When to stop immunotherapy for advanced melanoma: the emulated target trials

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Summary

Background Immune checkpoint inhibitors (ICIs) have demonstrated their efficacy with a 7.5-year overall survival (OS) close to 50% for advanced stages. The design of clinical trials provides for treatment until progression or toxicity, or for a maximum duration of two years. Prolonged follow-up of responders after treatment cessation shows sustained response and a low risk of relapse in the months following cessation. To date, the optimal duration of anti-PD-1 therapy for metastatic melanoma remains unestablished. The objective of this work was to evaluate the optimal duration of ICI administration.

Methods We emulated target trials using the cloning, weighting and censoring approach. Each emulation trial aimed to compare the effect of discontinuing versus continuing ICIs at a specific timepoint, among patients still under treatment and with disease control at that time. Patients were from MelBase between 2015 and 2021.

Findings 435 participants in the MelBase cohort were eligible and were included in the 6-month discontinuation emulated trial. The results showed significantly lower OS when treatment was discontinued, than when treatment was prolonged for at least three months. The 48-month survival difference was 37.8% (95% confidence interval [CI] 19.8–60.5), and the corresponding restricted mean survival time difference was 8.3 months (95% CI: 4.1–12.7). Neither the 12-month nor the 18-month discontinuation emulated trials showed evidence of benefit of either discontinuing or continuing ICIs at either of these timepoints. The 24-month discontinuation emulated

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trial results were more in favor of discontinuing than continuing treatment at that time point, with an absolute 48-month survival rate that was 10.5% higher (95% CI 4.4–18.1).

Interpretation These results suggest that a one-year course of immunotherapy is both necessary and sufficient for patients with advanced melanoma. Prolonged treatment beyond 2 years does not appear to be beneficial in terms of survival and could even be detrimental.

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Keywords: Advanced melanoma; Duration of treatment; Immunotherapy; Emulated trial

Research in context

Evidence before this study

Immune checkpoint inhibitors have demonstrated their efficacy in advanced melanoma. In trials, treatment was continued until progression, toxicity or a maximum of 2 years. Continuing treatment indefinitely predisposes patients to immune toxicities, interferes with their quality of life and represents a major economic cost. Some studies have suggested that immune checkpoint inhibitors could be discontinued, especially for responders, but did not formally compare different treatment durations in comparable patients. We searched PubMed for all randomized controlled clinical trials evaluating the efficacy of immunotherapy in advanced melanoma and tackling the issue of the duration of treatment. Since no randomized controlled trials was found, we extended our search to observational data. The PubMed search was not limited by date. Search terms were "PD-1", "CTLA-4", "duration", "advanced melanoma", "pembrolizumab", "nivolumab" and "ipilimumab". We identified four retrospective studies, two of which looked at discontinuation in the absence of progression or toxicity, and one single-center prospective study on 38 patients which limited treatment to 6 months. We then searched ClinicalTrials.gov for registered studies, and found three ongoing randomized controlled trials, that evaluate the impact of stopping treatment among patients who achieve response; results are not expected to be available until the upcoming years. As of now, the optimal duration has yet been to be determined.

Added value of this study

Our study shows that stopping at 6 months is not ideal. Beyond 2 years, continuation was less beneficial. Although these findings need to be confirmed by randomized controlled trials, they provide useful indications for everyday clinical practice.

Implications of all the available evidence

Our results are in-line with existing evidence and support treatment for at least one year. Further studies are needed to investigate whether different treatment durations may be used depending on response achieved and the duration of this response.

Introduction

Melanoma is a malignant tumor derived from melanocytes, accounting for only 10% of skin cancers but 90% of skin cancer-related deaths. Historically, 10–12% of patients with advanced stages respond to chemotherapy with a median survival of 6–9 months.[1] Significant progress in treatment has been achieved in the last decade thanks to a better understanding of molecular changes occurring during melanoma progression and interactions with the immune system. Immune checkpoint inhibitors (ICIs) and targeted therapies inhibiting the MAPK (*Mitogen-Activated Protein Kinase*) pathway have demonstrated their effectiveness and are now part of the therapeutic arsenal in the earliest stages. In fact, adjuvant therapies have shown efficacy, with a reduced risk of recurrence. The estimated 3-year incidence of relapse-free survival (RFS) has been reported to be 58% in the group receiving a combination of BRAF/MEK inhibitors (dabrafenib/trametinib) and 39% in the placebo group (hazard ratio (HR) for relapse or death, 0.47; 95% confidence interval (CI), 0.39–0.58; $P < 0.001$).[2] Immunotherapy with anti-programmed death-1 antibodies (anti-PD1) has also proved effective[3,4] and the use of these therapies has even been extended to stages IIB and IIC[5] which are not accessible to treatment with anti-BRAF/MEK in the absence of available trials for these stages. In this study by Luke JJ et al., with a median follow-up of 20,9 months, 15% patients with completely resected stage IIB or IIC melanoma in the pembrolizumab group and 24% in the placebo group had a first recurrence or died (HR 0.61 95% CI [0.45–0.82]. Concerning advanced stages, regular data updates

confirm unprecedented responses to these therapies, with a 7.5-year overall survival close to 50% under anti-PD1 ± anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4).[6] The design of clinical trials provides for immunotherapy treatment until progression or toxicity, or for a maximum duration of two years.[7–9] Prolonged follow-up of responders after cessation shows sustained response and a low risk of relapse in the months following cessation, especially in cases of complete response (CR).[10–12] Prolonged use of ICIs exposes patients to an increased risk of toxicities, impacting their quality of life and generating a societal cost. In this respect, the latest recommendations published by ESMO in 2020[13] suggest that discontinuation of ICI treatment can be considered for patients with CR who have received at least 6 months of treatment, and for patients with partial response (PR) or stable disease (SD) who have received at least 2 years of treatment. However, there are no currently available prospective studies to determine the optimal duration of ICI treatment in advanced melanomas.

Regarding causal inferences, randomized clinical trials (RCTs) are the gold standard, but their implementation is not always feasible for reasons of ethical concerns, cost, and lengthy duration. Recently, a new statistical approach using emulated trials has emerged to optimize the use of observational data to address questions of causality in the absence of RCTs.

The objective of our work was to evaluate the optimal duration of ICI treatment, using observational survival data derived from patients with advanced melanoma.

Methods

Study design

To estimate the effect of ICI treatment duration, we conducted an open-label series of four emulated trials using the cloning, weighting and censoring approach.[14–16] Each emulated trial aimed to compare the causal effect of discontinuing versus continuing ICIs at a specific timepoint, among patients still under treatment and with disease control (non-progressive disease) at that time. Patients who discontinued treatment as a result of toxicity or progression were excluded at each assessment time point.

Data sources

Patients were selected from the national database MelBase. In brief, this is a French multicenter national cohort dedicated to the prospective monitoring of adult patients with unresectable stage III or IV melanoma running from February 2013 to March 2021.

The inclusion criteria for our study targeted individuals aged ≥18 years, with a histologically confirmed diagnosis of advanced melanoma (unresectable stage III or stage IV) and treated with anti-PD1 ± anti-CTLA4 for at least 6 months in first-line setting. Patients were required to have controlled disease at the time of the decision to discontinue treatment (CR, PR or SD). Patients treated for less than 6 months or those who discontinued treatment as a result of toxicity or progression were excluded.

Ethics

MelBase protocol was approved by the French ethics committee (CPP Ile-de-France XI, n°12027, 2012), the local ethics committee, as well as the ethics committees of all the participating institutions. MelBase was registered in the National Institutes of Health clinical trials database (NCT02828202). Written informed consent was obtained from all patients.

Statistics

The approach for emulation of a target trial using observational data consisted in the following steps: (1) specification of the target trial and eligibility criteria; (2) defining a grace period to determine whether or not a participant would be compliant with the protocol; (3) cloning participants so that each study participant is allocated to each treatment duration group; (4) censoring the clones when their actual treatment deviates from their group; (5) deriving inverse probability weights to account for the selection bias arising from artificial censoring; (6) analyzing the data using these weights.

We considered a first hypothetical trial where participants with disease control under ICIs at 6 months would be randomized to either discontinue or continue treatment. In the primary analysis, we allowed for a grace period of three months, thus targeting a trial where participants would be randomized either to discontinue treatment within three months or to continue treatment for at least three months. The grace period duration was determined according to the usual monitoring interval in Melbase, where monitoring occurs every three months. The primary outcome would be survival up to 42 months following randomization (i.e. 48 months from immune checkpoint initiation), and the between-group comparison would be expressed in terms of difference in survival at 42 months from randomization, and difference in restricted mean survival time at 42 months from randomization. A synopsis of the target trial and emulated trial is given in Supplementary Table S1. Three other similar trials were then emulated, considering decision points beyond 6 months, namely 12, 18, and 24 months. The approach was exactly the same as for the first emulated trial, except for the time-horizon for the primary outcome (survival), which was modified so that it always corresponded to 48 months from immune checkpoint inhibitor initiation. Accordingly, the time horizon was set at 36, 30 and 24 months respectively.

To adjust for indication bias in the actual decisions to discontinue or continue treatment at the target trial decision point (6, 12, 18 or 24 months), a Cox model for the time to deviation from the assigned strategy was

fitted separately in each group (discontinuing treatment at the decision timepoint or continuing), with time-dependent covariates. Weights corresponded to the inverse group-specific probability of remaining (artificially) uncensored in the course of follow-up, according to individual covariates. To ensure stability, weights were truncated at their 99th percentile. The analytic strategy closely followed that outlined in Maringe et al., except for the use of time-dependent covariates in our analysis.[15] A predefined set of covariates (confounders of the treatment continuation-outcome relationship) was determined on the basis of clinical knowledge. These were calendar year, sex, age, American Joint Committee on Cancer (AJCC) stage, brain metastases, liver metastases, lactate dehydrogenase (LDH) levels >2 ULN, and response, the last being considered as a time-dependent variable to account for longitudinal evaluations of response. Because of the possibly limited number of deviations from the assigned strategy in some of the emulation trials, a minimum set of covariates among those predefined was determined for each emulated trial and group, in order to balance the treatment groups as far as possible immediately after the grace period, while preserving model fit. The final analysis consisted in estimating survival in each group in the weighted sample[17] and computing the survival difference and restricted mean survival difference at the prespecified time horizon.[18] In view of the complexity of trial emulation, all standard errors of estimates were obtained using bootstrapping, where all steps of trial emulation were repeated in 500 bootstrap samples.

Several sensitivity analyses were carried out, first varying the grace period from 2 months to 4 months, and then setting the decision timepoint one month back, i.e. at 5, 11, 17 and 23 months, instead of 6, 12, 18 and 24 months, still with three values for the grace period duration, i.e. 2, 3 or 4 months. In another sensitivity analysis, we analyzed OS up to 36 months from the decision timepoint.

All analyses were carried out using R statistical software version 4.0.5 (R Foundation for Statistical Computing. Vienna, Austria, 2021).

Role of funding source

This work did not receive any funding. MelBase is a database financed by the French National Cancer Institute and a share from the pharmaceutical industry: Roche, BMS, Novartis, MSD and Pierre Fabre. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

The study comprised 1017 participants in the MELBASE cohort who initiated immune checkpoint inhibitor treatment from March 2015 to December 2021 (Table 1). Patient characteristics were well balanced. Of the 1017 patients included, 221 were treated with the combination of ipilimumab and nivolumab, 475 were treated with pembrolizumab and 321 with nivolumab. Supplementary Fig. S1 shows OS according to the treatment received. We did not observe any differences relating to whether patients were treated with monotherapy or combination therapies. Almost half of the patients discontinued treatment within the first 6 months (Fig. 1). Supplementary Fig. S2 shows that the two main reasons for early discontinuation of immunotherapy were toxicity and disease progression, but that elective discontinuation also occurred regularly over time.

Overall, 435 participants were eligible and included in the 6-month discontinuation emulated trial, 43 of whom discontinued ICIs within the 3-month grace period, 316 in the 12-month discontinuation emulated trial (39 discontinued), 199 in the 18-month discontinuation emulated trial (24 discontinued), and 133 in the 24-month discontinuation emulated trial (14 discontinued).

Results of the 6-month discontinuation emulated trial showed a clearly lower OS for individuals for whom treatment was discontinued, compared to those whose treatment was continued for at least three months (Fig. 2A). The 48-month survival difference was 37.8% (95% confidence interval [CI] 19.8–60.5), and the corresponding restricted mean survival time difference was 8.3 months (95% CI 4.1–12.7), meaning that those continuing treatment gained an average 8 months of additional life duration over the next 42 months (Table 2). It can be noted that although the characteristics of the two groups were quite different, weighting was fairly successful in reducing the imbalance, with standardized mean differences below 15% and often under 10% (Supplementary Table S2). The treatment discontinuation group comprised a slightly larger proportion of patients with progressive disease at the end of the grace period after weighting, but the difference (less than 5% absolute difference) is unlikely to explain the considerable benefit observed in terms of survival and restricted mean survival time in favor of the continuation group. These results were confirmed by all sensitivity analyses (Supplementary Fig. S3).

Neither the 12-month nor the 18-month discontinuation emulated trials showed evidence of benefit of either discontinuing or continuing immune checkpoint inhibitors at either of these timepoints (Fig. 2B and C respectively). Stopping treatment at either 12 or 18 months yielded a 48-month survival that was 3.7% higher (95% CI –8.3 to 14.1) or 4.2% (95% CI –5.3 to 14.9) than for continuing treatment. In both cases, the 48-month restricted mean survival difference between continuing versus discontinuing treatment was 0.7 months (95% CI –1.8 to 4.5) at 12 months and 0.4

months (95% CI –1.5 to 2.5) at 18 months. Again, the sensitivity analyses yielded similar results, although for the 18-month trial, results were rather more in favor of continuing treatment when the decision points were set one month earlier.

The 24-month discontinuation emulated trial results were more in favor of discontinuing than continuing treatment at that decision point, with an absolute 48-month survival difference that was 10.5% higher (95% CI 4.4–18.1), and a 48-month restricted mean survival increased by 1.0 month (95% CI 0.3–1.8), which was computed over the next 24 months of eligibility (Figs. 1 and 2). However, these results were not confirmed by any of the five sensitivity analyses, showing no evidence of a difference between the two strategies (Supplementary Fig. S3). Analyses at a 36-month horizon from the decision point yielded comparable results (Table 2).

The analysis of progression-free survival up to 36 months yielded results close to overall survival for decision points at 12, 18 or 24 months (Fig. 3, Table 3). At 6 months, the results were quite different and no evidence of a lower PFS when discontinuing immune checkpoint inhibitors was found.

Discussion

Immunotherapy has shown unprecedented results in terms of survival among patients with advanced melanoma. The exact duration of treatment that provides maximum antitumor effect without undertreating patients and that minimizes treatment time is not yet known. Continuing immunotherapy indefinitely exposes patients to an increased risk of toxicities, generates cost in terms of public health and has a direct impact on patients' quality of life (toxicities, time spent in hospital, etc.).[19]

The 5-year follow-up data from the KEYNOTE-001[10] trial reported that the median duration of treatment was only 5.6 months. Nearly 90% of patients who achieved CR were disease-free after a median follow-up of 3.5 years. Interestingly, the duration of treatment was much longer for patients who achieved CR, with a median treatment duration of 24 months and most of them received at least 12 months of treatment, suggesting that a longer course of treatment would obtain a better response. Similarly, patients treated in the KEYNOTE-006[11] trial received treatment for a median duration of 6 months. Only 19% of the patients received treatment for the 2-year duration provided for by the protocol. After a median follow-up of 20 months after treatment discontinuation 86% remained progression-free. Patients with CR treated for less than 2 years showed a PFS similar to patients with CR who received the full 2 years of treatment. Finally, 8% of patients with PR achieved CR after stopping immunotherapy. This data suggests sustained response after discontinuation and challenges the idea of lengthy treatment, especially for patients with CR.

Characteristic	Overall (n = 1017)	Pembrolizumab (n = 475)	Nivolumab (n = 321)	Ipilimumab + nivolumab (n = 221)
Period, no. (%)				
2015–2017	408 (40)	261 (55)	128 (40)	19 (9)
2018–2019	351 (35)	163 (34)	141 (44)	47 (21)
2020–2021	258 (25)	51 (11)	52 (16)	155 (70)
Male, no. (%)	593 (58)	245 (52)	205 (64)	143 (65)
Age, mean (SD) years	66.8 (14.4)	69.6 (13.3)	68.6 (13.6)	58.3 (14.4)
Performance Status, no. (%)				
0	718 (71)	340 (72)	209 (65)	169 (76)
1	247 (24)	113 (24)	93 (29)	41 (19)
2	34 (3)	15 (3)	15 (5)	4 (2)
3	16 (2)	7 (1)	4 (1)	5 (2)
4	2 (<1)	0 (0)	0 (0)	2 (1)
AJCC stage, no. (%)				
IIIB	40 (4)	24 (5)	14 (4)	2 (1)
IIIC	151 (15)	78 (16)	49 (15)	24 (11)
IV M1a	108 (11)	48 (10)	40 (12)	20 (9)
IV M1b	170 (17)	88 (19)	52 (16)	30 (14)
IV M1c	548 (54)	237 (50)	166 (52)	145 (66)
LDH >2 ULN, no. (%)	147 (14)	63 (13)	54 (17)	30 (14)
BRAF status, no. (%)				
MUT	214 (21)	81 (17)	63 (20)	70 (32)
WT	782 (77)	385 (81)	255 (79)	142 (64)
Unknown	21 (2)	9 (2)	3 (1)	9 (4)
No. organs involved, median (IQR)	2 (1–3)[a]	2 (1–3)[b]	2 (1–3)[c]	2 (1–4)[d]
Brain metastases, no. (%)	182 (18)[a]	69 (15)[b]	52 (17)[c]	61 (28)[d]
Liver metastases, no. (%)	186 (19)[a]	84 (18)[b]	55 (18)[c]	47 (21)[d]

AJCC: American Joint Committee on Cancer; LDH: Lactate Dehydrogenase ULN: Upper Limit Normal; MUT: BRAFV600E-mutated; WT: BRAF Wild-Type. [a]n = 986. [b]n = 459. [c]n = 308. [d]n = 219.

Table 1: **Characteristics of the participants at immune checkpoint inhibitor initiation.**

Preliminary data for patients with non-small cell lung cancer (NSCLC) who stopped nivolumab treatment after 12 months compared to those who continued until progression or toxicity reflects a trend favoring continuing treatment over discontinuation.[20] No prospective study is currently available in advanced melanoma, and results for NSCLC are difficult to extrapolate to melanoma, as these two cancers have different biological characteristics, they evolve differently, and response duration to immunotherapy is longer among melanoma patients. Nevertheless, this data alerts us to the risk of progression and poorer survival in the event of too early discontinuation of immunotherapy, and therefore to the difficulty of carrying out a randomized trial given the risk for PFS and OS.

Our study results demonstrate that stopping ICIs at 6 months is probably not a good idea. Indeed, patients who continued treatment beyond 6 months gained over 8 months of life compared to those who discontinued. There was no significant survival difference for patients treated for durations of 6–12 months, 12–18 months, or 18–24 months. Beyond 2 years of treatment, continuing

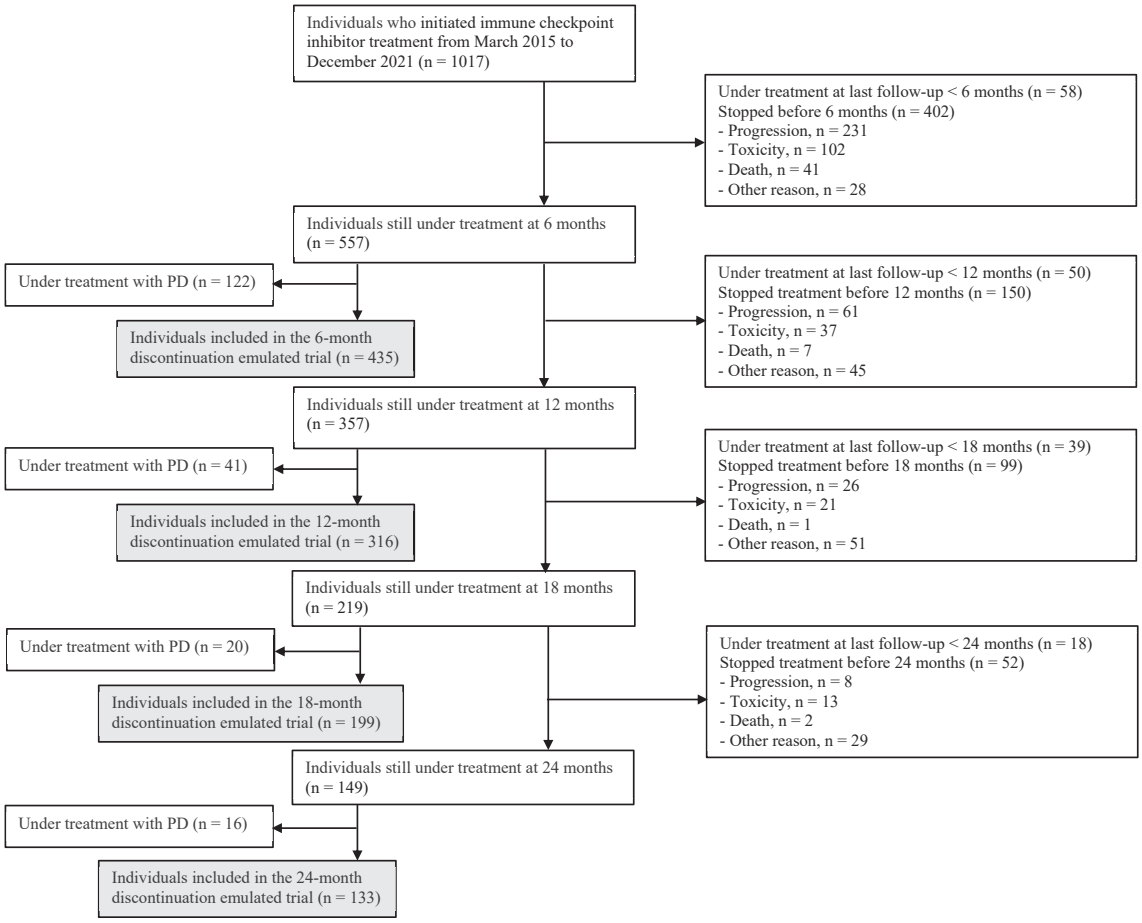

***Fig. 1:* Flow chart of participants.** PD: Progression Disease.

treatment could be less beneficial than discontinuation, but these results should be considered in the light of the study limitations, such as the small number of patients at 24 months and a very low event occurrence rate. Indeed, nearly 40% of the patients could not be included in the 6-month analysis because they discontinued treatment before 6 months as a result of progression (23.5%), toxicities (10.3%), or death (4.1%).

These findings are in line with those of the real-world retrospective observational study by Jansen et al.,[12] reporting survival data for 185 patients with advanced melanoma who electively discontinued anti-PD1 treatment. Patients with CR treated for less than 6 months had a significantly higher risk of subsequent progression. The authors did not find any significant difference for longer treatment durations. The median treatment duration was 12 months for the 185 patients, and those with CR were treated for a median of 11 months. However, this study population was quite different from ours, with 63% of patients with CR at the time of discontinuation compared to the 15–20% typically found in clinical trials or other retrospective data. Unlike our study, Jansen's analysis did not correct for selection/confounding bias and was at risk for time-dependent bias, which the emulation trial methodology was able to avoid.

Another study in the US[21] reported on the outcomes of advanced melanoma patients who electively stopped ICI treatment in the absence of toxicity or progression. The patients were treated for a median of 11.1 months. Among the 52 patients included, 25% had achieved CR at discontinuation. The 20.5-month PFS rate was 75%.

A prospective study conducted by a Finnish team[22] provided for a maximum treatment duration of 6 months. Thirty-eight patients were included, with only 45% able to complete the 6-month protocol-defined treatment, as 21 patients progressed or had to discontinue immunotherapy due to toxicity, which aligns with our study findings. The median treatment duration was 3 months. Fifteen patients achieved a response at discontinuation (CR or PR), with 11 out of 15 patients completing the protocol-defined 6 months of treatment. These results suggest the possibility of a response despite a short exposure to immunotherapy. However,

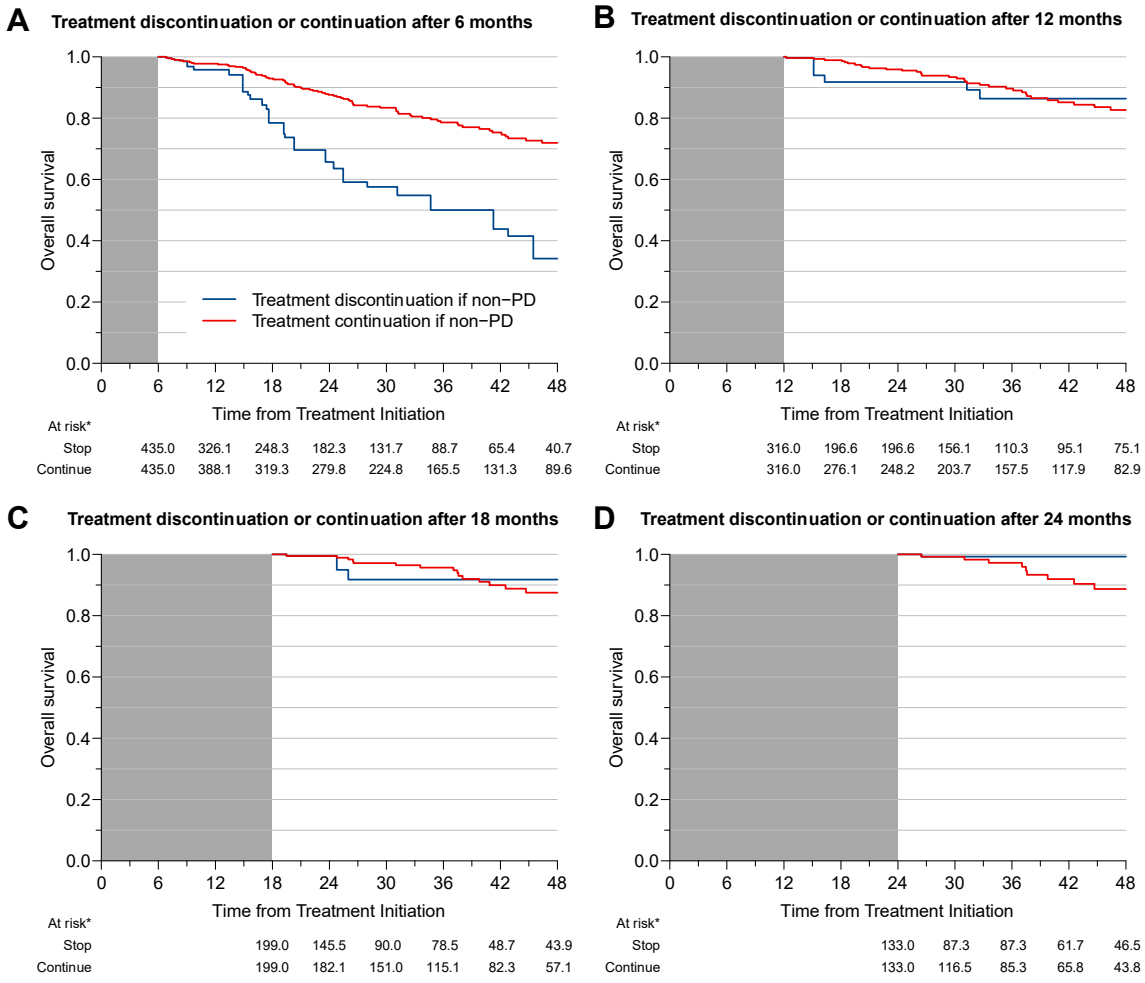

***Fig. 2:* Weighted overall survival curves in the four emulated trials.** *Sum of weights of at-risk individuals at each time.

after a median follow-up of 30.5 months, only 33% of patients remained free from progression, while 74% of the patients treated for 2 years in KEYNOTE-006 had not progressed after a median follow-up of 58 months.[11] Considering these results, it appears that exposure to ICIs for more than 6 months is necessary to sustain a response after discontinuation.

Three clinical trials are ongoing in metastatic or unresectable melanoma to evaluate the impact of stopping treatment among patients who achieve response. The Canadian STOP-GAP trial (NCT02821013)[23] is a randomized phase 3 trial on the duration of anti-PD-1 therapy in metastatic melanoma. The investigators conducting this study are interested in determining whether patients with melanoma live as long when the PD-1 inhibitors are given continuously (non-stop) or in an intermittent schedule (taking breaks). The primary endpoint of the Dutch Safe Stop Trial (Safe Stop-T, NTR7502)[24] is the proportion of ongoing response at 12 months among patients with irresectable stage III or metastatic melanoma treated with first line ipilimumab-nivolumab and with early discontinuation of nivolumab when they reached CR or PR according to RECIST v1.1. Finally, the DANTE trial[23] is a randomized, non-blinded, non-inferiority phase III trial comparing time-limited treatment of 1 year of anti-PD-1 therapy to the current standard duration of anti-PD-1 therapy (consisting of

Decision timepoint	Time horizon from treatment initiation (mo.)	Survival difference (95% CI)	RMST difference (95% CI)
6 months	48	37.8% (19.8–60.5)	+8.3 (4.1–12.7)
12 months	48	−3.7% (−14.1 to 8.3)	+0.7 (−1.8 to 4.5)
18 months	48	−4.2% (−14.9 to 5.4)	+0.4 (−1.5 to 2.5)
24 months	48	−10.5% (−18.1 to −4.4)	−1.0 (−1.8 to −0.3)

A positive survival difference or RMST differences indicate longer average survival with immune checkpoint inhibitor continuation at the decision timepoint. RMST: Restricted mean survival time.

***Table 2:* Overall survival: analysis up to 48 months from immune checkpoint inhibitor initiation.**

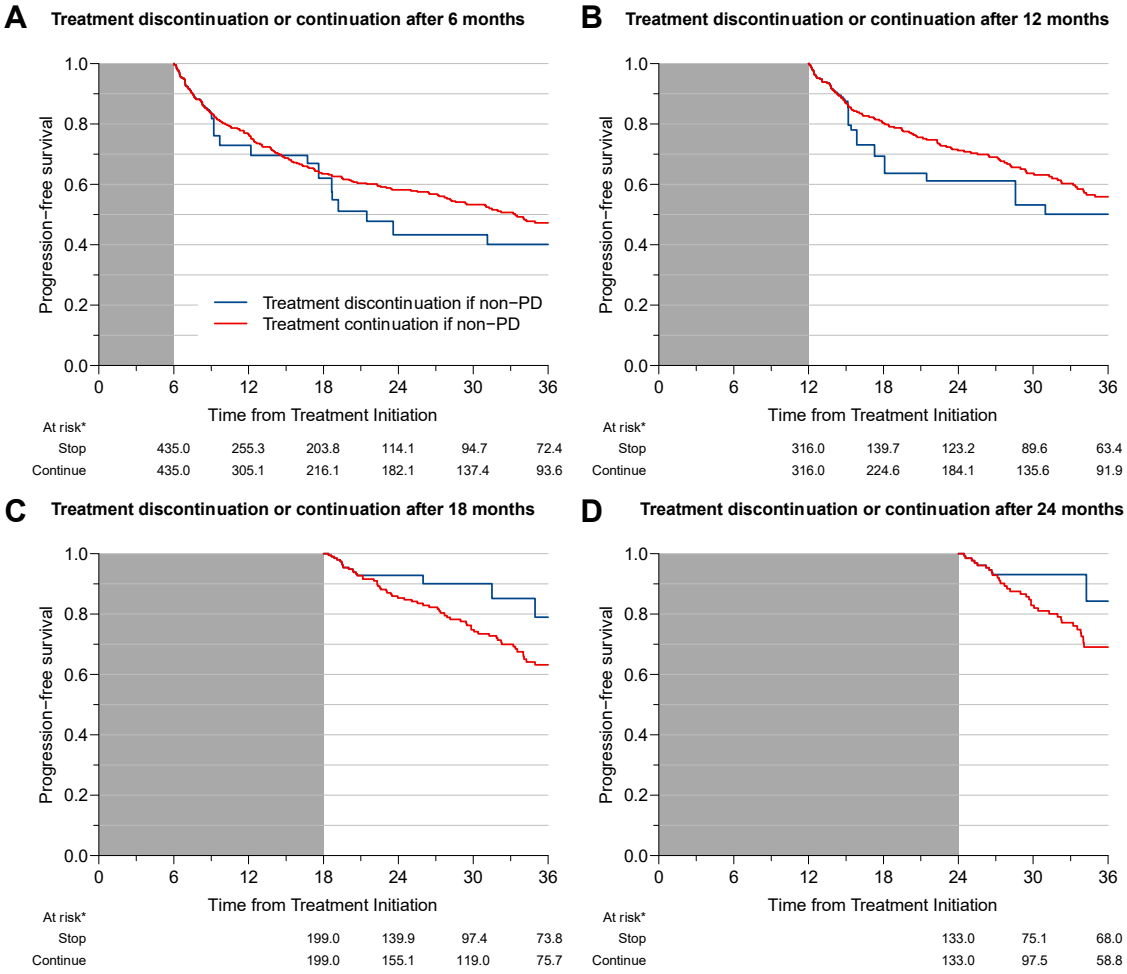

***Fig. 3:* Weighted progression-free survival curves in the four emulated trials.** *Sum of weights of at-risk individuals at each time.

treatment until disease progression or unacceptable toxicity, or for 2 years or more in the absence of disease progression or unacceptable toxicity). The first results, which should be available by the end of 2025 for the SAFE-STOP trial and 2027 for the STOP-GAP trial, will provide further evidence.

Decision timepoint	Time horizon from treatment initiation (mo.)	PFS difference (95% CI)	RMST difference (95% CI)
6 months	36	7.1% (−9.1 to 24.5)	+2.1 (−1.3 to 5.4)
12 months	36	5.8% (−17.0 to 21.7)	+2.1 (−1.3 to 4.2)
18 months	36	−15.8% (−29.3 to 9.9)	−1.7 (−2.5 to −0.6)
24 months	36	−15.2% (−31.2 to −0.1)	−1.1 (−1.6 to −0.5)

A positive (progression-free) survival difference or RMST difference indicates longer average survival with immune checkpoint inhibitor continuation at the decision timepoint. PFS: progression-free survival; RMST: Restricted mean (progression-free) survival time.

***Table 3:* Analysis of progression-free survival up to 36 months from immune checkpoint inhibitor initiation.**

The main strength of our study is its design. Targeted trial emulation enabled us to approach the format of a randomized controlled trial (RCT) and estimate the effect of an intervention, taking account of real-world variability by way of the grace period, and using observational survival data. This type of analysis has not been used previously to study immunotherapy duration in advanced melanoma, and it provides more robust results than traditional observational studies by avoiding common biases in observational studies, such as selection bias in the absence of randomization, even so mitigated by matching, as well as immortal time bias, which has been noted in other studies on ICIs.[25] Furthermore, all our patients received treatment outside a clinical trial, thus forming a representative real-world cohort.

There is great potential for emulating target trials in providing relevant answers in the area of cancer. Several potential applications can be foreseen. The first is the analysis of effectiveness of treatments in a real-world

setting, as opposed to the more narrow populations of RCTs, possibly providing data on large samples.[26–28] Another potential application is the comparison of effectiveness, in a setting where it is obvious that we do not have the means (whether financial or operational) to conduct trials to compare all existing treatments or treatment durations that could be useful for treatment decisions, and for better planning of new studies.[29] One important issue is also the time required to obtain useful information, which could be much shorter when emulating a target trial with existing data, compared to setting up a new RCT and conducting it prospectively (including a follow-up over several years before results would be available). A last promising application of target trial emulation relates to personalised medicine, and the identification and assessment of individual treatment strategies, including dynamic treatment regimens.[30,31]

Our study has some limitations. We were unable to perform subgroup analyses on the basis of response type because of the small sample size. However, response assessment is rarely standardized in non-protocol trials, potentially introducing bias in multi-center studies. While the survival data is more favorable under treatment with combined immunotherapy with ipilimumab plus nivolumab, we were unable to conclude on the basis of the treatment received (monotherapy versus combination of immunotherapy) because of the lack of power. As with all observational studies, we cannot exclude the possibility of failure to take account of residual confounding factors. Finally, the number of events was small, even for the 6-month analysis, with 2.9% of patients discontinuing electively, leading to a wide confidence interval despite significant results. This data is in line with that from clinical trials, where early discontinuation is mainly driven by progression or toxicity.

Among the factors associated with better survival at the time of discontinuation of immunotherapy, the type of response at discontinuation, rapid achievement of response following initiation of treatment, and achievement of CR within the first 6 months of treatment initiation have been reported.[32] These factors can assist in the decision to discontinue or continue immunotherapy. Predictive factors for response and maintenance at the time of discontinuation remain to be identified. PD-L1 status and tumor size were significantly associated with achieving CR in KEYNOTE-001, with CR reaching 42.7% for PDL1 expression and tumor size <5 cm, compared to 1.9% in the absence of PDL1 expression and tumor size >10 cm.[10] However, this association was not found in the ipilimumab + nivolumab combination therapy group in the pooled CheckMate 066, 067, and 069[32] analyses. BRAF mutation status was associated with improved OS and PFS in CheckMate 067.[33] The reasons for treatment discontinuation remain contrasted, as some authors have reported similar survival outcomes for patients discontinuing due to toxicity and outcomes among those discontinuing electively, while others found better survival among patients who discontinued electively than among those discontinuing as a result of toxicity[34]

Finally, in the case of progression at the time of discontinuation, data on rechallenge with immunotherapy is limited and contrasted. In KEYNOTE-006,[11] 8 patients who initially achieved CR were rechallenged, with 1 patient achieving CR and 3 patients achieving PR. Regarding the analysis by Jansen et al.,[12] 19 patients were rechallenged with a 32% response rate to this new exposure to immunotherapy. 78 out of 396 patients from the analysis of Betof Warner et al.,[35] whatever their reason for discontinuing treatment, were retreated, with fewer responses following rechallenge, as only 16 patients responded. In the study by Pokorny et al.,[21] 13 patients experienced relapse after discontinuation, 8 patients were re-treated, among whom 7 achieved a response, but no complete response was observed. Further to this, prolonged exposure to first-line immunotherapy could induce selective pressure which carries a risk of non-response in case of rechallenge after progression following discontinuation.

In conclusion, our study shows that immunotherapy treatment for advanced melanoma should be continued for a minimum of 1 year, although intermediate time-points (e.g. 9 months) were not investigated. The benefit of treating beyond one year appears unlikely. In the absence of clinical trials assessing different treatment durations available to date, these results provide useful guidance to clinicians in their daily practice. The results of ongoing prospective trials should provide further information on ICI treatment duration among patients with advanced melanoma.[23,24]

Contributors

MA, BO, CL and RP were responsible for the conception and design of the study. BO and RP did statistical analyses. MA, CL and RP collaboratively wrote the first draft of the manuscript, had full access to and verified all study data, and had final responsibility for the decision to submit for publication. BO and RP verified the underlying data. All authors had full access to data reported in the manuscript, interpreted the data, critically reviewed the manuscript and approved the final version.

Data sharing statement

According to European regulation, the pseudonymized participant data cannot be openly shared, given no specific consent for sharing was obtained. De-identified participant data can be made available to bona fide researchers registered with an appropriate institution, upon the submission of a research protocol. Requests should be sent to the corresponding author and will be reviewed by the scientific committee of MELBASE.

The computer code can be shared upon request to the corresponding author.

Declaration of interests

LM reports advisory board and travel expenses from Bristol Myers Squibb, Merck Sharp and Dhome, Pierre Fabre, Novartis and Sun Pharm. SD reports advisory board and travel expenses from Bristol Myers Squibb and Merck Sharp, and Dhome; research fundings from Bristol Myers Squibb, Merck Sharp and Dhome, and Pierre Fabre. FBP

reports financial support outside the submitted work from Bristol Myers Squibb, Merck Sharp and Dhome, Pierre Fabre and Novartis. JDQ reports advisory board from Merck Sharp and Dhome, Pierre Fabre, Novartis and Bristol Myers Squibb. CGM reports advisory board and travel expenses from Pierre Fabre, Bristol Myers Squibb and Merck Sharp and Dhome. PS reports advisory board and travel expenses from Bristol Myers Squibb, Merck Sharp and Dhome and Pierre Fabre and Novartis; consulting fees from Bristol Myers Squibb, Merck Sharp and Dhome, Pierre Fabre, Regeneron, Sanofi, Damae and Novartis. TL reports advisory board and travel expenses from Bristol Myers Squibb, Merck Sharp and Dhome, Pierre Fabre and Novartis. HM reports advisory board from Pierre Fabre, Bristol Myers Squibb, Merck Sharp and Dhome, Novartis, Regeneron and Sun Pharma; research funding from Pierre Fabre, Bristol Myers Squibb, Merck Sharp and Dhome, Novartis, Regeneron, Nektar Therapeutics, 4SC and Incyte; and research grant from Leo Pharma and Merck Sharp and Dhome. All other authors declare no completing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102960.

References

1 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517–2526. https://doi.org/10.1056/NEJMoa1104621. Epub 2011 Jun 5. PMID: 21639810.

2 Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med*. 2017;377(19):1813–1823. https://doi.org/10.1056/NEJMoa1708539. Epub 2017 Sep 10. PMID: 28891408.

3 Eggermont AMM, Blank CU, Mandala M, et al. Follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. *J Clin Oncol*. 2020;38(33):3925–3936. https://doi.org/10.1200/JCO.20.02110. Epub 2020 Sep 18. PMID: 32946353; PMCID: PMC7676886.

4 Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(11):1465–1477. https://doi.org/10.1016/S1470-2045(20)30494-0. Epub 2020 Sep 19. Erratum in: Lancet Oncol. 2021 Oct;22(10):e428. PMID: 32961119.

5 Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet*. 2022;399(10336):1718–1729. https://doi.org/10.1016/S0140-6736(22)00562-1. Epub 2022 Apr 1. PMID: 35367007.

6 Stephen Hodi F, Chiarion -Sileni Vanna, Lewis Karl D, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. *J Clin Oncol*. 2022;40(16_suppl):9522.

7 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320–330. https://doi.org/10.1056/NEJMoa1412082. Epub 2014 Nov 16. PMID: 25399552.

8 Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet*. 2017;390(10105):1853–1862. https://doi.org/10.1016/S0140-6736(17)31601-X. Epub 2017 Aug 16. PMID: 28822576.

9 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23–34. https://doi.org/10.1056/NEJMoa1504030. Epub 2015 May 31. Erratum in: N Engl J Med. 2018;379(22):2185. PMID: 26027431; PMCID: PMC5698905.

10 Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol*. 2019;30(4):582–588. https://doi.org/10.1093/annonc/mdz011. PMID: 30715153; PMCID: PMC6503622.

11 Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20(9):1239–1251. https://doi.org/10.1016/S1470-2045(19)30388-2. Epub 2019 Jul 22. PMID: 31345627.

12 Jansen YJL, Rozeman EA, Mason R, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Ann Oncol*. 2019;30(7):1154–1161. https://doi.org/10.1093/annonc/mdz110.

13 Keilholz U, Ascierto PA, Dummer R, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol*. 2020;31(11):1435–1448. https://doi.org/10.1016/j.annonc.2020.07.004. Epub 2020 Aug 4. PMID: 32763453.

14 Hernán MA. How to estimate the effect of treatment duration on survival outcomes using observational data. *BMJ*. 2018;360:k182. https://doi.org/10.1136/bmj.k182. PMID: 29419381; PMCID: PMC6889975.

15 Maringe C, Benitez Majano S, Exarchakou A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol*. 2020;49(5):1719–1729. https://doi.org/10.1093/ije/dyaa057. PMID: 32386426; PMCID: PMC7823243.

16 Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. *BMJ*. 2022;378:e071108. https://doi.org/10.1136/bmj-2022-071108. PMID: 36041749.

17 Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004;75(1):45–49. https://doi.org/10.1016/j.cmpb.2003.10.004. PMID: 15158046.

18 Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*. 2011;30(19):2409–2421. https://doi.org/10.1002/sim.4274. Epub 2011 May 25. PMID: 21611958.

19 Carlet C, Dalle S, Leccia MT, et al. Late-onset adverse events of anti-PD1 therapy in melanoma patients: an observational study from MELBASE, a nationwide prospective cohort. *J Am Acad Dermatol*. 2022;86(2):345–352. https://doi.org/10.1016/j.jaad.2021.06.849. Epub 2021 Jun 18. PMID: 34153388.

20 Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153. *J Clin Oncol*. 2020;38(33):3863–3873. https://doi.org/10.1200/JCO.20.00131. Epub 2020 Sep 10. PMID: 32910710; PMCID: PMC7676888.

21 Pokorny R, McPherson JP, Haaland B, et al. Real-world experience with elective discontinuation of PD-1 inhibitors at 1 year in patients with metastatic melanoma. *J Immunother Cancer*. 2021;9(1):e001781. https://doi.org/10.1136/jitc-2020-001781. PMID: 33500258; PMCID: PMC7843310.

22 Mäkelä S, Kohtamäki L, Laukka M, Juteau S, Hernberg M. Limited-duration anti-PD-1 therapy for patients with metastatic melanoma. *Acta Oncol*. 2020;59(4):438–443. https://doi.org/10.1080/0284186X.2020.1716388. Epub 2020 Jan 31. PMID: 32000554. 18 C. Robert et al. 5-Year characterization of complete responses. ESMO Abstract #1082MO.

23 Coen O, Corrie P, Marshall H, et al. The DANTE trial protocol: a randomised phase III trial to evaluate the Duration of ANti-PD-1 monoclonal antibody Treatment in patients with metastatic mElanoma. *BMC Cancer*. 2021;21(1):761. https://doi.org/10.1186/s12885-021-08509-w. PMID: 34210290; PMCID: PMC8246129.

24 Mulder EEAP, de Joode K, Litière S, et al. Early discontinuation of PD-1 blockade upon achieving a complete or partial response in patients with advanced melanoma: the multicentre prospective Safe Stop trial. *BMC Cancer*. 2021;21(1):323. https://doi.org/10.1186/s12885-021-08018-w. PMID: 33765967; PMCID: PMC7993897.

25 Dall'Olio FG, Rizzo A, Mollica V, Massucci M, Maggio I, Massari F. Immortal time bias in the association between toxicity and response for immune checkpoint inhibitors: a meta-analysis. *Immunotherapy*. 2021;13(3):257–270. https://doi.org/10.2217/imt-2020-0179. Epub 2020 Nov 23. PMID: 33225800.

26 Antoine A, Pérol D, Robain M, Delaloge S, Lasset C, Drouet Y. Target trial emulation to assess real-world efficacy in the Epidemiological Strategy and Medical Economics metastatic breast cancer cohort. *J Natl Cancer Inst*. 2023;115(8):971–980. https://doi.org/10.1093/jnci/djad092. PMID: 37220893; PMCID: PMC10407701.

27 Kirkegård J, Gaber C, Heide-Jørgensen U, et al. Effect of surgery versus chemotherapy in pancreatic cancer patients: a target trial emulation. *J Natl Cancer Inst*. 2024;4:djae024. https://doi.org/10.1093/jnci/djae024. Epub ahead of print. PMID: 38310365.

28 Pellat A, Grinda T, Prelaj A, et al. 1689O Comprehensive mapping review of real-world evidence publications focusing on targeted therapies in solid tumors: a collaborative work from ESMO real-world data and Digital Health Working Group. *Ann Oncol*. 2023;34:S925.

29 Kwee SA, Wong LL, Ludema C, et al. Target trial emulation: a design tool for cancer clinical trials. *JCO Clin Cancer Inform*. 2023;7:e2200140. https://doi.org/10.1200/CCI.22.00140. PMID: 36608311; PMCID: PMC10166475.

30 Morzywołek P, Steen J, Vansteelandt S, Decruyenaere J, Sterckx S, Van Biesen W. Timing of dialysis in acute kidney injury using routinely collected data and dynamic treatment regimes. *Crit Care*. 2022;26(1):365. https://doi.org/10.1186/s13054-022-04252-1. PMID: 36443861; PMCID: PMC9706864.

31 Grolleau F, Petit F, Gaudry S, et al. Personalizing renal replacement therapy initiation in the intensive care unit: a reinforcement learning-based strategy with external validation on the AKIKI randomized controlled trials. *J Am Med Inform Assoc*. 2024;31(5):1074–1083. https://doi.org/10.1093/jamia/ocae004. PMID: 38452293; PMCID: PMC11031229.

32 Robert C, Long GV, Larkin J, et al. 5-year characterization of complete responses in patients with advanced melanoma who received nivolumab plus ipilimumab (NIVO+IPI) or NIVO alone. *Ann Oncol*. 2020;31:S734–S735. https://doi.org/10.1016/j.annonc.2020.08.1206.

33 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535–1546. https://doi.org/10.1056/NEJMoa1910836. Epub 2019 Sep 28. PMID: 31562797.

34 Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J Clin Oncol*. 2017;35(34):3807–3814. https://doi.org/10.1200/JCO.2017.73.2289. Epub 2017 Aug 25. PMID: 28841387; PMCID: PMC5791828.

35 Betof Warner A, Palmer JS, Shoushtari AN, et al. Long-Term outcomes and responses to retreatment in patients with melanoma treated with PD-1 blockade. *J Clin Oncol*. 2020;38(15):1655–1663. https://doi.org/10.1200/JCO.19.01464. Epub 2020 Feb 13. PMID: 32053428; PMCID: PMC7238490.