

## Review

---

# Immune Checkpoint Inhibitors in Metastatic Bladder and Other Solid Malignancies: How Long is Enough?

Vivek Kumar<sup>a</sup> and Xiao X. Wei<sup>b,\*</sup>

<sup>a</sup>*Brigham and Women's Hospital, Boston, MA, USA*

<sup>b</sup>*Dana-Farber Cancer Institute, Boston, MA, USA*

Received 16 May 2023

Accepted 24 July 2023

Pre-press 11 August 2023

Published 25 September 2023

**Abstract.** The introduction of T-cell targeted immunomodulators blocking the PD-1 and PD-L1 axis is unquestionably one of the most notable advancements in the treatment of advanced or metastatic solid malignancies, including bladder cancer. Immune checkpoint antibodies are now widely utilized as monotherapies or in combination with other systemic therapies in the first or subsequent lines of treatment in approximately 50 cancer types. Deep and durable responses and long tails of survival curves are hallmarks of patients treated with immune checkpoint inhibitors. However, treatment can have negative impacts, including serious treatment-related side effects as well as a high financial burden to individual patients and the healthcare system. There is increasing data that the benefit of immune checkpoint treatment may persist after treatment is discontinued for reasons other than progressive disease, particularly in patients who have achieved a durable complete response. However, the optimal treatment duration and activity after treatment reinitiation remains undefined and will likely be influenced by disease biology (histology and genomics), treatment (monotherapy or combination therapy), and disease context (depth and duration of response). Well-designed prospective clinical trials and the development and validation of biomarkers that predict outcomes after treatment cessation are needed to move the field forward.

**Keywords:** Bladder cancer, immunotherapy, treatment discontinuation, treatment deintensification, solid cancers

## DURABLE RESPONSES AND PROLONGED SURVIVAL AFTER IMMUNE CHECKPOINT THERAPY

Programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1) checkpoint blockade immunotherapy elicit antitumor responses that translate into durable tumor shrinkage and prolonged survival in multiple cancer types. Response rates vary by tumor type, line of treatment, and single

or combination therapy. In 2014, pembrolizumab was the first monoclonal antibody targeting the PD-1/PD-L1 axis that was granted accelerated FDA approval for patients with advanced or metastatic melanoma, the tumor histology with the most robust long-term clinical data. In patients with treatment-naïve and pretreated advanced or metastatic melanoma, long-term follow-up ( $\geq 4.5$  years) on the KEYNOTE-001 and KEYNOTE-006 trials demonstrated response rates of approximately 40% [1, 2]. The median time to response was approximately 3 months, and the median duration of response was unprecedented (not reached in KEYNOTE-001 and 53.5 months

---

\*Correspondence to: Xiao X. Wei, Dana-Farber Cancer Institute, Boston, MA, USA. E-mail: xiaox.wei@dfci.harvard.edu.

in KEYNOTE-006). In these studies, approximately 15% of patients had a complete response (CR), and this subset of patients did particularly well long-term. Over 90% had ongoing responses in KEYNOTE-001, and the 24-month progression-free survival (PFS) was 85.4% in patients who achieved CR in KEYNOTE-006. Notably, the estimated 5-year overall survival (OS) exceeds 33% in both studies on long-term follow-up, reflecting the “long tails of survival curves,” which is a hallmark of immunotherapy.

In advanced or metastatic urothelial carcinoma (UC), the long-term activity of PD-1/PD-L1 immune checkpoint inhibitors was best evaluated in KEYNOTE-045, a randomized open-label phase 3 trial comparing pembrolizumab and investigator's choice chemotherapy (paclitaxel, docetaxel or vinflunine) in advanced or metastatic UC after progression on platinum-containing chemotherapy [3]. At a median follow-up of 62.9 months, the objective response rate was higher for pembrolizumab (21.9% vs. 11.0%), and the duration of response was higher for pembrolizumab (29.7 months vs. 4.4 months). Accordingly, 5-year OS favored pembrolizumab (14.9% vs. 8.7%), with median OS not reached for the subset of patients who achieved CR or partial response (PR) ( $n=59$ ). Taken together, the early pembrolizumab trials in melanoma as well as more recent trials of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway in UC and other solid malignancies, have consistently demonstrated the potential for durable responses and prolonged survival in a subset of patients (Table 1).

### **DISCONTINUATION OF IMMUNE CHECKPOINT THERAPY BEFORE DISEASE PROGRESSION**

There is growing clinical evidence that patients with various tumor histologies who stop immune checkpoint inhibitors for reasons other than disease progression may continue to derive long-term clinical benefits. Due to the maturity of follow-up, much of these data stem from post-hoc analyses of trials in advanced or metastatic melanoma, which evaluated outcomes of patients who stopped treatment for toxicity or after completing a defined period of treatment.

In KEYNOTE-001, patients with ipilimumab-naïve and ipilimumab-treated advanced or metastatic melanoma were treated with pembrolizumab (one of three dose regimens). Patients were allowed to dis-

continue pembrolizumab if they had received at least 6 months of treatment and at least 2 treatments after confirmed CR. 105 of 655 (15.8%) patients had confirmed CR as the best overall response. At a median follow-up of 43 months, 67 patients who achieved confirmed CR elected to stop treatment and proceeded to observation without further cancer-directed therapy. Among these 67 patients, the median time to overall response was 3 months, the median time to CR was 13 months, and the median time receiving pembrolizumab was 23 months. After a median off-treatment interval of 22 months, most of these patients ( $n=61$ , 91%) maintained CR [4].

In the pivotal phase 3 KEYNOTE-006 study, which demonstrated the superiority of pembrolizumab over ipilimumab in advanced or metastatic melanoma, patients who were randomized to the pembrolizumab arms (10 mg/kg q2wk or 10 mg/kg q3wk) continued treatment for up to 2 years or until disease progression or intolerable toxicity [2]. A total of 556 patients received pembrolizumab, 103 (19%) of whom completed 2 years of pembrolizumab. Of these 103 patients, 21 (20%) achieved complete response, 69 (67%) partial response, and 13 (13%) stable disease. After a median follow-up of 34.2 months from completion of pembrolizumab, the 24-month PFS from pembrolizumab completion for the 103 patients was 78.4%. The 24-month and 36-month overall survival estimates were 95.9% and 93.8%, respectively. Responses were ongoing in 16 of 21 (76%) patients with CR, 53 of 69 (77%) patients with PR, and 7 of 13 (54%) with stable disease (SD) [2].

In a pooled post-hoc analysis of CheckMate 069 and CheckMate 067, double-blind phase 2 and phase 3 studies which demonstrated the superiority of ipilimumab plus nivolumab over ipilimumab monotherapy in treatment-naïve unresectable stage III or IV melanoma, 96 patients in the nivolumab plus ipilimumab arms discontinued treatment for treatment-related adverse events [5]. The median number of nivolumab and ipilimumab doses received in the patients who discontinued treatment was three. At a minimum follow-up of 18 months, these 96 patients had similar objective response rates (58.3% vs. 50.2%), PFS (median PFS 8.4 months vs. 10.8 months,  $p=0.97$ ), and OS (median not reached for both) compared to the overall population randomized to nivolumab plus ipilimumab [5].

Favorable long-term outcomes after discontinuation of immune checkpoint inhibitors in other advanced solid malignancies have also been reported; however, the proportion of patients with sustained

Table 1  
Durability of response and overall survival in immune checkpoint trials in advanced or metastatic solid malignancies: Long-term follow-up in selected trials

Cancer type	Study	Agent(s)	N	Median f/u, Months	ORR (95% CI), %	Median DOR, months (range)	Median OS, months (range)	Ref
Melanoma	KEYNOTE-001[1]	Pembrolizumab	655	55	41 (37–45)	NR	23.8 (20.2–30.4)	[1]
Melanoma	KEYNOTE-006	Pembrolizumab*	556	57.7	42 (38.1–46.5)	53.5 (50.99-NE)	32.7 (24.5–41.6)	[2]
Melanoma	CheckMate 067	Nivolumab+Ipilimumab	314	57.5	58 (53–64)	NR	72.1 (38.2-NR)	[28]
UC	KEYNOTE-045	Pembrolizumab	270	62.9	21.9 (17.1–27.3)	29.7 (1.6+–60.5+)	10.1 (8.0–12.3)	[29]
UC	KEYNOTE-052	Pembrolizumab	370	56.3	28.9 (24.3–33.8)	33.4 (1.4+–60.7+)	11.3 (9.7–13.1)	[29]
NSCLC	KEYNOTE-024	Pembrolizumab	154	59.9	46.1 (38.1–54.3)	29.1 (2.2–60.8+)	26.3 (18.3–40.4)	[6]
NSCLC	CheckMate 017 and 057 (pooled)	Nivolumab	427	69.4–69.5	19.7 (16.0–23.8)	19.9 (11.4–30.8)	11.1 (9.2–13.1)	[30]
RCC	CheckMate 025	Nivolumab	410	72	22.9 (18.9–27.3)	18.2 (12.9–25.8)	25.8 (22.2–29.8)	[31]
SCCHN	KEYNOTE-048	Pembrolizumab (PD-L1 CPS $\geq$ 1)	257	45	19 (14.5–24.4)	24.8 (6.9–35.9)	12.3 (10.8–14.8)	[32, 33]

\*Two pembrolizumab dosing regimens: 10 mg/kg Q2 W ( $n = 279$ ) and 10 mg/kg Q3 W ( $n = 277$ ). Abbreviations: 1 L, first line; CPS, Combined Positive Score; DOR, duration of response; f/u, follow-up; N, number of patients; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival, RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of head and neck; UC, urothelial carcinoma.

urable responses after stopping treatment appears lower than that observed in advanced or metastatic melanoma trials. For example, in 5-year follow-up of KEYNOTE-024, a phase 3, randomized study of pembrolizumab versus platinum-based chemotherapy in treatment-naïve non-small cell lung cancer (NSCLC) with PD-L1 tumor proportion score of  $\geq 50\%$  and no sensitizing EGFR or ALK alterations, 39 of 154 (25.3%) patients randomized to pembrolizumab completed 2 years of treatment. Among these patients, the best response was CR in 4 (10.3%), PR in 28 (71.8%), SD in 6 (15.4%), and PD in 1 (2.6%). With a median follow-up was 5 years, 32 of these 39 (82.0%) patients were alive, and 18 patients (46.2%) were alive without PD or subsequent therapy. 36-month OS rate from the completion of 2 years of treatment was 81.4% [6].

Consistent with post-hoc analyses from clinical trials, real-world data evaluating the outcome of patients with advanced or metastatic melanoma who discontinued PD-1 inhibitors in the absence of progressive disease have also demonstrated that a substantial ( $\geq 70\%$ ) proportion of patients remained progression-free or were alive without the need for additional cancer-directed therapy after a median follow-up of  $\geq 18$  months [7, 8]. Of note, patients who achieve CR appear to have the highest chance of durable response after stopping treatment, compared to PR then SD [8].

Comparable clinical data focused on UC is currently lacking; however, patients with UC are included in some large retrospective studies, including a cohort of 262 patients treated with PD-1/PD-L1 monotherapy across multiple cancer types in phase 1 clinical trials conducted in Gustave Roussy [9]. Twenty-five of the 262 (9%) patients in this cohort had UC. The maximum treatment duration was 12 months in durvalumab and atezolizumab trials, 24 months in pembrolizumab trials, and until disease progression in nivolumab trials. In this cohort, 39 (15%) of patients discontinued immunotherapy without the presence of disease progression (30 patients for prolonged response and 9 patients for toxicity). Fifteen of the 39 patients (38%) relapsed after stopping treatment, and the chance of relapse was lower when patients achieved deeper response at the time of treatment discontinuation: 12% for CR, 53% for PR, and 80% for SD. Of note, in this analysis, the median treatment duration prior to discontinuation was longer in patients who did not relapse. Treatment discontinuation within the first 12 months of PD-1/PD-L1 inhibitor treatment was associated with a

higher risk of relapse than after 12 months ( $p = 0.002$ ) [9].

The only study to date that evaluated the treatment duration of a PD1/PD-L1 inhibitor in a prospective randomized trial is CheckMate 153 [10]. In this study, patients with advanced or metastatic non-small cell lung cancer (NSCLC) who had received at least one prior systemic therapy and remained on treatment for 1 year were randomized to continue or stop nivolumab, regardless of response status at the time of randomization. When the subset of patients who had SD, PR, and CR at randomization was evaluated for efficacy (174 of 252 randomized) at a median follow-up of 13.5 months, PFS was found to be significantly longer for those who continued nivolumab (median PFS 24.7 months vs. 9.4 months, HR 0.56 [95% CI: 0.37–0.84]). OS also favored continuous treatment (median OS not reached vs. 28.8 months, HR 0.62 [95% CI: 0.42–0.92] in the IIT population). However, the primary endpoint was safety, and not all randomized patients were evaluated for efficacy, contributing to imbalances in baseline characteristics, including frequency of squamous histology. Therefore, further prospective studies with adequate statistical design are needed.

## IMMUNE CHECKPOINT RETREATMENT AFTER TREATMENT DISCONTINUATION

Clinical data on patients with disease response or stabilization on PD-1/PD-L1 immune checkpoint inhibitors, followed by an off-treatment period and subsequent retreatment for progressive disease, are limited in sample size, heterogeneous in methodology, and descriptive in nature. In the aforementioned KEYNOTE-006 trial, 13 patients with advanced or metastatic melanoma received a second course of pembrolizumab, 6 (46%) of whom had CR, 6 (46%) had PR, and 1 (8%) had SD as the best response to the initial course of pembrolizumab. With a median follow-up of 14.3 months after retreatment, 3 (23%) patients had CR (2 of whom had surgical CR before starting the second course of pembrolizumab), 4 (31%) had PR, 3 (23%) had SD, and 1 (8%) had PD as the best response to retreatment. Response to retreatment was unevaluable for 2 patients. Of the 6 patients with CR after the first course of pembrolizumab, 3 (50%) recaptured CR upon retreatment, two of whom had undergone surgical resection with no evidence of disease before pembrolizumab reinitiation. The remaining patients who had CR after the first course

Table 2  
Response after PD-1/PD-L1 immune checkpoint therapy retreatment: Summary of post-hoc analyses from selected trials

Cancer type	Study ( <i>N</i> Retreated)	First-course best objective response	Retreatment best objective response, <i>n</i> (%)					Ref
			CR	PR	SD	PD	Unevaluable	
Melanoma	KEYNOTE-006 ( <i>n</i> = 13)	CR ( <i>n</i> = 6)	3 (30)*	1 (31)	1 (31)	0 (0)	1 (31)	[2]
		PR ( <i>n</i> = 6)	0 (0)	3 (30)	1 (31)	1 (31)	1 (31)	
		SD ( <i>n</i> = 1)	0 (0)	0 (0)	1 (31)	0 (0)	0 (0)	
NSCLC	KEYNOTE-024 ( <i>n</i> = 12)	CR ( <i>n</i> = 1)	0 (0)	0 (0)	1 (31)	0 (0)	0 (0)	[6]
		PR ( <i>n</i> = 8)	0 (0)	4 (33)	3 (25)	0 (0)	1 (31)	
		SD ( <i>n</i> = 3)	0 (0)	0 (0)	2 (17)	1 (31)	0 (0)	
UC	KEYNOTE-045 ( <i>n</i> = 11)	CR ( <i>n</i> = 5)	3 (27)	1 (9)	1 (9)	0 (0)	0 (0)	[11]
		PR ( <i>n</i> = 5)	0 (0)	1 (9)	4 (36)	0 (0)	0 (0)	
		SD ( <i>n</i> = 1)	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	
UC	KEYNOTE-052 ( <i>n</i> = 10)	CR ( <i>n</i> = 6)	1 (10)	3 (30)	2 (20)	0 (0)	0 (0)	[11]
		PR ( <i>n</i> = 4)	0 (0)	1 (10)	2 (20)	1 (10)	0 (0)	

\*Two of the 3 patients underwent surgical resection with no evidence of disease before retreatment with pembrolizumab. Abbreviations: CR, complete response; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

of pembrolizumab attained PR (*n* = 1) and SD (*n* = 1). One patient was unevaluable for the response after retreatment [2].

In the KEYNOTE-024 study, patients with advanced or metastatic NSCLC who had completed 35 cycles of pembrolizumab or achieved confirmed CR with at least 6 months of pembrolizumab and at least 2 additional cycles of treatment after CR were eligible to receive a second course of pembrolizumab upon progression [6]. Twelve patients were retreated with pembrolizumab, and their initial responses for the first course of pembrolizumab were CR (*n* = 1, 8%), PR (*n* = 8, 67%), and SD (*n* = 3, 25%). Upon retreatment, 4 (33%) attained objective responses, all of which were partial. Six (50%) of the retreated patients had SD, and 1 (8%) had PD as the best retreatment response. One patient was unevaluable in this cohort.

In patients with advanced or metastatic UC, post-hoc analysis of the phase 3 KEYNOTE-045 (second-line post platinum) and phase 2 KEYNOTE-052 (first-line cisplatin-ineligible), trials evaluated pembrolizumab retreatment in patients who either stopped pembrolizumab after achieving CR before 2 years or completed 2 years of treatment with best response of CR, PR or SD. Patients had investigator-confirmed radiographic PD after treatment cessation, ECOG performance status of 0 or 1, and no intervening cancer-directed therapy before pembrolizumab retreatment [11]. The median time off-treatment was 7.7 months (IQR 3.6–16.5 months) in the KEYNOTE-045 cohort and 13.0 months (IQR 9.2–16.6 months) in the KEYNOTE-052 cohort. Of 11 patients retreated with pembrolizumab in KEYNOTE-045, all achieved CR (*n* = 3, 27%), PR

(*n* = 2, 18%), or SD (*n* = 6, 55%) with a disease control rate (DCR) of 100%. Of 10 patients retreated in KEYNOTE-052, 1 (10%) patient achieved CR, 4 (40%) patients PR, and 4 (40%) SD, with DCR of 90%. However, only a minority of patients who had CR or PR with the first course of pembrolizumab recaptured CR or PR, respectively, during retreatment (4 of 10 in KEYNOTE-045 and 2 of 10 patients in KEYNOTE-052) [11].

Taken together, clinical data to date (Table 2) suggest that retreatment with PD-1/PD-L1 immune checkpoint antibodies after achieving clinical benefit and stopping treatment for reasons other than progression has the potential to restore antitumor activity; however, the depth of response may be lower than that of initial treatment. Of note, this contrasts with retreatment after progression with prior immune checkpoint inhibitor therapy. Recent data from the CONTACT-03 trial showed that the addition of atezolizumab to cabozantinib did not improve clinical outcomes and led to increased toxicity compared to cabozantinib alone in patients with locally advanced or metastatic renal cell carcinoma after progression on an immune checkpoint inhibitor [12]. Therefore, there is currently no prospective data to support continuing or rechallenging with a PD-1/PD-L1 inhibitor after progression on these immunotherapy agents.

### PHYSICAL AND FINANCIAL TOXICITY FROM IMMUNE CHECKPOINT THERAPY

Immune checkpoint therapy targeting the PD-1/PD-L1 axis is generally well tolerated; however, a subset of patients develops immune-related adverse

events (irAEs) that can be serious and, in rare incidences, even fatal. The incidence of grade  $\geq 3$  irAEs in patients receiving anti-PD-1/PD-L1 antibodies, CTLA-4 antibodies, or a combination of the two are approximately 6%, 24%, and 55%, respectively. The mechanism and spectrum of irAEs are distinctly different from toxicities seen with traditional chemotherapy or targeted therapy. Clinical presentations are heterogeneous, and a broad range of organs can be affected. Fatal irAEs occur in 0.4–1.2% of patients [13]. Reported causes of treatment-related deaths include colitis, encephalitis, pneumonitis, myocardial infarction, and liver failure [14].

Immune checkpoint antibodies have long half-lives, and the immune system may remain activated for a long period of time after these antibodies are cleared. While there are patterns in the kinetics of the main classes of irAEs, there is a wide dispersion of onset times of irAEs. Patients who have tolerated immune checkpoint therapy well can develop new irAEs many months or even years after starting treatment [15]. Chronic irAEs affect up to 40% of patients and are most commonly endocrine or rheumatological in nature but can affect other organs [13]. A real-world dataset of 437 melanoma and lung cancer patients that evaluated the incidence of late-onset and long-lasting irAEs showed that the cumulative probability of irAE onset from treatment initiation at 6, 12, and 24 months were 42.8%, 51.0%, and 57.3%, respectively. The rate of ongoing toxicity from the time of first toxicity onset at 6, 12, and 24 months were 42.8%, 38.4%, and 35.7%, respectively [16].

Longer duration of immune checkpoint therapy may be associated with a higher incidence of irAEs. Consistent with this, the CheckMate 153 study that randomized patients with advanced or metastatic NSCLC to continuous versus 1-year fixed duration of nivolumab reported a higher incidence of treatment-related AEs (TRAEs) in the treatment continuation arm (48.0% vs. 26.4%). A higher proportion of patients also experienced grade 3–4 TRAEs in the treatment continuation arm (9.4% vs. 3.2%), and more patients randomized to continue treatment experienced TRAEs that led to treatment discontinuation (9.4% vs. 1.6%). One treatment-related death was reported in the continuous treatment arm, and no grade 5 AE was reported in the 1-year fixed duration arm [10]. Therefore, if treatment can be discontinued while maintaining durable clinical efficacy, patients may be able to avoid serious and late irAEs with subsequent detriment to their overall health.

In addition to side effects related to treatment, immunotherapy can have a substantial financial burden on individual patients and the healthcare system. Countries in North America and Europe that utilize national-level health coverage systems are under pressure to provide access of these expensive agents to patients, which translates into substantial societal costs. In the United States, immune checkpoint inhibitors cost approximately \$150,000 annually for drugs alone [17]. This imposes a major cost on the healthcare system; ultimately, these costs are translated into higher healthcare premiums across the entire population. For individual patients, the magnitude of financial impact depends on how well patients are insured. Some patients have minimal co-insurance and co-pay requirements; however, many are increasingly members of plans where significant co-payments result in financial hardship. In addition, patients may experience objective financial burden and subjective financial distress because of cancer treatment, termed “financial toxicity” [18, 19]. Studies have also shown that financial burden is associated with decreased patient-perceived quality of life (QOL) assessed by multiple validated instruments [18, 20]. Therefore, if a shorter course of immune checkpoint inhibitors can be used to derive comparable long-term clinical outcomes, this also may have significant personal health and health economics impact on patients.

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Immune checkpoint inhibitors targeting PD-1/PD-L1 are now an established core pillar of cancer therapy for a wide spectrum of advanced or metastatic solid malignancies. Treatment is generally continued until disease progression, development of an unacceptable level of side effects, or in some instances, after completion of 2 years of therapy. The length of treatment is based on how these therapies were administered in prospective registrational clinical trials. Post-hoc analyses after long-term follow-up in some of these trials, as well as real-world data, have demonstrated potential for durable response and long-term survival after immune checkpoint therapy is discontinued. Potential mechanisms underlying this durable benefit include immune-mediated eradication of tumor cells, the development of a balance between tumor cells and immune

cells leading to chronic deadlock, and the generation of memory T-cells inhibiting tumor recurrence [21, 22].

Prospective clinical trials with thoughtful patient selection and adequate statistical design are needed to answer the clinically important question of optimal duration of PD-1/PD-L1 immune checkpoint therapy in advanced or metastatic solid cancers. The answer to this question is unlikely to be one-size-fits-all and will likely depend on (1) tumor histology, (2) genetics (e.g., mismatch repair and circulating tumor DNA status), (3) treatment regimen (monotherapy vs. combination with anti-CTLA-4 antibody vs. combination with chemotherapy), and (4) disease context (CR/PR/SD and duration of response). These factors should be proactively considered during the design of clinical trials and incorporated into eligibility criteria and stratification factors. Studies should also prospectively capture the incidence of irAEs as well as health-related QOL and economic impact. A likely challenge that these studies that de-intensify treatment will face is patient enrollment, particularly if randomized. A phase 3, randomized non-inferiority trial which compared the continuous treatment to stopping PD-1/PD-L1 immune checkpoint therapy at approximately 1 year in advanced or metastatic UC was stopped for low accrual (Alliance A031901). Table 3 summarizes ongoing prospective trials evaluating the potential to stop anti-PD-1/PD-L1 immune checkpoint inhibitors, predominantly in advanced and metastatic melanoma. Results of these studies should pave the way for and guide future studies in other tumor histologies.

In addition to the optimal duration of treatment, the dose and frequency of PD-1/PD-L1 immune checkpoint inhibitors also need to be optimized. In phase 1 clinical trials, immune checkpoint inhibitors have consistently demonstrated full target engagement and comparable efficacy at lower doses than the approved dosages of these agents. Pembrolizumab showed full target engagement at dosages of  $\geq 1$  mg/kg every 3 weeks, and response rates were comparable at dosages between 2 mg/kg and 10 mg/kg [23, 24]. Nivolumab showed comparable response rates, survival, and target engagement at dosages between 0.1 mg/kg to 10 mg/kg every 2 weeks. Further, target occupancy lasted for at least 2 months at dosage of 0.3 mg/kg, which is 10 times lower than the recommended phase 2 dose of nivolumab 3 mg/kg [25]. Prospective randomized trials are ongoing evaluating longer cycle length or lower dosages of PD-1/PD-L1 inhibitors, including REFINE-Lung (NCT05085028)

and NVALT-30 Dedication (EudraCT 2020-000493-15) in NSCLC. Therefore, the optimization of dosing (i.e. reduced unit dose), schedule (i.e. longer cycle length), and treatment duration (i.e. shorter total duration) have the potential to reduce costs and toxicity related to treatment exposure. These studies should be supported with enthusiasm by the medical community.

The development and validation of biomarkers that detect minimal residual disease (MRD) may be a powerful tool to help select the best patients to stop immune checkpoint treatment early, specifically those who have non-detectable MRD in addition to radiographic CR. Such technologies could include circulating tumor DNA (ctDNA) and cell-free methylated DNA patterns [26, 27] and may also be utilized for longitudinal disease monitoring to detect early disease progression. For example, a phase 2 study evaluating patients with advanced or metastatic solid tumors treated with pembrolizumab showed that baseline ctDNA level, as well as changes in ctDNA level with treatment, correlates with PFS and OS after immunotherapy [26]. The ongoing Alliance A032103 study will evaluate ctDNA prospectively in patients with muscle-invasive bladder cancer who have adverse pathologic features after radical cystectomy. Patients with detectable ctDNA are randomized to standard-of-care adjuvant nivolumab versus nivolumab plus relatlimab (treatment intensification). Conversely, patients with undetectable ctDNA are randomized to standard-of-care adjuvant nivolumab versus surveillance with the potential to receive nivolumab if ctDNA becomes detectable (treatment de-intensification). Similar biomarker-based, patient-adapted study designs could be utilized in the advanced and metastatic setting to inform optimal treatment duration.

Until more clinical data emerges, patients with advanced or metastatic malignancies treated with PD-1/PD-L1 immunotherapy should continue treatment per standard practice. In the absence of unacceptable toxicity, treatment should be continued for 2 years or until disease progression. Patients who are interested in stopping treatment earlier should be encouraged to participate in clinical trials evaluating treatment de-intensification, whenever possible. Patients should also be counseled that based on clinical data to date, response rate after retreatment may be lower than that with the first course of treatment. If an MRD assay is commercially available for the patient's tumor type, this could be utilized to guide personalized management decision.

Table 3  
Prospective clinical trials evaluating discontinuation of PD-1/PD-L1 immune checkpoint inhibitors in advanced or metastatic solid malignancies

Cancer type(s)	NCT or other ID	Randomization	Study Arm(s)	Primary Endpoint	N	Status
Melanoma, stage III or IV	NCT02821013 (STOP-GAP)	Yes (1 : 1)	1. Continuous treatment 2. Intermittent treatment: Stop at maximal tumor response, and resume on progression	OS	614	Recruiting
Melanoma, stage III or IV (first-line)	ISRCTN15837212 (DANTE)	Yes (1 : 1)	1. Continuous treatment 2. Stop if at least 12 months of treatment and progression-free at 1 year	PFS	1208	Recruiting
Melanoma, stage III or IV (first-line)	NTR7502 (Safe Stop)	No	Stop treatment within 6 weeks of confirmed CR or ongoing PR	Rate of ongoing radiological response 24 months after stopping treatment	200	Recruiting
Melanoma, stage III or IV	NCT04462406, EA6192 (PET-Stop)	No	Stop treatment at 1 year if PET negative or PET-positive with negative biopsy	12-month EFS	150	Recruiting
Melanoma, stage III or IV (first-line)	NCT05652673	No	Stop maintenance nivolumab (or pembrolizumab) within 4 weeks of confirmed CR/PR to ipilimumab/nivolumab	Rate of ongoing radiographic response at 12 months	80	Not yet recruiting
Urothelial carcinoma	NCT04637594 (IMAGINE)	Yes (1 : 1)	1. Continuous treatment 2. Stop if ongoing SD/PR/CR after 9–18 months	OS	1038	Closed for low accrual
NSCLC (first-line)	NCT05255302 (DIAL)	Yes	1. Continuous treatment, up to 2 years 2. Stop if confirmed disease control at 6 months after first-line chemotherapy+pembrolizumab	OS	1360	Recruiting
NSCLC	NCT04880382 (OPTIMUNE-LUNG)	Yes (1 : 1)	3. Continuous treatment 4. Stop treatment after confirmed PR/CR between 6–12 months	12-month PFS	80	Recruiting
Multiple advanced solid tumors*	NCT04157985	Yes	1. Continuous treatment 2. Stop if SD/PR/CR after 1 year of treatment	Time to next treatment PFS	578	Recruiting

\*Tumor histologies include NSCLC, bladder cancer, head and neck squamous cell carcinoma (HNSCC), renal cancer, melanoma, anal cancer, colorectal cancer, cholangiocarcinoma, gastric cancer, hepatocellular carcinoma, Merkel cell carcinoma, and cervical cancer. Abbreviations: EFS, event-free survival; N, number of patients; OS, overall survival; PET, positron emission tomography; NSCLC, non-small cell lung cancer; PFS, progression-free survival.



## ACKNOWLEDGMENTS

The authors have no acknowledgements.

## FUNDING

The authors report no funding.

## AUTHOR CONTRIBUTIONS

VK: Performance of work, interpretation of data, writing the article.

XW: Conception, performance of work, interpretation of data, writing the article.

All authors have access to the data presented in the study.

## CONFLICTS OF INTEREST

XW: Bristol Meyers Squibb (Research support, institutional); Novartis (consultant).

VK: No conflict of interest to report.

## REFERENCES

- [1] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Annals of Oncology*. 2019;30(4):582-8.
- [2] Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, 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. *The Lancet Oncology*. 2019;20(9):1239-51.
- [3] Bellmunt J, Necchi A, Wit RD, Lee J-L, Fong L, Vogelzang NJ, et al. Pembrolizumab (pembro) versus investigator's choice of paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC): 5-year follow-up from the phase 3 KEYNOTE-045 trial. *Journal of Clinical Oncology*. 2021;39(15\_suppl):4532.
- [4] Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma. *Journal of Clinical Oncology*. 2018;36(17):1668-74.
- [5] Schadendorf D, Wolchok JD, Hodi FS, Chiarion-Sileni V, Gonzalez R, Rutkowski P, 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. *Journal of Clinical Oncology*. 2017;35(34):3807-14.
- [6] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score  $\geq 50\%$ . *Journal of Clinical Oncology*. 2021;39(21):2339.
- [7] Betof Warner A, Palmer JS, Shoushtari AN, Goldman DA, Panageas KS, Hayes SA, et al. Long-Term Outcomes and Responses to Retreatment in Patients With Melanoma Treated With PD-1 Blockade. *Journal of Clinical Oncology*. 2020;38(15):1655-63.
- [8] Jansen Y, Rozeman E, Mason R, Goldinger S, Foppen MG, Hojberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Annals of Oncology*. 2019;30(7):1154-61.
- [9] Gauci ML, Lanoy E, Champiat S, Caramella C, Ammari S, Aspeslagh S, et al. Long-Term Survival in Patients Responding to Anti-PD-1/PD-L1 Therapy and Disease Outcome upon Treatment Discontinuation. *Clinical Cancer Research*. 2019;25(3):946-56.
- [10] Waterhouse DM, Garon EB, Chandler J, McCleod M, Hussein M, Jotte R, et al. Continuous Versus 1-Year Fixed-Duration Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: CheckMate 153. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2020;38(33):3863-73.
- [11] Castellano DE, Balar AV, O'Donnell PH, Grivas P, Vaughn DJ, Powles T, et al. Post hoc analysis of the efficacy of pembrolizumab retreatment after progression of advanced urothelial carcinoma (UC) in KEYNOTE-045 and KEYNOTE-052. *Journal of Clinical Oncology*. 2022;40(6\_suppl):512.
- [12] Pal SK, Albiges L, Tomczak P, Suárez C, Voss MH, de Velasco G, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *The Lancet*. 2023.
- [13] Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nature Reviews Clinical Oncology*. 2022;19(4):254-67.
- [14] Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nature Reviews Clinical Oncology*. 2019;16(9):563-80.
- [15] Naidoo J, Murphy C, Atkins MB, Brahmer JR, Champiat S, Feltquate D, et al. Society for Immunotherapy of Cancer (SITC) consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events (irAEs) terminology. *Journal for Immunotherapy of Cancer*. 2023;11(3).
- [16] Ghisoni E, Wicky A, Bouchaab H, Imbimbo M, Delyon J, Gautron Moura B, et al. Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. *European Journal of Cancer (Oxford, England: 1990)*. 2021;149:153-64.
- [17] Couzin-Frankel J. Sticker shock. *American Association for the Advancement of Science*; 2018.
- [18] Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. *CA: A Cancer Journal for Clinicians*. 2018;68(2):153-65.
- [19] Zafar SY, Peppercorn JM, Schrag D, Taylor DH, Goetzinger AM, Zhong X, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *The Oncologist*. 2013;18(4):381-90.

- [20] Tran G, Zafar SY. Financial toxicity and implications for cancer care in the era of molecular and immune therapies. *Annals of Translational Medicine*. 2018;6(9).
- [21] Han J, Zhao Y, Shirai K, Molodtsov A, Kolling FW, Fisher JL, et al. Resident and circulating memory T cells persist for years in melanoma patients with durable responses to immunotherapy. *Nature Cancer*. 2021;2(3):300-11.
- [22] Ribas A, Shin DS, Zaretsky J, Frederiksen J, Cornish A, Avramis E, et al. PD-1 Blockade Expands Intratumoral Memory T Cells Description of Pembrolizomab on TILs. *Cancer Immunology Research*. 2016;4(3):194-203.
- [23] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Ellassaish-Schaap J, Beeram M, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clinical Cancer Research*. 2015;21(19):4286-93.
- [24] Lindauer A, Valiathan C, Mehta K, Sriram V, De Greef R, Ellassaish-Schaap J, et al. Translational pharmacokinetic/pharmacodynamic modeling of tumor growth inhibition supports dose-range selection of the anti-PD-1 antibody pembrolizumab. *CPT: Pharmacometrics & Systems Pharmacology*. 2017;6(1):11-20.
- [25] Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *Journal for Immunotherapy of Cancer*. 2016;4:1-11.
- [26] Bratman SV, Yang SC, Iafolla MA, Liu Z, Hansen AR, Bedard PL, et al. Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. *Nature Cancer*. 2020;1(9):873-81.
- [27] Francini E, Fanelli GN, Pederzoli F, Spisak S, Minonne E, Raffo M, et al. Circulating Cell-Free DNA in Renal Cell Carcinoma: The New Era of Precision Medicine. *Cancers*. 2022;14(18):4359.
- [28] Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *Journal of Clinical Oncology*. 2022;40(2):127-37.
- [29] Balar A, Castellano D, Grivas P, Vaughn D, Powles T, Vuky J, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Annals of Oncology*. 2023;34(3):289-99.
- [30] Borghaei H, Gettinger S, Vokes EE, Chow LQ, Burgio MA, de Castro Carpeno J, et al. Five-year outcomes from the randomized, phase III trials checkmate 017 and 057: nivolumab versus docetaxel in previously treated non-small-cell lung cancer. *Journal of Clinical Oncology*. 2021;39(7):723.
- [31] Motzer RJ, Escudier B, George S, Hammers HJ, Srinivas S, Tykodi SS, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. *Cancer*. 2020;126(18):4156-67.
- [32] Burtneß B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet*. 2019;394(10212):1915-28.
- [33] Harrington KJ, Burtneß B, Greil R, Soulières D, Tahara M, de Castro G, et al. Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study. *J Clin Oncol*. 2023;41(4):790-802. doi: 101200/JCO2102508 Epub 2022 Oct 11 PMID: 36219809; PMCID: PMC9902012. 2023.