Is It Safe to Stop Anti–PD-1 Immunotherapy in Patients With Metastatic Melanoma Who Achieve a Complete Response?

Michael A. Davies, MD, PhD[1]

The long-term survival of patients with metastatic melanoma has improved dramatically over the last decade. Importantly, melanoma was one of the first diseases to demonstrate that long-term cures with immunotherapy are possible in patients with stage IV disease, based on clinical trials of high-dose interleukin-2 (HD IL2) and the anti–cytotoxic T-cell lymphocyte-4 (CTLA4) checkpoint inhibitor ipilimumab.[1,2] HD IL2 and ipilimumab can achieve these durable responses in survival despite the fact that treatment with these agents is completed in 3 months or less, providing the proof of concept that the clinical benefit of immunotherapy can endure for years after active treatment has ceased. However, HD IL2 and ipilimumab incur a significant rate of severe toxicities and have response rates of < 20%. Thus, the development of anti–programmed death (PD)-1 immunotherapy was a tremendous breakthrough, because clinical trials with both pembrolizumab and nivolumab reported clinical response rates of approximately 40% in patients with treatment-naïve stage IV melanoma with low rates of high-grade toxicities. Recent reports have confirmed that most of these responses are ongoing 5 years after the start of treatment.[3-5] In contrast to the short duration of HD IL2 and ipilimumab therapy, anti–PD-1 antibodies are administered for up to 2 years, because this was the treatment duration used in registration studies. In addition to growing evidence demonstrating durable benefit from anti–PD-1 therapy after treatment cessation, recent studies support that shorter treatment may be appropriate for a subset of patients.

In the KEYNOTE-001 clinical trial, durable responses after early treatment cessation were reported in patients with metastatic melanoma who had achieved a complete response (CR) with pembrolizumab.[6] Although the initial design of this trial did not mandate a specific duration of therapy, a trial amendment allowed for treatment cessation for patients who had achieved a CR if they had received ≥ 6 months of treatment and had at least 2 treatments after confirmation of CR. Among 105 patients with a confirmed CR, 67 chose to stop treatment and were subsequently observed. Those patients received a median of 24 months of treatment, with most receiving at least 12 months. With a median follow-up of 30 months since CR, 63 (94%) of the 67 patients remained disease free. A recent update of KEYNOTE-001 after a minimum of 5 years of follow-up reported that 61 (91%) of the 67 patients remained free of disease.[4] The 5-year analysis of patients treated with pembrolizumab for 2 years in the KEYNOTE-006 trial provides additional evidence of durable benefit after cessation of anti–PD-1 therapy. Among the 103 patients who completed 2 years of treatment, after an additional 2 years of follow-up, the progression-free survival rate was 78.4% (95.9% overall survival rate), including 85.4% for patients who achieved a CR and 82.3% for partial responses (PRs).[3] Both reports indicated that for CR patients who stopped treatment and subsequently relapsed, retreatment with anti–PD-1 therapy could be effective. Responses were reported in 2 of 4 CR patients in KEYNOTE-001 retreated with pembrolizumab after progression and in 4 of 5 assessable CR patients in KEYNOTE-006.

These data have generated tremendous interest in the safety and long-term outcomes with early treatment cessation in patients with metastatic melanoma who achieve a CR with anti–PD-1 therapy. In the article that accompanies this editorial, Betof Warner et al[7] present the outcomes of a large cohort of patients with metastatic melanoma treated with anti–PD-1 that had follow-up for at least 3 months after treatment discontinuation. The cohort largely consisted of patients treated outside of clinical trials, thus reflecting the flexibility and variability of clinical practice. The investigators focused first on the outcomes of patients who discontinued treatment after achieving a CR, which was defined as (1) being free of radiographic evidence of disease; (2) having evidence of disease after radiographic response, with a biopsy that showed no evidence of viable tumor; or (3) achieving complete regression of disease in the absence of radiographically measurable tumors. Patients with uveal melanoma were excluded. A total of 396 evaluable patients were identified, which included 102 (25.8%) patients classified as having a best response of a CR before treatment cessation. The median time to treatment failure for CR patients has not been reached, and the probability of being alive without additional therapy at 3 years was 72.1%. Although this supports that the majority of the CR patients continued to do well, the

rate of progression after treatment discontinuation for CR appears higher than that observed in KEYNOTE-001 and KEYNOTE-006. Notably, the median duration of treatment of the CR patients in this cohort was 9.4 months, significantly shorter than in the KEYNOTE-001/-006 cohorts, and the median duration of treatment after achieving a CR was 0 months. The investigators did not identify a significant association between the duration of anti–PD-1 treatment before CR and the risk of subsequent treatment failure in this cohort. However, a recent report by Jansen et al[8] that characterized 117 CR (by immune-related response criteria) patients that electively discontinued anti–PD-1 therapy (median treatment duration, 11 months) did identify a significantly increased risk of subsequent relapse in patients treated with anti–PD-1 treatment for < 6 months versus > 6 months. Warner et al[7] also report that among CR patients in their cohort who subsequently relapsed, only 1 (12.5%) of the 8 patients responded to subsequent single-agent anti–PD-1 (1 of 2 responded to anti–PD-1 plus anti-CTLA4). In the article by Jansen et al,[8] 4 of 9 (44%) patients who relapsed after a CR responded to anti–PD-1 retreatment.

The data across these studies supports that the majority of patients who achieve a CR with anti–PD-1 therapy have good outcomes after treatment discontinuation. However, together, the data suggest that the development of criteria for stopping treatment could be improved and merits additional investigation. In this new cohort, the criteria for CR differed from the clinical trial criteria used in the other cohorts and suggests that even patients without complete radiographic resolution of lesions can be free of disease. This conclusion is supported by the favorable post-treatment cessation outcomes of patients with PRs in KEYNOTE-006, as well as data from neoadjuvant immunotherapy trials in which patients have been noted to have pathologic CRs without complete radiographic responses.[9] This cohort also appears to differ from others in that the patients received, on average, shorter duration of treatment, particularly after achieving a CR. Although it remains unknown whether longer treatment yields additional benefit, review of individual patient data across the studies demonstrates that many patients with short duration of treatment remain disease free. A prospective randomized discontinuation study in CR patients could provide important information and is supported by results observed in the CheckMate 153 trial in patients with non–small-cell lung cancer.[10] However, additional analyses of existing data and biospecimens could also be helpful. Collaborative efforts to pool data from the available cohorts would empower analyses to determine whether baseline factors influence subsequent relapse risk. It should also be determined whether detection of minimal residual disease through blood-based analysis of circulating tumor cells or circulating tumor DNA, which has proven valuable in other cancers, could predict risk of relapse in patients with melanoma with CRs. The association of immune-related adverse events, which often result in treatment cessation, with better outcomes with anti–PD-1 therapy in patients with stage IV disease also supports the rationale for the continued search for biomarkers of immune activation that could signify long-term benefit and, thus, safe treatment discontinuation.[11] Notably, insights into/predictors of durable benefit in patients with stage IV disease should also be interrogated in patients with melanoma receiving adjuvant anti–PD-1 treatment for stage III disease, which is given for up to 12 months without a particular rationale.

The compendium of available data also supports that retreatment with anti–PD-1 therapy can be effective for patients who relapse after a CR, but not all patients will respond. Indeed, the response rates are particularly low in this new cohort, but much higher in KEYNOTE-006. Although response rates have been reported in each cohort, there is currently no information available about whether factors that predict response in treatment-naïve patients (ie, serum lactate dehydrogenase, tumor burden, PD-ligand 1 expression) also correlate in this setting. Such analyses will again benefit from pooling data because of the small number of patients reported in each study. Perhaps most importantly, obtaining biospecimens at the time of relapse to determine whether predictive molecular or immune features can be identified and targeted holds the greatest promise for improving outcomes.

In summary, patients with metastatic melanoma who achieve a CR with anti–PD-1 therapy have excellent long-term outcomes that endure for years after treatment discontinuation in the majority of patients. However, relapses are possible. In the absence of prospective trial data, the available data support discussions with patients who achieve CR about the potential risks and benefits of treatment cessation after 6 to 12 months of treatment and with continued treatment until the CR is confirmed. The opportunity for additional research to optimize the management and outcomes of these patients reflects how far this field has come and the novel questions that are emerging in the new landscape of this disease.

AFFILIATION

[1]Department of Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR

Michael A. Davies, MD, PhD, Department of Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0430, Houston, TX 77030; e-mail: mdavies@mdanderson.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Michael A. Davies
Consulting or Advisory Role: GlaxoSmithKline, Genentech, Novartis, Sanofi, Vaccinex, Bristol-Myers Squibb, Syndax, NanoString Technologies, Array BioPharma
Research Funding: GlaxoSmithKline (Inst), Genentech (Inst), AstraZeneca (Inst), Merck (Inst), Oncothyreon (Inst), Myriad Genetics (Inst), Sanofi (Inst)

No other potential conflicts of interest were reported.