Editorial Commentary

CheckMate-915: does adjuvant CTLA-4 blockade play a role in resected melanoma?

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The CTLA-4 inhibitor ipilimumab is a vital component of the treatment armamentarium for patients with unresectable stage III/IV melanoma. Ipilimumab was Food and Drug Administration (FDA) approved in 2011 after demonstrating a survival benefit in advanced melanoma (1). The PD-1 inhibitor pembrolizumab subsequently prolonged overall survival (OS) compared to ipilimumab and was approved in 2014, as was nivolumab (2). Since then, PD-1 inhibitor-based therapies have persisted as the standard of care for advanced melanoma, often with the use of immune checkpoint inhibitor (ICI) doublets such as ipilimumab plus nivolumab, approved in 2015, or nivolumab plus the LAG-3 inhibitor relatlimab, approved in 2022 (3,4). The success of ICI for patients with unresectable stage III/IV melanoma has led to investigation of these agents in earlier stages of disease, on the assumption of biological equivalence between residual microscopic versus macroscopic disease.

In resected stage III melanoma, adjuvant ipilimumab was initially studied at 10 mg/kg and improved recurrence-free survival (RFS) and OS compared to placebo (5). Subsequently, adjuvant PD-1 inhibition with pembrolizumab versus placebo (6), pembrolizumab versus interferon or ipilimumab (7), and nivolumab versus ipilimumab (8) improved RFS in resected stage III, IIIA(N2)-IV, and IIIB-IV melanoma, respectively. It is unknown whether the addition of adjuvant ipilimumab to nivolumab can improve outcomes in resected stage III/IV melanoma, however the benefit is clear in advanced melanoma. Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg has numerically doubled OS compared to nivolumab monotherapy, as demonstrated in the 6.5 years follow-up of CheckMate-067 (3,9). Therefore, the purpose of CheckMate-915 by Weber *et al.* was to determine whether adjuvant ipilimumab plus nivolumab could improve RFS compared to adjuvant nivolumab monotherapy, which we review in this editorial. The study was entitled "Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma" and was published in the *Journal of Clinical Oncology* in September 2022 (10).

In CheckMate-915, there was no improvement in RFS for patients with resected stage IIIB-IV melanoma treated with combination therapy compared to adjuvant anti-PD-1 alone, the standard of care. Nor were there any differences in RFS for any of the examined subgroups, including stage. Twenty-four-month RFS was 64.6% in the combination group and 63.2% in the nivolumab group, which was unexpected given the superior activity of the combination in the metastatic setting (10). Importantly, the chosen ipilimumab dose in the trial was 1 mg/kg every 6 weeks. This dose and dosing interval has not been previously studied in melanoma and is a lower and less frequent dose than the standard 3 mg/kg administered every 3 weeks for up to 4 doses in advanced disease. The ipilimumab dosing

in CheckMate-915 was selected in an attempt to mitigate toxicity risk in a patient population with no evidence of macroscopic disease and in which a proportion might be cured by surgery alone. It had also been investigated in other tumor types such as muscle-invasive bladder cancer and metastatic renal cell carcinoma, in which higher doses of ipilimumab administered in earlier phase trials had not been well tolerated (11,12).

The lack of RFS benefit seems to be a result of ipilimumab being administered at too low a dose and too infrequently to achieve adequate drug exposure. Multiple studies in melanoma have demonstrated that both activity and toxicity from ipilimumab are dose dependent. In the metastatic setting, ipilimumab dose escalation from 0.3 to 3 to 10 mg/kg every 3 weeks numerically improved OS survival rates (not all studies were powered to compare the doses) and clearly increased toxicity rates (13,14). In a randomized trial in the frontline setting, ipilimumab 10 versus 3 mg/kg every 3 weeks resulted in improved median OS (15.7 *vs.* 11.5 months) but an almost doubling of grade 3-4 treatment-related adverse events (TRAEs) (34% *vs.* 18%) (14). ECOG1609 attempted to address the question of 10 mg/kg ipilimumab versus 3 mg/kg ipilimumab (versus interferon) in the adjuvant setting for melanoma (15). Eight deaths were observed on 10 mg/kg ipilimumab arm, leading to hesitation regarding use of a potentially lethal regimen in patients who might be cured from surgery alone. Alternate doses of ipilimumab when combined with nivolumab have been investigated in melanoma and other tumor types in the metastatic setting. In CheckMate-511, flipped dosing with ipilimumab 1 mg/kg plus nivolumab 3 mg/kg every three weeks was compared to the standard melanoma regimen of ipilimumab 3 mg/kg with nivolumab 1 mg/kg in the first four cycles, and the lower dose of ipilimumab was associated with a lower grade 3–4 TRAE rate of 33.3%, however the trial was not designed to show non-inferiority in efficacy of this dosing regimen (16).

A balance must be achieved between reaching the highest potential for efficacy and minimizing the risk of high-grade toxicity, which cannot be underemphasized in the adjuvant setting. In CheckMate-915, the rate of grade 3–4 TRAEs was almost tripled in the combination group *vs.* the nivolumab group (32.6% *vs.* 12.8%) and four patients in the combination group died from TRAEs. We note that in other adjuvant trials with anti-PD-1 monotherapy, deaths have occurred with anti-PD-1 alone (7). More patients treated in the combination group versus the nivolumab group discontinued treatment early for toxicity (34.6% *vs.* 11.3%) which resulted in a shorter median duration of therapy (7.6 *vs.* 11.1 months) and a lower cumulative nivolumab dose (3,840 *vs.* 6,240 mg) for the patients treated with combination therapy. However, while the optimal duration of therapy is unknown, early discontinuation of therapy alone does not fully explain the lack of RFS difference. RFS rates were similar for patients who discontinued treatment within 6 months of starting therapy compared to those who did not (74.9% *vs.* 79.6%) (10).

In addition to the numerical ipilimumab dose, the optimal number of cycles of combination therapy is also unclear. In the phase II ADAPT-IT trial, patients treated with combination ipilimumab plus nivolumab who had a favorable early response after 2 cycles had the third and fourth cycles omitted and proceeded directly to nivolumab monotherapy. The efficacy here appeared similar to that of the 4-cycle regimen and toxicity was similar whether 2 or 4 doses were administered (17). While this approach is not possible in the adjuvant setting, it has merit in the neoadjuvant setting in which two cycles of flipped dose ipilimumab plus nivolumab in patients with resectable stage III melanoma have resulted in high pathologic response rates of 72–77% in the PRADO (18) and OpACIN-neo trials (19). Although these studies were small, they may suggest that early upfront and more frequent ipilimumab dosing is what is needed to confer improved activity, as opposed to the approach taken in CheckMate-915 (19).

The question of frequency of dosing might also be important in melanoma. The anti-CTLA-4 antibody tremelimumab was administered every 12 weeks in advanced melanoma, with insufficient benefit when compared to chemotherapy in a randomized trial, raising the question of whether more frequent dosing is necessary to increase efficacy (20). Several other CTLA-4 inhibitors are currently under investigation in multiple tumor types, at varying doses and timing intervals. Quavonlimab, for example, was administered as 25 mg every 6 weeks in patients with anti-PD-1 resistant unresectable melanoma, however response rates in combination with pembrolizumab or as monotherapy (9% *vs.* 3%) were lower than those demonstrated for ipilimumab 3 mg/kg every 3 weeks in the same clinical settings (21).

Although CheckMate-915 shows no benefit for the adjuvant dosing of ipilimumab every 6 weeks, there are data suggesting potential benefit for adjuvant ipilimumab plus nivolumab at standard dosing. The IMMUNED trial treated patients with resected stage IV melanoma with adjuvant conventional dose ipilimumab plus nivolumab *vs.*

nivolumab *vs.* placebo and showed improved 4-year RFS for the combination (64.2%, 31.4%, 15%, respectively) (22). Additionally, several small pilot studies have demonstrated potential benefit for adjuvant ipilimumab plus nivolumab. In another study, patients with resected stage IIIB/C-IV melanoma were randomized to induction therapy with either conventional dose or flipped dose ipilimumab plus nivolumab (23). Rates of recurrence were similar at roughly 30% and 5-year RFS and OS for all patients was 71% and 94%, respectively (23). However, the potential added benefit of higher doses of ipilimumab need to be weighed against the higher risk of toxicity, particularly in the adjuvant setting.

In the absence of validated biomarkers that can accurately select patients most likely to benefit from adjuvant therapy, and/or from ipilimumab specifically, the optimal dosing, frequency, and duration of ipilimumab continues to remain an unanswered question, although 1 mg/kg every 6 weeks in the adjuvant setting is clearly too low. Selection of the ipilimumab plus nivolumab regimen in advanced melanoma is typically indicated for patients with poorer prognostic features such as high tumor burden, elevated lactate dehydrogenase, the presence of liver and/or brain metastases, *BRAF* mutated melanomas, and in more aggressive melanoma subtypes such as acral, mucosal, and ocular melanomas. CheckMate-915 did not identify any subgroup of patients who might benefit from the addition of adjuvant ipilimumab. Importantly, the investigators attempted to stratify patients using PD-L1 as a biomarker, expecting greater benefit in patients with PD-L1 negative tumors than positive tumors, as suggested by prior analyses of Checkmate 067. However, there was no difference in 24-month RFS rates for the PD-L1 <1% population by treatment arm (53.6% *vs.* 52.4%). This result confirms the urgent need for improved biomarkers to select patients in the greatest need for the most aggressive therapies, those with no need for adjuvant therapy, and those who will likely be cured with anti-PD-1 alone.

Other pre-defined baseline characteristics known to predict outcome in resected melanoma were also assessed in Checkmate 915. No benefit was found in the combined therapy arm versus monotherapy in patients with higher stage disease [resected stage IV (63.6% *vs.* 61.1%) despite data from the IMMUNED trial] (22). Further study may be warranted to understand whether groups at particularly high risk of recurrence (which may include resected acral and mucosal melanomas, and patients with resected or treated brain metastases without extracranial disease) may benefit from adjuvant ipilimumab plus nivolumab at standard dosing. These subgroups were not specifically studied in Checkmate 915.

The mechanism of action of anti-CTLA-4 has been widely studied but has yet to be fully defined. In theory, CTLA-4 inhibition early in the immune cascade should be key for T-cell priming and proliferation and activation of effector and regulatory T-cells. Neoadjuvant trials, such as OpACIN (24), which compared neoadjuvant to adjuvant ipilimumab plus nivolumab, have shown a greater expansion of new and existing tumor resident T-cell clones and an overt primary tumor response. This may suggest that neoantigens derived from the primary tumor may augment the immune-priming reaction and immune response against distant micrometastases. Hence, lack of sufficient antigen burden in the micrometastatic setting may attenuate the effect of adjuvant anti-CTLA-4 therapy, potentially contributing to the negative results. Measuring residual disease using circulating tumor DNA may be able to address the challenges of adjuvant trials in demonstrating increased efficacy in the addition of CTLA-4 blockade. Nonetheless, it remains to be determined whether the addition of anti-CTLA-4 inhibitors to PD-1 inhibition is as effective in microscopic disease as it is in advanced disease.

Currently, the management of stage III/IV resectable melanoma remains in a state of flux. It is still unknown whether neoadjuvant therapy, adjuvant therapy, both, or simple observation followed by salvage therapy at the time of unresectable relapse should prevail in the treatment of resectable melanoma. Although the death rate in this trial was low, one could argue that any deaths in the adjuvant setting are unacceptable. Other potentially life-altering adverse events occur in patients treated on ICI. For example, the incidence of hypophysitis on the dual therapy arm was reported as 10.5% and 1.6% on the monotherapy arm. Given the irreversible nature of hypophysitis, combined with the implications for fertility, combatting severe illness, and managing trauma, the potential for development of these toxicities remains an important consideration when administering adjuvant therapy. The gold-standard clinical trial endpoint of OS is challenging given the availability of highly active and potentially curative salvage therapies for subsets of patients. Neoadjuvant approaches are rapidly being adopted in clinical practice for patients with clinical stage III melanoma and trials are looking to determine how much adjuvant therapy, if any, should be given after neoadjuvant therapy based upon pathologic response criteria. The phase III NADINA trial is evaluating a crucial

clinical question, whether to approach resectable melanoma with neoadjuvant therapy followed by surgery and response-driven adjuvant therapy, or to perform upfront surgery followed by adjuvant therapy. Incorporation of ctDNA may also be able to identify patients at particularly high risk of recurrence who would benefit from more intensive therapy interventions. In CheckMate-915, patients who were ctDNA positive after resection had increased rates of recurrence, independent of treatment arm, and many studies moving forward are incorporating ctDNA status (25). Moreover, as new treatment regimens emerge for advanced melanoma, the question of adjuvant or neoadjuvant therapy requires constant reassessment. For now, with the negative results of CheckMate-915, adjuvant anti-PD-1 therapy remains the standard of care, although ipilimumab remains an important treatment consideration for any patient with advanced melanoma.

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Footnote

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