INTERVIEW

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Tracks 1-8

Select Excerpts from the Interview

Tracks 3-6

DR LOVE: Would you discuss current options for immunotherapy in melanoma?

DR SOSMAN: At our center, we administer high-dose IL-2 for healthy patients age 70 years or younger with good organ function and without aggressive disease because we know that a small but real cure rate exists. We would consider ipilimumab for patients with disease unresponsive to IL-2.

We don't administer first-line ipilimumab because of the concern about a late onset of the toxic effects of ipilimumab that could manifest while the patient is receiving IL-2. Although adverse events such as diarrhea, liver problems and rash usually occur earlier, they can occur later on. So IL-2 followed by ipilimumab makes more sense.

Another reason we treat in this manner is because we can determine whether the disease is responding to IL-2 by week 7 or 8. If the disease is progressing at week 8, we have no reason to continue IL-2.

However, it sometimes takes a while to see the full benefit of ipilimumab. Some patients with progressive disease at week 12 see a response at week 20 with tumor shrinkage and regression. With IL-2, I don't consider stable disease a success. I do not continue IL-2 nor do I initiate therapy with ipilimumab for those patients. I watch closely but will administer ipilimumab when the disease progresses.

DR LOVE: How soon after treatment do you observe the toxic effects of ipilimumab?

DR SOSMAN: In the metastatic setting, major toxic effects after the first dose are extremely rare but begin to occur after the second dose, with manifestations within the first 12 weeks. For most patients, rash is manageable and tolerable. In some cases it looks like a typical drug-reaction rash — maculopapular, usually papular. If the rash coalesces, we become much more concerned.

DR LOVE: How do you manage the side effects of ipilimumab?

DR SOSMAN: For the rash, we rarely use corticosteroids systemically, but we may administer them topically. We use antihistamines, including cimetidine, ranitidine and diphenhydramine cream. The rash begins to fade away once ipilimumab is discontinued but worsens after the next dose is initiated. Patients may experience pruritus early on before the second dose.

Some patients may develop colitis. We start monitoring patients early so that we can treat immediately if explosive diarrhea occurs. We'll admit a sick patient and intravenously administer steroids and perform a colonoscopy.

We also observe endocrine-related side effects — thyroiditis, adrenalitis, panhypopituitarism and hypophysitis. Of these, hypophysitis is the most troubling and most frequent issue. We monitor cortisol and thyroid-stimulating hormone levels and thyroid function every 3 weeks to ensure that we don't miss these issues because they can be major causes of severe fatigue.

DR LOVE: How do you initially treat asymptomatic, BRAF-mutant metastatic melanoma?

DR SOSMAN: Asymptomatic patients generally have low-volume disease and normal LDH and usually don't have liver metastases. So we may consider immunotherapy with first-line IL-2 followed by ipilimumab. I've seen cases in which the disease accelerates after progression on a BRAF inhibitor. Many of those patients did not receive a full round of immune therapy. A major concern is that if I start treatment with a BRAF inhibitor, the patient may not be able to receive an immunotherapeutic agent after that.

DR LOVE: How do you manage brain metastases from BRAF-mutant melanoma?

DR SOSMAN: In a situation in which the tumor is small, I administer vemurafenib and wait on local therapy. Although it's difficult to hold off on performing stereotactic radiosurgery for 1 or 2 small isolated lesions because it's easy to do, it's reasonable to monitor the systemic and brain disease closely and if the brain tumor begins to grow and stays isolated treat with stereotactic radiosurgery at that time.

DR LOVE: What are your thoughts on combination therapy with vemurafenib and ipilimumab?

DR SOSMAN: A study combining vemurafenib with ipilimumab in metastatic melanoma had to be discontinued because of hepatitis, the limiting factor (Ribas 2013a). The combination of these agents required dose reductions to an uncomfortable level.

Track 7

DR LOVE: Would you discuss the efficacy and side effects of anti-PD-1 antibodies in melanoma?

DR SOSMAN: Anti-PD-1 antibodies bind to PD-1, a checkpoint molecule on T cells. PD-1 is a marker on exhausted T cells. So far, 2 large Phase I trials of the anti-PD-1 antibody have been performed in patients with melanoma.

The first studied nivolumab and demonstrated a robust response rate of about 30% (Sznol 2013; [4.1]). The duration of response is more than 1 year and is currently approaching 2 years. A few of the patients who responded have experienced relapse, and many have completed 2 years of therapy.

Lambrolizumab (MK-3475) is another promising monoclonal antibody that initially showed a high response rate with short follow-up. It has a similar response rate in patients with or without previous ipilimumab treatment (Ribas 2013b; [4.1]). So we may be able to use one agent and then switch to another and still provide an additional benefit.

Overall, targeting PD-1 causes less toxicity than ipilimumab. Patients experience less fatigue, but rash occurs. Less gastrointestinal and hepatobiliary toxicity is seen. Some cases of hypothyroidism have been reported. Although infrequent, pneumonitis is most concerning and requires vigilance. ■

4.1

Results from 2 Phase I Anti-PD-1 Trials: Clinical Efficacy and Safety of Nivolumab (MDX-1106) or Lambrolizumab (MK-3475) in Patients with Advanced Melanoma

Efficacy (all doses)	Nivolumab (n = 107)[1]	Lambrolizumab (n = 135)[2]
ORR	31%	38%
Median DoR	24 mo	Not reached
Median OS	16.8 mo	NR
Median PFS	3.7 mo	NR

Select AEs (all grades)	Nivolumab (n = 107)	Select AEs (all grades)	Lambrolizumab (n = 135)
Dermatologic	38%	Rash	20.7%
Gastrointestinal	19%	Fatigue	30.4%
Hepatic	7%	Diarrhea	20.0%
Pulmonary	4%	Pneumonitis	4.4%
Endocrinopathies	14%	Hypothyroidism	8.1%

ORR = objective response rate; DoR = duration of response; OS = overall survival; NR = not reported; PFS = progression-free survival; AEs = adverse events

[1] Sznol M et al. *Proc ASCO* 2013;**Abstract CRA9006**; [2] Ribas A et al. *Proc ASCO* 2013b;**Abstract 9009**.

SELECT PUBLICATIONS

Ribas A et al. **Hepatotoxicity with combination of vemurafenib and ipilimumab.** *N Engl J Med* 2013a;368(14):1365-6.

Ribas A et al. **Clinical efficacy and safety of lambrolizumab (MK-3475, anti-PD-1 monoclonal antibody) in patients with advanced melanoma.** *Proc ASCO* 2013b;**Abstract 9009**.

Sznol M et al. **Survival and long-term follow-up of safety and response in patients (pts) with advanced melanoma (MEL) in a phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538).** *Proc ASCO* 2013;**Abstract CRA9006**.