

Immune Checkpoint Inhibitor Duration in Advanced Solid Tumors: Should Treatment Stop at Two Years?

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Dear Editor,

Immune checkpoint inhibitors (ICIs) have transformed the natural history of several advanced/metastatic malignancies, producing durable responses that may persist after therapy is stopped. Yet the optimal treatment duration remains uncertain. This article addresses treatment duration only in the advanced/metastatic setting; adjuvant, consolidation, and other curative-intent settings have different therapeutic objectives, relapse risks, and trial-defined durations and should not be extrapolated directly to metastatic disease [1].

The widely used two-year duration is largely protocol-derived. Several pivotal pembrolizumab trials capped treatment at 35 cycles (approximately two years), whereas early nivolumab studies generally continued therapy until progression or unacceptable toxicity [2,3]. These designs established effective regimens, but they did not demonstrate that two years is a biologically optimal stopping point. Conversely, absence of evidence that two years is biologically necessary should not be confused with evidence that earlier discontinuation is equivalent to continuation.

Prospective randomized evidence, although sparse, provides the most direct basis for causal comparison. In CheckMate 153, patients with previously treated advanced non-small-cell lung cancer (NSCLC) who remained on nivolumab at one year were randomized to continuous treatment or a one-year fixed duration. Among patients who were progression-free at randomization, median progression-free survival was 24.7 versus 9.4 months in favor of continuation (HR 0.56; 95% CI 0.37–0.84), and overall survival also favored continued therapy [4]. However, the duration comparison was exploratory: the study was not powered for efficacy, only 252 of 1,428 treated

patients were randomized at one year, response status was not a randomization stratification factor, and radiographic assessments were not centrally blinded. These limitations materially constrain precision and generalizability. Thus, CheckMate 153 argues against assuming that stopping at one year is equivalent to continuation, but it neither defines an optimal duration nor answers whether treatment beyond two years is necessary.

More recent randomized de-escalation trials further illustrate both the feasibility and the difficulty of duration research. In metastatic melanoma, the phase III DANTE trial randomized patients who were progression-free after one year of first-line anti-PD-1-based therapy to stop treatment or continue for at least two years. Recruitment was slow and the study closed after only 166 of a planned 1,208 patients were randomized. One-year progression-free survival after randomization was 87.6% with continuation and 80.2% with discontinuation (HR 1.76; 90% CI 1.03–3.03). Because enrollment fell far short of the planned sample size, statistical power and precision were substantially reduced, and the findings cannot establish non-inferiority of stopping at one year [5]. In advanced NSCLC, the randomized IFCT-1701 DICIPE trial evaluated stopping nivolumab plus ipilimumab after six months versus continuation among patients with disease control. Only 71 patients were randomized before premature closure; median progression-free-survival follow-up was 47.8 months. At four years, no statistically significant survival disadvantage was detected with discontinuation; however, given the limited sample size and premature closure, this finding should not be interpreted as evidence of equivalent survival. Grade 3–5 treatment-related adverse events were lower and time to definitive quality-of-life deterioration was longer in the discontinuation arm [6]. The very small randomized sample,

premature closure, and regimen-specific design preclude a definitive non-inferiority conclusion. The ongoing phase II/III DIAL trial (NCT05255302) is evaluating discontinuation of pembrolizumab maintenance after six months of chemoimmunotherapy induction versus continuation and may provide more definitive evidence in NSCLC [7].

Observational evidence should be interpreted separately from randomized evidence because treatment duration is selected rather than assigned. In a US cohort of patients with advanced NSCLC who were progression-free after approximately two years of frontline ICI-based therapy, no statistically significant overall-survival difference was observed between patients who stopped at two years and those who continued beyond two years (adjusted HR for death 1.33; 95% CI 0.78–2.25) [8]. However, non-random treatment selection, residual confounding, potential misclassification of reasons for treatment cessation, and restriction to patients remaining progression-free at the two-year landmark limit causal inference. Crucially, failure to detect a statistically significant difference in an observational cohort represents absence of evidence for a difference; it is not evidence of equivalence or proof that outcomes are the same. Taken together, current evidence does not support a single universal duration rule across tumor types or regimens. Results from melanoma cannot automatically be applied to NSCLC, renal-cell carcinoma, or other advanced/metastatic solid tumors; likewise, PD-1 monotherapy, chemoimmunotherapy, and combined CTLA-4/PD-1 blockade should be considered separately.

In advanced/metastatic disease, toxicity is similarly regimen- and time-dependent. With combined CTLA-4/PD-1 blockade, severe immune-related adverse events (irAEs) often occur during the early combination-induction period, whereas with PD-1/PD-L1 monotherapy new events may arise throughout treatment and occasionally after discontinuation. Some endocrinopathies, inflammatory arthritis, neurologic events, and other toxicities can become chronic and persist despite stopping therapy [9]. Therefore, prolonged exposure should not be described simply as causing a linear accumulation of toxicity; rather, the incremental risk depends on regimen, prior toxicity, organ system, and treatment duration.

Treatment duration also has patient-centered consequences that are not captured by survival endpoints alone. Repeated infusions, travel, time away from work or caregiving, financial burden, cumulative monitoring, and anxiety related to either continuing or stopping therapy may influence preferences in different directions. These preferences should be elicited explicitly when evidence does not clearly favor one duration strategy. The DICIPLE quality-of-life signal favoring discontinuation is clinically relevant but, given the small sample, should be considered hypothesis-generating rather

than definitive [6]. Future duration trials should treat quality of life, treatment burden, and patient-reported outcomes as core endpoints rather than ancillary measures.

At the same time, durable disease control after treatment cessation is well documented in selected patients. A pooled analysis of nivolumab plus ipilimumab trials in advanced melanoma showed similar efficacy outcomes among patients who discontinued during induction because of adverse events and those who did not discontinue for adverse events [10]. In the extended treatment-free survival analysis of CheckMate 067, at 60 months 39%, 24%, and 11% of patients assigned to nivolumab plus ipilimumab, nivolumab, and ipilimumab, respectively, were alive and treatment-free [11]. Treatment-free survival analyses from CheckMate 214 in renal-cell carcinoma likewise demonstrate that a proportion of patients can remain alive and free of subsequent systemic therapy after ICI cessation [12]. These observations support investigation of planned discontinuation, but they do not establish a universal stopping time.

Dose optimization and treatment-duration optimization should also be kept conceptually distinct. Pharmacokinetic and receptor-occupancy data for nivolumab demonstrate substantial PD-1 target engagement at low doses and a relatively flat exposure-response relationship across clinically evaluated dose ranges; however, such findings cannot establish that therapy can safely be stopped earlier [13]. Accordingly, region- or ethnicity-specific dosing observations should not be used as evidence for shorter treatment duration without direct clinical outcome data.

Biomarkers may ultimately improve patient selection for ICI discontinuation in advanced/metastatic disease, but the evidence remains preliminary. In melanoma cohorts, detectable circulating tumor DNA (ctDNA) around treatment cessation has been associated with subsequent progression, whereas undetectable ctDNA has correlated with more favorable treatment-free outcomes [14,15]. A negative plasma result, however, does not exclude residual disease: sensitivity varies by assay, tumor burden, anatomic site, and tumor shedding, and central-nervous-system-only progression may be missed. No assay platform, analytical threshold, or required sequence of negative samples has been prospectively validated as an ICI-stopping rule [14,15].

Functional imaging should be interpreted with similar caution. Complete metabolic response on 18F-FDG PET/CT is potentially informative, but immune-mediated inflammation, pseudoprogression, and sarcoid-like reactions can produce FDG uptake that mimics residual or progressive malignancy [16,17]. Thus, neither negative ctDNA nor PET negativity is currently validated as a stand-alone criterion for stopping ICI therapy in advanced/metastatic solid tumors.

Rather than proposing a new fixed interval such as 18 months, a more defensible framework is to test biomarker-informed discontinuation prospectively. Such studies should stratify by tumor type and treatment regimen, define the depth and duration of response, prespecify ctDNA methodology and sampling intervals, incorporate appropriate imaging criteria, capture chronic and late irAEs, and include treatment-free survival, quality of life, patient-reported treatment burden, health-economic outcomes, and outcomes after rechallenge. Rechallenge itself remains feasible in selected patients, but response rates are heterogeneous and available evidence is dominated by non-randomized studies [18].

In conclusion, in advanced/metastatic solid tumors, two years remains a trial-derived convention rather than a biologically validated stopping point. Randomized data do not justify assuming that shorter therapy is equivalent to continuation, while observational studies suggesting similar outcomes after stopping at two years cannot establish equivalence. Biomarker-guided discontinuation using ctDNA, PET/CT, or other tools remains investigational and should be evaluated prospectively rather than used as routine stand-alone guidance.

Conflict of Interest

None declared.

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