INTERVIEW

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Tracks 1-12

Track 1 CheckMate 067: Efficacy and safety results of a Phase III trial of nivolumab, ipilimumab or the combination for patients with untreated advanced melanoma

Track 2 Mechanistic underpinnings for the increased progression-free survival rates with the nivolumab/ipilimumab combination among patients with a negative PD-L1 tumor status on the CheckMate 067 trial

Track 3 Depth and duration of response with nivolumab/ipilimumab versus nivolumab or ipilimumab monotherapy

Track 4 Sequence and selection of first-line therapy for patients with metastatic melanoma — Role of immunotherapy versus BRAF inhibition

Track 5 Response to anti-PD-1/PD-L1 therapy in patients with metastatic desmoplastic melanoma

Track 6 Considerations for the use of BRAF and/or MEK inhibitor-based first-line therapy for BRAF mutation-positive metastatic melanoma

Track 7 Activity of BRAF or MEK inhibition or the combination versus immunotherapy as treatment for patients with BRAF mutation-positive melanoma and CNS metastases

Track 8 Atypical patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial

Track 9 Response rates of anti-PD-1 antibodies versus ipilimumab as first-line therapy for metastatic melanoma

Track 10 Activity and ongoing investigations of anti-PD-L1-based strategies in metastatic melanoma

Track 11 Counseling patients about the side-effect profiles of anti-PD-1/CTLA-4 combination therapy

Track 12 Use of immune checkpoint blockade in patients with prior autoimmune disorders

Select Excerpts from the Interview

Tracks 4, 6

DR LOVE: What is your usual approach to patients with newly diagnosed metastatic melanoma outside a clinical trial?

DR RIBAS: I now consider immunotherapy as the first line of therapy in the majority of patients with metastatic melanoma. I am comfortable discussing this option with patients even before the results of BRAF testing are available. BRAF/MEK inhibitors are effective therapies but yield a much shorter duration of response compared to immunotherapy. The duration of response to immunotherapies can be measured in years.

DR LOVE: When would you consider using a single-agent anti-PD-1 antibody versus the combination with ipilimumab?

DR RIBAS: The majority of immune responses to cancer are mediated by T cells that recognize something that's altered in the tumor. In melanoma, damage from UV radiation induces a high mutational load. These tumors are more likely to induce an immune response that then is inhibited by PD-1.

So if I have a 65-year-old patient with melanoma that started in a sun-exposed area such as the scalp and became metastatic, I would offer this patient single-agent anti-PD-1 therapy. This tumor is likely to have a high mutational load that would promote T-cell infiltration. I believe that we would see a higher response rate to single-agent anti-PD-1 antibodies. This is not based on clinical trial data but on my clinical experience.

In randomized trials, the anti-PD-1 antibodies pembrolizumab and nivolumab have shown greater efficacy than ipilimumab. So if I decide to use a checkpoint inhibitor, I would consider either pembrolizumab or nivolumab, which elicit similar response rates. The only practical difference is that pembrolizumab is administered every 3 weeks and nivolumab is administered every 2 weeks.

The combination of nivolumab and ipilimumab has recently demonstrated promising results (Larkin 2015; [1.1, page 4]). A biopsy of the tumor would be useful as a guide to help determine who would benefit from single-agent therapy versus a combination approach. Currently assays focus on evaluating PD-L1 expression alone. I foresee in the future we will be able to assess if T-cells are colocalizing with PD-L1. If T-cell infiltration and interaction of T-cells occur with the tumor, single-agent anti-PD-1- or PD-L1-blocking antibodies would be effective. However, if T-cells are absent, combination therapy that facilitates T-cell infiltration may be more appropriate.

DR LOVE: What are the clinical situations in which you would start with BRAF/MEK inhibitor therapy?

DR RIBAS: BRAF/MEK inhibitors in combination are outstanding therapies that elicit approximately a 70% objective response rate and a median overall survival of more than 2 years (Long 2015). So they have shifted the survival curve of patients with metastatic melanoma and changed the natural course of the disease. The median duration of response to combination therapy is 13 months. Some patients experience long-lasting responses, but the majority of patients who respond will experience relapse.

Patients who present with more aggressive disease may be less likely to respond to immunotherapy because their tumors have overwhelmed the immune system and the immune system is no longer capable of recognizing them. Although these patients tend to experience spectacular responses to BRAF/MEK inhibitor combination therapy, these responses are short-lived. Bulky tumors rarely show evidence of T-cell infiltration, and patients with these BRAF-mutant tumors would benefit from BRAF/MEK inhibitor combination therapy.

Patients with more indolent BRAF-mutant melanoma may derive benefit from BRAF/MEK inhibitors for years. I have a couple of patients who were on the Phase I trial of the BRAF inhibitor vemurafenib who have survived for more than 5 years. However, patients with indolent disease are more likely to respond to immunotherapy with fewer side effects, and the majority of these patients usually experience a durable response.

Track 5

DR LOVE: Would you describe the role of anti-PD-1/PD-L1 therapy for patients with metastatic desmoplastic melanoma?

DR RIBAS: Desmoplastic melanoma is a subset of the disease that comprises approximately 1% of melanomas. It tends to appear in the chronically sun-exposed areas of the head and neck and is usually a local disease with infrequent metastases. These patients require surgery that can be disfiguring.

Typically, desmoplastic melanomas are not responsive to most treatments. However, these tumors respond well to PD-1 blockade (Eroglu 2015; [4.1]). It is likely that this is because desmoplastic melanomas are tumors that have a higher mutational load caused by chronic sun exposure. One of the diagnostic features is a T-cell response in the tumor. Those T cells were turned off by PD-L1, and this inhibition must be released to elicit an immune response.

4.1

Response to Anti-PD-1/PD-L1 Therapy in Patients with Metastatic Desmoplastic Melanoma

Efficacy	N = 24
Overall response rate	71%
Complete response	42%
Partial response	29%
Median progression-free survival (PFS)	Not reached
6-month PFS rate	77%
Median overall survival (OS)	Not reached
1-year OS rate	80%

Ongoing responses: 14 of 17 patients (82%); 2 patients with partial responses had no evidence of disease after resection of progressing metastases

Eroglu Z et al. *Proc ASCO* 2015;**Abstract 9011**.

Track 8

DR LOVE: You were part of a group that presented data at ASCO on atypical patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial. Would you discuss those results?

DR RIBAS: The presentation at ASCO was based on a large series of patients with metastatic melanoma who received pembrolizumab. Responses were assessed using immune-related response criteria (irRC) in addition to conventional response criteria. If a patient had an initial readout of disease progression, that patient was allowed to stay on study at the discretion of the investigator. Progression had to be confirmed by irRC. If an initial readout of disease progression was observed on a scan but the patient eventually experienced a response, we defined that as pseudoprogression. The frequency of pseudoprogression was approximately 5% (Wolchok 2015; [4.2]).

A similar incidence of pseudoprogression has been observed with CTLA-4 and PD-1 blockade. To determine what is actually occurring in the tumor, a biopsy is required.

It could be that the tumor continues to progress but responds eventually or that the tumor is actually responding but an influx of immune cells induces inflammation and makes the tumor appear larger. The majority of biopsies we have performed on patients with pseudoprogression show tumor growth with an immune response that increases with time. The immune infiltrate eventually predominates and destroys the cancer. I've also seen biopsies of an inflammatory reaction, and the amount of tumor is small. The inflammatory reaction makes the tumor appear larger. That tends to happen more frequently in my experience in lymph nodes rather than in visceral metastases.

DR LOVE: How do you distinguish pseudoprogression from real tumor progression clinically?

DR RIBAS: Clinical judgment should be used in determining the best course of action. If the scans show objective disease progression and the patient is feeling worse with more overall symptoms, I would not conclude this is pseudoprogression and would not wait for an eventual response. If a scan shows that a lesion is bigger but the patient feels better, I may decide to continue therapy because these patients can sometimes experience response. The best approach would be to biopsy the tumor. If the tumor is growing larger and no immune infiltrate is present, I would not consider it to be pseudoprogression but rather true disease progression. ■

4.2

Early and Late Pseudoprogression in Patients with Metastatic Melanoma Treated with Pembrolizumab on the Phase III KEYNOTE-001 Trial

Timing of pseudoprogression	Definition	Rate of pseudoprogression
Early	≥25% increase in tumor burden at week 12 not confirmed as progressive disease (PD) on the 2 subsequent assessments	4.6%
Late	≥25% increase in tumor burden at any assessment after week 12 not confirmed as PD at the next assessment	4.3%

Wolchok J et al. *Proc ASCO* 2015;**Abstract 3000**.

SELECT PUBLICATIONS

Eroglu Z et al. **Response to anti-PD1/PDL1 therapy in patients with metastatic desmoplastic melanoma.** *Proc ASCO* 2015;**Abstract 9011**.

Flaherty KT et al. **Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.** *N Engl J Med* 2012;367(18):1694-703.

Han D et al. **Clinicopathologic predictors of survival in patients with desmoplastic melanoma.** *PLoS One* 2015;10(3):e0119716.

Larkin J et al. **Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.** *N Engl J Med* 2015;373(1):23-34.

Long GV et al. **Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial.** *Lancet* 2015;386(9992):444-51.

Mahoney KM et al. **The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma.** *Clin Ther* 2015;37(4):764-82.

Wolchok J et al. **Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001.** *Proc ASCO* 2015;**Abstract 3000**.