INTERVIEW

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Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: What is your take on the emerging data with BRAF inhibitors in melanoma?

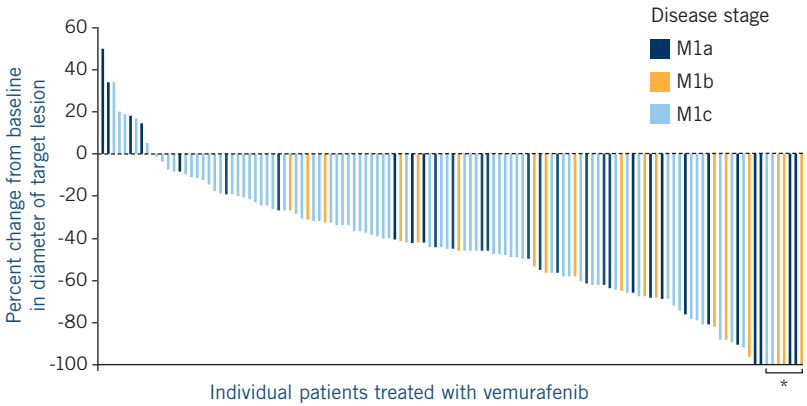
DR WOLCHOK: Once BRAF was identified as important based on the Cancer Genome Project, then various groups started to look for inhibitors of BRAF, the most well studied of those now being vemurafenib. Phase II data have

shown that a patient with a BRAF mutation has a 60 to 70 percent likelihood of experiencing a major response with this agent (Ribas 2011; [2.1]).

Results were also recently announced from the Phase III randomized trial evaluating vemurafenib versus dacarbazine. The authors reported improvements in both progression-free survival and overall survival with the BRAF inhibitor compared to dacarbazine (page 19).

2.1

Antitumor Response in Patients Receiving Treatment on a Phase II Trial of the Oral BRAF Inhibitor Vemurafenib (PLX4032)



*7 confirmed CRs

With permission from Ribas A et al. *Proc ASCO* 2011;**Abstract 8509**.

Track 6

DR LOVE: Would you describe ipilimumab's mechanism of action?

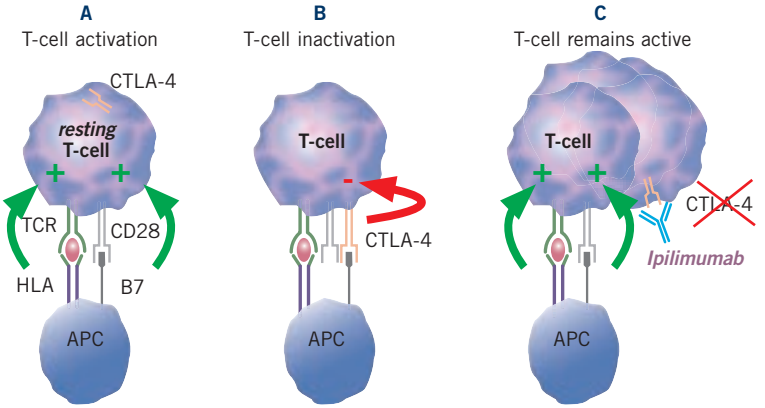
DR WOLCHOK: CTLA-4, a molecule found on the surface of T cells, prevents the overactivation of T cells. Laboratory studies have shown that mice lacking CTLA-4 cannot survive more than three weeks because a lack of CTLA-4 results in T cell-mediated organ destruction. Temporarily blocking CTLA-4 using an antibody such as ipilimumab allows the immune system to work harder than it would otherwise (Wolchok 2011; [2.2]). However, because this is not a permanent blockade — antibodies only have about a two-week half-life — the severe consequences associated with a complete loss of CTLA-4, such as in the mouse studies, are not a serious concern.

Specific side effects are associated with this class of drugs. Two CTLA-4-blocking antibodies, ipilimumab and tremelimumab, have been evaluated in clinical trials and have similar clinical activity and side effects (Hodi 2010; Kirkwood 2010). Ipilimumab has recently received FDA approval for the treatment of metastatic melanoma. Not surprisingly, the side effects are associ-

ated with excessive activation of the immune system. The most common areas affected are the skin and the gastrointestinal tract. With proper vigilant management, these side effects are reversible (Hodi 2010; [2.3]).

2.2

Ipilimumab, a CTLA-4-Blocking Monoclonal Antibody, Augments T-Cell Activation



(A) The antigen-presenting cell (APC) presents a peptide or protein on its cell surface to bind the T-cell receptor (TCR). For T-cell activation, B7 must also bind to CD28, leading to the upregulation of CTLA-4.

(B) CTLA-4 has a higher affinity for B7 than CD28, causing the inhibition of T-cell activation.

(C) Ipilimumab, a fully human monoclonal antibody, blocks CTLA-4 leading to T-cell potentiation.

With permission from Wolchok J et al. *Proc ASCO* 2011;**Abstract LBA5**.

2.3

Incidence and Management of Adverse Events During a Phase III Study of Ipilimumab with or without Vaccine Therapy Compared to Vaccine Therapy Alone in Metastatic Melanoma

"The frequency of grade 3 or 4 immune-related adverse events was 10 to 15% in the ipilimumab groups and 3.0% in the gp100-alone group...the majority of adverse events being immune-related and consistent with the proposed mechanism of action of ipilimumab. As shown in phase 2 studies, prompt medical attention and early administration of corticosteroids are critical to the management of immune-related adverse events. Management guidelines (algorithms) for immune-related adverse events involve close patient follow-up and the administration of high-dose systemic corticosteroids — which were used as necessary in our study — for grade 3 or 4 events."

Hodi FS et al. *N Engl J Med* 2010;262(8):711-23.

Track 7

DR LOVE: Can you comment on the use of corticosteroids for immune-mediated toxicity associated with the use of ipilimumab?

DR WOLCHOK: We're not sure how steroids specifically work to improve the side effect. We know steroids are lympholytic — they kill lymphocytes — and are anti-inflammatory. The real mystery is why steroids interfere with the side effects but heretofore do not interfere with the antitumor effect. The pathway underlying the antitumor activity must differ from the pathway associated with side effects and the observed steroid sensitivity.

DR LOVE: Are the antitumor effects of ipilimumab compromised in a patient who receives concomitant corticosteroids?

DR WOLCHOK: We don't know the exact answer at this time, but I believe timing is important. Administering steroids up front along with anti-CTLA-4 antibodies may be harmful. However, in the treatment of side effects, steroids are used six to 10 weeks later, and that could be why we haven't seen any interference with antitumor effects.

Tracks 8-9

DR LOVE: Would you review some of the unique aspects of evaluating response after immunotherapy for melanoma and what data are available with these agents?

DR WOLCHOK: Response to immunotherapy must be considered differently from response to chemotherapy — we're treating the patient, not the tumor, with immunotherapy. Traditional response criteria evaluate response to chemotherapy, which damages DNA, resulting in tumor shrinkage four to six weeks later.

Tumors may grow before they get smaller with immunotherapy. For this reason, evaluating response at a predetermined empiric time point will prevent the recognition of response in 10 to 25 percent of patients, who will respond later. The traditional paradigm by which new lesions automatically represent disease progression must be reconsidered — with immunotherapy, some tumors may become smaller as a new tumor appears. The new tumor may dissipate later because the immune system takes longer to recognize it.

Based on these facts, we have proposed a new set of response criteria called the Immune-Related Response Criteria. These response criteria do not involve complicated science. Only two distinctions from standard WHO or RECIST criteria are used. The first distinction requires confirmation of disease progression in the same manner in which we usually confirm response. For example, if a patient's tumor has worsened at week 12 according to the imaging results but the patient's condition is not clinically deteriorating and performance status is maintained, the scans should be repeated in four to six weeks. Between 10 and 25 percent of patients will improve in that period. The second distinction states that total tumor burden — that is, new and index lesions — must be considered when response is judged. By contrast, using standard response criteria, treatment is considered a failure if a new tumor appears despite the regression of index lesions.

According to Phase II data with ipilimumab, 24.2 percent of patients are alive two years after diagnosis (Wolchok 2010), which is respectable for a disease with a nine- to 11-month median survival. Phase III data have been published, and according to the standard response criteria, the response rate to ipilimumab was between five and 17 percent. If you include long-term stable disease, the response rate is closer to 25 percent. A slightly longer than three-month improvement in overall survival was reported for patients receiving ipilimumab compared to control. Approximately twice as many patients who received ipilimumab were alive at the landmark time points of one and two years as those who received the vaccine alone (Hodi 2010).

Tracks 10, 12

DR LOVE: Are there any trials evaluating combination immunotherapy in melanoma?

DR WOLCHOK: A molecule called PD-1 is the "emergency brake" on T cells — it mediates programmed T cell death. Not unexpectedly, melanoma cells express the ligand on their surface that causes T cell death. This is the ultimate weapon that a tumor cell can use to defend itself against an attacking T cell, as it has the ligand that triggers apoptosis of an attacking T cell. The antibody that blocks this interaction in trials of melanoma is called MDX-1106. Some encouraging data have been reported in melanoma, renal cell cancer and lung cancer documenting the importance of this PD-1 pathway in the immunobiology of these tumors (Sznol 2010).

At this time, a trial is evaluating the combined use of ipilimumab with MDX-1106 to determine whether the combination will produce a more potent type of tumor immunity. Preclinical models support this rationale. In the ongoing Phase I dose escalation trial, we are carefully evaluating potential synergistic side effects and proceeding cautiously. ■

SELECT PUBLICATIONS

Hodi FS et al. **Improved survival with ipilimumab in patients with metastatic melanoma.** *N Engl J Med* 2010;262(8):711-23.

Kirkwood JM et al. **Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma.** *Clin Cancer Res* 2010;16(3):1042-8.

Ribas A et al. **BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma.** *Proc ASCO* 2011;**Abstract 8509**.

Sznol M et al. **Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies.** *Proc ASCO* 2010;**Abstract 2506**.

Wolchok J et al. **Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma.** *Proc ASCO* 2011;**Abstract LBA5**.

Wolchok JD et al. **Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study.** *Lancet Oncol* 2010;11(2):155-64.