by the data of Makela et al. In their prospective trial, thepatients discontinued treatment per protocol after 6 months independent of BOR. Of the 40 included patients, 17 patients discontinued treatment in the absence of PD or TLT, and recurrences were seen in 14 of the 17 patients [22]. Warner et al. also advocate a longer treatment continuation and indicate a better PFS after treatment discontinuation at 24 months [18]. Across trials, there is a tendency to discontinue treatment more rapidly following CR compared to PR and SD [18, 23].

Prognostic baseline factors such as lactate dehydrogenase (LDH), tumor burden, PD-1 immunohistochemistry, and previous therapies do not seem to correlate with the risk of progression after treatment discontinuation in patients with metastatic melanoma [18, 22–27, 29, 31, 32].

Follow-up and Treatment Rechallenge

After treatment discontinuation, a deepening of patient's tumor response can occur. The patients with a PR at the time of elective discontinuation can evolve to a CR (8–25% of all the patients in PR) after treatment discontinuation. The patients with a SD at discontinuation can obtain PR or CR after discontinuation; however, this occurs less frequently [5, 23, 31, 32]. Disease recurrences are usually seen early following treatment discontinuation of anti-PD1 [2, 3, 5–8, 18, 20, 22–27, 29, 31, 32]. Warner et al. state that up to 87%

of relapses occur within the first 2 years following treatment discontinuation [18].

In the current era, there are many different cohorts of patients, and anti-PD-1 antibodies are re-introduced in different clinical settings. We will use the terms as proposed by Gebhardt et al. [40]. The results on retreatment (Table 2) are scarce and limited to the case series. In the KEYNOTE 001 trial [5, 7, 16], a total of 67 patients with CR and 5 patients with PR discontinued treatment in the absence of PD and TLT. In total, six patients experienced a relapse after a median follow-up of 18 months of whom four were retreated with anti-PD-1 antibodies leading to 2 new objective responses (1 CR and 1 PR). In the KEYNOTE 006, there are two patient populations in which anti-PD1 was discontinued: the largest cohort, 103 patients, who discontinued after 2 years of treatment and a smaller cohort of 23 patients with a CR who electively discontinued treatment after at least 6 months plus 2 additional doses. Survival between the two cohorts were comparable and relapses were seen in 13 patients. Anti-PD-1 antibodies were reintroduced leading to 3 CR, 4 PR, and 3 SD [4, 8, 19]. The trial by Warner et al. is the largest cohort (78 patients of 396 patients) in whom immunotherapy was re-introduced [18]. Their studied patient population is very heterogeneous (all the reasons for discontinuation including PD), and rechallenge was both with anti-PD-1 monotherapy (5/34 ORR with CR in 2 patients) and escalation to anti-PD-1 monotherapy and anti-CTLA-4 (11/44 ORR and CR in 3 patients). All the other data concern a lower number of patients [18, 22–25, 27, 29, 31]. New objective responses are seen in up to 40% of patients with up to 25% of patients obtaining a CR.

No correlation was found between BOR on the initial course of the disease and the response to retreatment. No correlation was found between time on treatment and time off treatment and response to rechallenge [18, 22–25, 27, 29, 31]. These data on retreatment must be interpreted with caution. Data were retrospectively collected, responses were not confirmed by central review or surgical resection, whereas radiotherapy was often performed for local control [22, 25], thereby limiting interpretation of response to the re-introduction with anti-PD-1 antibodies.

Predictors of Safe Stop

One of the major questions is the identification of patients who can safely discontinue treatment. BOR seems to be the major predictor of relapse after discontinuation. The patients with a CR do equally well across trials. Data on patients with PR are more heterogeneous. Residual lesions on CT might present scarring, which is more prevalent in lung nodules and lymph nodes [37]. 18-FDG PET CT might help to identify patients with a PR or SD who have a low risk of recurrence [35]. A landmark analysis at 1 year by Tan et al. in the patients treated with anti-PD-1 antibodies, demonstrated that more patients obtained a CMR than a CR at 1 year [37]. A significant difference was found in PFS in the patients with CMR on 18-FDG PET compared with non-CMR (median NR versus 12.8 months; HR 0.06 [95% CI 0.02–0.23]; $p < 0.01$). The underlying BOR on CT (PR/SD versus CR) did not impact prognosis.

The trial by Shank et al., that was described earlier, retrospectively evaluated the use of 18-FDG PET CT in the prediction of durable response after treatment discontinuation [32]. They confirmed a significant difference in PFS in patients with CMR versus non-CMR on 18-FDG PET CT (not reached, versus 34.7 months (95% CI: 9.6–59.8). In a multivariate analysis, the metabolic response was the only predictive factor for PFS. In a total of five patients (4 PR and 1 SD), response was upscaled to a CMR after 18-FDG PET CT. The authors also evaluated the use of circulating tumor DNA (ctDNA) in this setting, but only two patients with a CMR were evaluated. The use of ctDNA to predict long-term response is interesting. A correlation between tumor burden and liquid biopsies has been demonstrated in patients with melanoma [41–45]. Liquid biopsies are an interesting biomarker as repetitive evaluations are possible. However, liquid biopsies are not feasible in all the patients (restricted to BRAF and NRAS patients), cannot be performed at all centers, and have limitations for the detection of progression in CNS [41–45].

The trial by Gibney also evaluated the use of 18-FDG PET CT in the prediction of long-term survival after treatment discontinuation. Eight patients with a non-CMR underwent a tumor biopsy of which six patients demonstrated non-viable tumor cells, and 2 patients demonstrated a new secondary primary. In a total of 24 patients who discontinued treatment in the absence of active disease, relapses were seen in two (8%) patients, 3-year PFS was 95%. This is in line with the data on treatment discontinuation after CR [26].

To evaluate the use of 18-FDG PET CT as a predictive biomarker, the PET STOP trial (EA6192) was designed (completion date 2026). The trial is designed as a non-randomized, sequential assignment trial. At 1 year of treatment, a 18-FDG PET CT will divide the patients into two arms: arm A: discontinuation in CMR or non-CMR, but biopsy confirmed non-viable tumor, arm B: non-CMR (±tumor cell in biopsy) continue treatment up to 24 months [46].

Future: Prospective Data

The Dutch Safe stop trial (Trial NL7293) will evaluate the rate of ongoing response in the patients with advanced melanoma who discontinue first-line monotherapy with

Table 2 Response after treatment rechallenge in patients with metastatic melanoma

Reference	Trial design	Reason for discontinuation	Time on treatment months	BOR at first course (*n*)	Number second course	Time to relapse (months)	Type of immunotherapy on second course	BOR on reintroduction
Keynote (001)	Prospective clinical trial	Elective discontinuation	23	ALL 72 CR 67 PR 5	4	18	Single-agent anti-PD-1	CR 1, SD/PR 1*
Keynote (006)	Prospective clinical trial	Elective discontinuation	24	ALL 103 CR 21 PR 69 SD 13	13 5 + 1 6 1	N.A	Single-agent anti-PD-1	CR 3, PR 4, SD 3 CR 3, PR 1, SD 1 PR 3, SD 1 SD 1
Jansen (2019)	Retrospective analysis	Elective discontinuation	12 11 15 14 7	185 CR 117 PR 44 SD 1 Ne 8	19 9 6 4	12	Single-agent anti-PD-1	CR 2, PR 4, SD 5 CR 2, PR 3, SD 1 PR 1, SD 2 SD 2
Pokorny (2020)	Retrospective analysis	Elective discontinuation	11.1	ALL 41 CR 10 PR 18 SD 13	7	3.9	Single-agent anti-PD-1 ± resection	4
Warner (2019)	Retrospective analysis	Elective discontinuation (n = 72), TLT toxicity (*n* = 24), **other (*n* = 5)	9.4 36.1	ALL 78 CR 10, PR 18, SD 13, PD 37	78	6.3	Single agent anti-PD-1 34 Anti-PD-1 + anti-CTLA-4 44	OR in 5 -CR 2 OR 11- CR 3
Asher (2021)	Retrospective analysis	Elective discontinuation (CR: n = 32, PR: n = 14) TLT (*n* = 60)	15.2	ALL 106 CR 80, PR 22, SD 4	21	8.5	Single-agent anti-PD-1 19 Anti-PD-1 + anti-CTLA-4 1 Single agent anti-CTLA-4 1	CR 5, PR 4, SD 4 CR 3, PR 2 PR 2, CR 3
Valentin (2021)	Retrospective analysis	Elective discontinuation	14.1	ALL 65 CR 25 PR/SD 12 AE 28	12 3 2 4	ALL 9 CR 9.3 PR 11.9 AE	Single-agent anti-PD-1	CR 4, SD 1 CR 1, SD 1 CR 1 CR 2
Makela (2020)	Prospective trial	Per protocol defined at 6 months	6	ALL 17 CR 4, PR 7, SD 4, PD 2	6		Single-agent anti-PD-1	RR 50%
Van Zeijl (2021)	Retrospective analysis	TLT (*n* = 53) or elective discontinuation (*n* = 67)	11 12 7	87 CR PR SD	27	N.A	Single-agent anti-PD-1	CR 2, PR 6, SD 9
Schwartsman (2018)	Retrospective analysis	Elective discontinuation (*n* = 41) TLT (*n* = 34)	19.5 6.5	CR 56%, PR 35%, SD 9%	2 1	N.A	Single-agent anti-PD-1 1 Single agent anti-CTLA-4 2	CR 1, PR 3

N.A. data not available in published manuscript, *n* number, *m* months, *pts* patients, *NR* not reached, *CR* complete response, *PR* partial response, *SD* stable disease, *OR* objective response

*Patient had SD at date cut-off and had PR two weeks later; **other = progression (3), per protocol (1) or other (2). Warner evaluated all the patients who discontinued due to all the reasons

nivolumab or pembrolizumab upon achieving CR or PR according to RECIST. The patients are required to obtain a confirmed PR/CR before treatment discontinuation [47].

The Canadian STOP-GAP study (NCT02821013) is designed to randomize patients between standard of care (treatment to 2 years) and discontinuation after confirmed maximum tumor response. The results are expected in 2029 [48].

The Dante trial is a multicenter, randomized, phase III, non-inferiority trial. Patients will be randomized at 12 months to continue anti-PD-1 for 2 years or discontinue independent of response at randomization [49].

Discussion

The efficacy of anti-PD-1 ICB has led to a growing number of patients with a durable response and the question of the optimal treatment duration is gaining interest [50–52]. While the oncological outcome is of main importance, avoiding exposure to unnecessary PD-1 ICB treatment lowers the risk for treatment-related adverse events as well as the economic burden of immunotherapy.

Based on available evidence, ESMO guidelines [53] propose discontinuing treatment in patients with a CR after 6 months of therapy and patients with a PR or SD after 2 years of therapy. The data by Warner et al., Makela et al. et al., and Jansen et al. indicate a correlation between treatment duration and risk of relapse with treatment duration of < 6 months leading to a higher risk of relapse. Cohorts that discontinue due to TLT overall have a shorter treatment duration, but their overall risk of relapse seems comparable to patients who electively discontinue treatment. However, in trials focusing on the difference of outcome between these two cohorts, it seems apparent that the patients with a PR tend to do worse after treatment discontinuation after TLT versus electively [23, 26]. Whether this is due to primary resistance or a worse outcome due to earlier discontinuation is unknown.

Depth of response is a clear prognostic factor for the risk of relapse after treatment discontinuation. The patients with a CR do well across all trials independent of reason of treatment discontinuation with a risk of relapse of < 15%; the patients with an SD have a significant worse outcome after treatment discontinuation with up to 50% relapsing after treatment discontinuation [13, 22, 23]. The patients with a PR represent a very heterogeneous cohort with relapses around 20–25% [22, 23]. One of the major reasons for this difference could be response evaluation. Warner et al. indicated that up to 24% with a CR by their treating physician will be downgraded to a PR by an experienced radiologist [18]. Trials on the use of 18-FDG PET CT demonstrated that up to 68% of the patients with a PR have a CMR on 18-FDG PET CT [37]. Obtaining a CMR at discontinuation or at 1 year of treatment seems to be indicative of a prolonged response [26, 32]. The PET STOP trial will help to evaluate the use of 18-FDG PET CT in treatment discontinuation [46].

Other biomarkers for the prognosis after discontinuation are currently lacking [18, 22–27, 29, 31, 32]. Baseline parameters are more linked to prognostic biomarkers of response and do not seem to influence risk of relapse after discontinuation. Gibney et al. indicated that tumor biopsies led to a change in treatment in 3/10 patients due to active metastatic melanoma or second malignancy [26]. In addition, the use of ctDNA or circulating tumor cells is also an attractive path [41–45].

The combination of ipilimumab and nivolumab has a significant impact on OS and PFS in patient with metastatic melanoma. However, up to 50% of the patients will develop a grade 3/4 toxicity leading to treatment discontinuation in one-third of the treated patients. Only 50% of the patients will receive the four doses of ipilimumab and nivolumab in the induction phase. Schadendorf et al. conducted a retrospective pooled analysis of the CHECKMATE 067 and 069, they could not demonstrate a significant difference in OS, PFS, and ORR between the patients that continued treatment and the patients that discontinue treatment [54]. This was recently confirmed by real-world data [55, 56]. Currently there is not any data on the treatment discontinuation in the absence of PD or TLT for the combination. The trials by Asher et al., Schank et al., and Gibney et al. included the patients treated with the combination of anti-CTLA-4 antibodies and anti-PD-1 antibodies [26, 31, 32]. Neither of them indicates or hints at a difference in outcome following combination therapy or single agent anti-PD-1 antibodies. Given the comparable outcome after treatment discontinuation following TLT, we can assume that the treatment discontinuation in the absence of PD or TLT, will have the same pattern of response and relapse as in single-agent therapy. However, more data are clearly needed.

The CHECKMATE 153 was the first trial evaluating the patients who discontinue nivolumab at 1 year versus treatment continuation in patients with non-small-cell lung cancer. The result show that the patients with continuous treatment of nivolumab had a significantly better prognosis than those with a fixed-duration treatment. Both durable responses and late relapses are seen in both the fixed duration cohort and the discontinuation cohorts. A high number of early relapses are also seen in the fixed-duration cohort, which might be influenced by another reason as treatment discontinuation as such [57]. Whether this data is extractable to melanoma patients is unknown. Another important remark is that the patients with a CR/PR were evaluated together. Data from melanoma demonstrates an important survival benefit in CR patients. This difference was also noted in the

retrospective trial by Gauci et al. on the discontinuation of anti-Pd-1 in different tumor types [12].

Most relapses occur the first 2 years of discontinuation (up to 90% [18]). Current follow-up after treatment discontinuation is limited to 1.5–3 years after treatment discontinuation in the absence of PD. With a follow-up after treatment discontinuation of 43 months, the results from the KEYNOTE 006 demonstrate the longest follow-up after elective treatment discontinuation and confirm the safety of treatment discontinuation [5, 19]. However more long-term data are needed to confirm the safety of treatment discontinuation.

Data on rechallenge are scarce; data on 105 patients were available, and up to 40% of the patients will obtain a renewed objective response with up to 25% achieving a CR and 20% a PR [18, 22–25, 27, 29, 31]. Across trials, time on treatment and time to relapse after treatment discontinuation do not appear to be linked. These data indicate that anti-PD-1 should be resumed in patients who experience a progression after discontinuation.

The major issue with the current available data is the inconsistencies across trials. Response evaluation, the determination of BOR, reasons for (early) discontinuation, follow-up, lacking data and more, are major issues. There is a clear need for prospective trials, ideally randomized controlled trials evaluating the difference in PFS and, more importantly, OS between treatment continuation and discontinuation. However, the results from the first trials are expected in over 5 years, and it is to be expected that the data on OS might even take longer given the low number of OS events. Whether indeterminate treatment continuation is still feasible and desired is the question. With only a minority of patients with an objective response experiencing a recurrence across trials, the question is whether it is ethical to continue treatment and risk irAEs. Even when treatment is continued, a small subset of patients will still develop PD after the first 12 months of immunotherapy, indicating secondary resistance. Another big issue is the high number of patients needed to obtain a sufficient high number of patients per cohort. Whether treatment discontinuation needs to be response-driven or per fixed duration is still unclear.

Conclusion

Treatment discontinuation of anti-PD-1 seems to be safe in patients with metastatic melanoma who obtain on objective response. More data are needed to determine the optimal timing of discontinuation and better select patients who will have a prolonged tumor response after treatment discontinuation. 18-FDG PET CT, liquid biopsy, or repetitive tumor biopsies might aid in the identification of active disease and guide decisions on treatment discontinuation.

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Data Availability The data presented in this study are available on reasonable request from the corresponding author.

Declarations

Conflict of Interest Y. Jansen: travel, accommodations, and expenses—MSD Oncology, Novartis, BMS.
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CHECKMATE 153 trials; the first randomized controlled trial on immune checkpoint discontinuation. Even though the trials concern NSCL; it is currently the only trial available that evaluates the outcome between discontinuation and continuation