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Nivolumab: Promising Survival Signal Coupled With Limited Toxicity Raises Expectations

Geraldine O'Sullivan Coyne, Ravi A. Madan, and James L. Gulley

National Cancer Institute, Bethesda, MD

Decades of research suggesting an association between tumors and immune tolerance have led to the development of an array of immunotherapeutic strategies to reactivate the adoptive and innate immune system against tumor antigens. Understanding of this association has led to the development of multiple immuno-therapy approaches, including immune checkpoint inhibition. Emerging clinical data, such as those presented in the article by Topalian et al¹ that accompanies this editorial, introduce the possibility that not only can these immunotherapy treatments be added to treatment regimens, but perhaps they can raise survival curves to new heights.

Identified in 1976,² interleukin-2 (IL-2) was the first treatment to show promise in advanced melanoma. Although positive outcomes were limited (approximately 20% response rate, with durable complete responses [CRs] of up to 8%^{3,4}), data were sufficient for the US Food and Drug Administration to approve the use of IL-2 in malignant melanoma in 1998. However, the substantial toxicity profile of IL-2 limited its application to select patient populations in specialized treatment centers. For the next 20 years, essentially palliative treatment options, including dacarbazine, temozolomide, and multiple combination drug regimens, resulted in reports of similar response rates, without the durable CRs seen with IL-2.^{5,6}

Ipilimumab (Yervoy; Bristol-Myers Squibb, Princeton, NJ), an anti-CTLA-4, immunoglobulin G₁ monoclonal antibody, was the first treatment to show improvement in overall survival (OS) in melanoma in randomized trials. Two separate, appropriately powered, randomized controlled trials in previously treated⁷ and untreated⁸ patients with advanced melanoma suggested a 28% to 34% decrease in mortality for patients receiving ipilimumab and a significant improvement in OS compared with the control arms. This landmark breakthrough for cancer immunotherapy led to US Food and Drug Administration approval of ipilimumab for melanoma in 2011, but also brought a novel group of adverse effects that were presumed to be secondary to host immunologic enhancement. These treatment-emergent, immune-related adverse events (irAE), which were associated with inflammation of nontarget tissues, proved to be reversible by cessation of the drug, with or without the addition of glucocorticoids.

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In previously treated patients receiving ipilimumab alone or with an active control (gp100 vaccine), OS was 10.1 months and 10.0 months versus 6.4 months for patients receiving the vaccine alone.⁷ In this second-line setting, an estimated 21.6% to 23.5% of patients treated with ipilimumab were alive at 24 months versus 13.7% of patients in the control group.⁷ In a subsequently reported trial, previously untreated patients had a median OS of 11.2 months versus 9.1 months when treated with ipilimumab with dacarbazine or placebo with dacarbazine, respectively.⁸ Approximately 40% of previously untreated patients who received ipilimumab-dacarbazine were still alive at 1 year, compared with 36.3% in the dacarbazine-placebo group.⁸ At 3 years, an estimated 20.8% of patients were alive in the ipilimumab-dacarbazine group versus 12.2% of patients in the dacarbazine-placebo arm. Both of these phase III ipilimumab trials had different patient populations. The study by Hodi et al⁷ included 676 patients treated with 3 mg/kg of ipilimumab in a second-line setting; 12% of patients had treated brain metastasis and 23% received previous IL-2 therapy. The trial by Robert et al⁸ included 502 previously untreated patients, excluded patients with brain metastasis, ocular melanoma, or previous adjuvant therapy, and used ipilimumab 10 mg/kg induction followed by maintenance therapy.

In the article that accompanies this editorial, Topalian et al¹ report pooled outcomes for their expansion-dose cohort of patients with melanoma treated with nivolumab, a fully human, immunoglobulin G₄ antagonist monoclonal antibody targeting PD-1, an immune checkpoint. Patients had participated in the phase I trial of nivolumab in locally advanced solid malignancies, which was published in 2012.⁹ The safety and outcome data cover a maximum follow-up of 4.3 years, the longest available for patients with melanoma treated with an anti-PD-1 agent. Topalian et al included 107 patients from pooled cohorts (62% had received at least two previous therapies), and included patients with ocular melanoma or clinically stable brain metastasis. Patients receiving nivolumab were enrolled in three dose-escalation cohorts, with dose-escalation permitted within the lower-dose groups at disease progression. The authors' analysis, which was based on findings of durable responses in this patient group, again confirmed noteworthy survival outcomes. Median OS was 16.8 months, with 1- and 2-year survival rates of 62% and 43%, respectively, and an estimated median response of 2 years' duration in patients with confirmed tumor regression (31%). Although the patient populations are different and the currently published data for nivolumab are less than for ipilimumab, the OS signal seen is encouraging.

Perhaps of greater interest is that the toxicity profile of nivolumab seems to compare favorably with the previous clinical experience with ipilimumab, although there are limitations to the comparison. In the first reported phase III ipilimumab trial, grade 3 and 4 irAEs occurred in 10% to 15% of patients treated with ipilimumab and included colitis and endocrinopathies that needed intervention with glucocorticoids or, in four cases, infliximab (an antitumor necrosis factor α antibody).⁷ There were 14 deaths related to the drug (2.1%), and seven were associated with irAEs. With the combination of ipilimumab plus dacarbazine, grade 3 and 4 irAEs were seen in 38.1% of patients versus 4.4% of patients treated with placebo plus dacarbazine; the most common AEs were hepatitis and enterocolitis, with no reported drug-related deaths.⁸ Topalian et al¹ report that the most common AE of any grade was fatigue (32%). Treatment-related select AEs or irAEs of any grade were reported in 54% of the patients, most commonly skin disorders (36%), GI events

(18%), and endocrinopathies (5%). However, grade 3 and 4 treatment-related select events were seen in only 5% of patients. The authors note that 17 patients discontinued therapy because of reasons other than disease progression, but do not specify whether the discontinuation was a result of treatment toxicity. There were no drug-related deaths in the population with melanoma (although, among 306 patients, there was a total of three episodes of grade 5 pneumonitis with this drug, all in patients without melanoma). It should be noted that with increased awareness of the unique irAEs seen with these immune checkpoint inhibitors, appropriate diagnosis and treatment may decrease the morbidity associated with this class of therapy.

An intriguing common denominator in the studies of immune checkpoint inhibitors has been the number of durable CRs or near CRs. The ipilimumab trials show an apparent plateauing of Kaplan-Meier OS curves after approximately 24 months, with survival to 4 or more years of approximately 20%. Topalian et al¹ also note this trend, reporting a flattening of the curve beyond the median for both progression-free survival and OS. This tail in the curve raises questions about how to increase the number of patients who receive long-term clinical benefit from immune checkpoint inhibitor therapy, and how to predict who those patients might be.

The most common strategy for improving outcomes among patients with cancer receiving drug therapy is to increase the dose of the agent. In the study by Topalian et al,¹ it is notable that at 10 mg/kg of nivolumab, there is a suggestion of reduced median progression-free survival and OS compared with lower doses of the drug (0.1, 0.3, and 1 mg/kg; Table 1 of the article by Topalian et al). It is possible that this difference is a result of the limited number of patients in this study along with differences in the baseline characteristics; however, it is also unclear whether patients at higher doses received less treatment because of earlier toxicity. These results raise the possibility that the optimal immunologic dosing may be below a maximum-tolerated dose. Unlike standard pharmaceutical agents, for which maximizing pharmacokinetics generally ensures greatest pharmacodynamic impact, a more bell-shaped response curve has been seen with some biologic agents, and for these agents, higher doses may not have the desired optimal biologic impact. This finding could become an important concept as nivolumab and other immunotherapies move forward in clinical development.

One promising strategy, referred to as immunogenic intensification, combines one immune checkpoint inhibitor with a different immune checkpoint inhibitor or a therapeutic vaccine.¹⁰ In one recent study,¹¹ approximately half of the patients with melanoma receiving the highest dose of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) had dramatic and durable objective responses, although at the cost of an apparent increase in toxicity: half of the patients experienced grade 3 AEs. Hypothetically, vaccine therapy could have a priming or steering effect on the immune system, potentially intensifying the effects of combination therapy.^{12,13} This could result in a more efficient, tumor-directed immune response, potentially reducing the need for higher doses of immune checkpoint inhibitor or multiple immune checkpoint inhibitors and lessening the risk of inducing autoimmunity. Such approaches may have the potential to improve clinical outcomes while minimizing adverse effects.

The continued demonstration of promising clinical outcomes with the use of modern immunotherapy strategies such as nivolumab may allow medical oncologists to have raised expectations for patients with metastatic cancer. Current treatment for meta-static solid tumors, apart from rare exceptions such as testicular cancer, remains palliative, but perhaps immune checkpoint inhibitors can be part of a strategy to enhance the number of patients who can enjoy sustained, durable responses. The data presented by Topalian et al¹ suggest that nivolumab could have clinical benefits similar to those of ipilimumab, but with less toxicity. A limited AE profile could be critical to deploying immunotherapy earlier in the adjuvant setting (perhaps in combination with antigen-specific vaccines). Initiating an ongoing, dynamic immune response with minimal tumor burden early in the disease course could allow for a sustained antitumor immune response long after treatment is discontinued, perhaps magnifying the proportion of durable responses seen in the metastatic setting. If future clinical trials validate the findings that have been seen in recent years, perhaps immunotherapy will not just raise expectations, but the all-important survival tail of Kaplan-Meier curves as well.

REFERENCES

1. Topalian SL, Sznol M, McDermott DF, et al.: Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 32:1020–1030, 2014 [PubMed: 24590637]
2. Morgan DA, Ruscetti FW, Gallo R: Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 193:1007–1008, 1976 [PubMed: 181845]
3. Atkins MB, Lotze MT, Dutcher JP, et al.: High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 17:2105–2116, 1999 [PubMed: 10561265]
4. Atkins MB, Kunkel L, Sznol M, et al.: High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: Long-term survival update. *Cancer J Sci Am* 6:S11–S14, 2000 (suppl 1) [PubMed: 10685652]
5. Chapman PB, Einhorn LH, Meyers ML, et al.: Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 17:2745–2751, 1999 [PubMed: 10561349]
6. Middleton MR, Grob JJ, Aaronson N, et al.: Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 18:158–166, 2000 [PubMed: 10623706]
7. Hodi FS, O'Day SJ, McDermott DF, et al.: Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363:711–723, 2010 [PubMed: 20525992]
8. Robert C, Thomas L, Bondarenko I, et al.: Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 364:2517–2526, 2011 [PubMed: 21639810]
9. Topalian SL, Hodi FS, Brahmer JR, et al.: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 366:2443–2454, 2012 [PubMed: 22658127]
10. Weber JS, Kudchadkar RR, Yu B, et al.: Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naïve melanoma. *J Clin Oncol* 31:4311–4318, 2013 [PubMed: 24145345]
11. Wolchok JD, Kluger H, Callahan MK, et al.: Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 369:122–133, 2013 [PubMed: 23724867]
12. Madan RA, Mohebtash M, Arlen PM, et al.: Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: A phase 1 dose-escalation trial. *Lancet Oncol* 13:501–508, 2012 [PubMed: 22326924]
13. van den Eertwegh AJ, Versluis J, van den Berg HP, et al.: Combined immuno-therapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and

ipilimumab in patients with metastatic castration-resistant prostate cancer: A phase 1 dose-escalation trial. *Lancet Oncol* 13:509–517, 2012 [PubMed: 22326922]

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