editorials

CheckMate-067: Raising the Bar for the Next Decade in Oncology

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Few effective systemic therapies were available for patients with advanced melanoma until recently, although durable complete responses were achieved in a small percentage of patients treated with high-dose interleukin-2. In 2015, results from the phase III CheckMate-067 trial[1] led to US Food and Drug Administration approval of ipilimumab plus nivolumab, the first immune checkpoint inhibitor (ICI) combination for front-line treatment of advanced melanoma.

In the article that accompanies this editorial, Wolchok et al[2] report the 6.5-year efficacy and safety outcomes of CheckMate-067, which studied the combination of ipilimumab plus nivolumab compared with either alone in patients with treatment-naive unresectable stage III or IV melanoma. Although the 6.5-year outcomes are similar to the 5-year follow-up data, the long-term benefit of the combination remains striking, with the survival curves remaining flat eight years after the first patient was enrolled. CheckMate-067 was not powered to compare the combination arm with the nivolumab arm, given the high response rate to nivolumab monotherapy. However, the 6.5-year follow-up highlights the near-doubling of median overall survival (OS) in patients treated with ipilimumab plus nivolumab (72.1 *v* 36.9 months), and although the median duration of response has not been reached in either group, the newly reported melanoma-specific survival was not reached in the combination arm and was 58.7 months in nivolumab-treated patients. In the nivolumab-containing arms, > 80% of patients with a best overall response of complete response were progression-free and alive at 6.5 years. However, more patients treated with ipilimumab plus nivolumab with a best overall response of partial response were progression-free at 6.5 years (77% *v* 61%), suggesting that residual disease on imaging might differ by ipilimumab treatment.

Despite the lack of statistical power to compare nivolumab with the combination, the difference in OS for the ipilimumab plus nivolumab arm is particularly noteworthy considering that 29% of patients in the nivolumab arm received subsequent anti–CTLA-4, which is active in the second-line setting alone or with anti–programmed death-1 (PD-1), with objective response rates of 16% and 21%-29%, respectively.[3,4] Subsequent BRAF and MEK inhibitor therapy in *BRAF*-mutant patients similarly did not result in equalization of the OS. Moreover, we note that the median duration of therapy was shorter in the dual ICI arm (3.6 *v* 8.6 months). Although the optimal duration of therapy is unknown, a previous pooled analysis showed no difference in the outcomes of patients who discontinued treatment because of adverse events (AEs) compared with those who did not discontinue because of AEs.[5]

The optimal sequencing of ICI and targeted therapy in patients with *BRAF*-mutant advanced melanoma is currently under evaluation in the DreamSeq[6] and SECOMBIT randomized controlled trials; however, CheckMate-067 may have already begun to resolve this question. OS for patients with *BRAF* V600-mutant melanoma treated with ipilimumab plus nivolumab has not been reached and is 45.5 months with nivolumab. Despite the pitfalls of cross-trial comparisons, the 5-year median OS for front-line dabrafenib plus trametinib or encorafenib plus binimetinib in *BRAF V600*$^{E/K}$–mutant patients is lower at 25.9 and 33.6 months, suggesting that the greater survival benefit lies with up-front ICI.[7,8] Definitive confirmation is pending the final results of the DreamSeq[6] and SECOMBIT trials, but the improved 2-year OS rates recently reported for frontline dual ICI versus dabrafenib plus trametinib (72% *v* 52%) in DREAMSeq reinforces the CheckMate-067 analysis.[1] However, situations certainly arise in which front-line BRAF and MEK inhibitor therapy is indicated in lieu of ICI, such as in patients with contraindications to ICI or where rapid tumor shrinkage is clinically necessary.

Two major outstanding questions relate to patient selection for these therapies: (1) Who can be treated with anti–PD-1 alone and achieve a similar outcome to the combination but be spared the increased toxicity risks and (2) can alternative regimens such as nivolumab plus the anti–LAG-3 antibody relatlimab be equally effective but less toxic?[9] The development of validated biomarkers to identify patients most in need of the combination is crucial, as toxicity is a key concern and the risk of irreversible and/or life-threatening toxicities cannot be ignored. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 59% of patients on the combination arm versus 24% on nivolumab. Forty-two percent of patients receiving the combination discontinued therapy because of TRAEs, in contrast to only 14% on nivolumab.

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THE TAKEAWAY

In the article that accompanies this editorial, Wolchok et al[2] report the 6.5-year survival and safety outcomes for CheckMate-067, highlighting the long-term durable benefit achieved with anti–programmed death-1–based regimens in advanced melanoma. Despite the drawbacks of toxicity and cost, the median survival on the ipilimumab plus nivolumab arm was double that of nivolumab monotherapy, and treatment-free survival was the longest reported in solid tumor immunooncology, suggesting that this regimen provides a new benchmark to which other regimens should be compared.

Although TRAEs certainly affect quality of life, the vast majority are reversible often with a course of an immunosuppressive agent(s). It is important to note that patients with TRAEs did not have inferior outcomes in general, although the infrequent neurologic or cardiac complications can be irreversible or even fatal.[10]

We note that four treatment-related deaths occurred: two on the combination arm and one on each of the other arms for a drug-related death rate of 0.6%, 0.3%, and 0.3%, respectively, which is on par with or lower than rates reported in a meta-analysis of ICI-associated fatalities[10] and lower than that seen in other tumor types. For example, the treatment-related death rates for nivolumab plus low-dose ipilimumab for renal cell or lung carcinoma in CheckMate-214 and CheckMate-227 were 1.5% and 1.4%, respectively.[11,12] Toxicities can vary across regimens and treatment types, but the superior activity and OS seen in CheckMate-067, combined with the treatment-free survival (TFS), suggest that for the majority of patients, dual ICIs are a viable choice. With over a decade of experience with ICI, the oncology community is well-versed in the recognition and management of immune-related AEs and close communication between patients, the treating oncologist, and medical support staff is key. Ongoing research is focused on strategies to predict and mitigate immune-mediated AEs.

RELATIVITY-047 compared nivolumab plus relatlimab with nivolumab alone.[9] We note that RELATIVITY-047 was conceived before reaching median OS on the nivolumab arm of CheckMate-067. Despite the fact that CheckMate-067 was not designed to compare median OS between dual ICI therapy and nivolumab monotherapy, the impressive long-term survival results presented by Wolchok et al[2] raise the question of the optimal control arm in the front-line setting in melanoma. With the ultimate goal of prolonging OS and minimizing cross-trial comparisons, ipilimumab plus nivolumab should be considered the standard of care to which other drugs and regimens should be compared in the future. Moreover, comparisons between high-grade toxicity rates should be considered when developing these regimens, as nivolumab plus relatlimab appears to be better tolerated.[9]

The impact of CheckMate-067 extends well beyond melanoma, and this trial presents a paradigm for assessing new regimens in the next decade. Phase III trials are typically designed to compare response rates, progression-free survival, and OS, but it is noteworthy to mention that of CheckMate-067 patients who received ipilimumab plus nivolumab and were alive at the data cutoff, 77% are off therapy and never received subsequent therapy. TFS is increasingly recognized as a valuable outcome measure. Prolonged TFS translates into less toxicity to the patient from a physical, psychological, and financial perspective.[13] In CheckMate-067, patients receiving ipilimumab plus nivolumab were treated for a median of only 3.6 months, probably partially attributable to drug discontinuation after the development of high-grade AEs. However, the majority of patients treated with the combination came off treatment and remained off treatment. For other stage IV diagnoses in solid tumor oncology, TFS has been largely unattainable, and for melanoma, it has been attainable only for interleukin-2 and adoptive cell therapy.

We would be remiss not to mention the high cost associated with ICI administration, with financial implications for both the individual patient and society. The estimated total cost per patient in the United States can range from $170,000 US dollars (USD) for anti–PD-1 to an estimated $230,000 USD for the combination.[14] At the ASCO 2015 plenary session where results of CheckMate-067 were initially presented, immunotherapy agents were projected to cost $174 billion USD annually, excluding adjuvant indications.[15] Identifying the ideal duration of therapy and reporting on TFS will become increasingly important to develop and select therapies that are fiscally responsible, without compromising efficacy. Unlike ipilimumab plus nivolumab, continuously dosed regimens are required for most advanced tumor types and the lack of a treatment-free period results in ongoing costs. For example, in renal cell carcinoma, continuous pembrolizumab plus axitinib administration was less cost-effective when compared with ipilimumab plus nivolumab, resulting in higher mean cancer drug-attributable costs ($562,927 *v* $458,961 USD) and extra incremental costs of $172,532 USD per quality-adjusted life years.[16] Future trials should incorporate outcomes such as TFS and up-front versus ongoing costs to determine the value of cancer drugs.[17]

Anti–PD-1-based immunotherapy has converted a historically incurable cancer into a potentially curable disease, with the possibility of long-term survival off treatment. As a regimen, ipilimumab plus nivolumab is arguably a new benchmark to which other regimens should be compared, with attention paid to the aforementioned considerations of toxicity and cost. After 6.5 years of follow-up, durable complete responses have been achieved in record numbers. These results raise the question of whether durable responses may actually be cures. Finally, although these long-term melanoma survival results are unmatched in immunotherapy for solid tumors, at 6.5 years, 43% of patients on the dual-therapy arm had succumbed to their disease, and the focus going forward is to decrease this percentage while striving for prolonged survival off therapy in other tumor types as well.

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