INTERVIEW

Evan J Lipson, MD

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Tracks 1-15

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your work investigating PD-L1 expression in Merkel cell carcinoma (MCC) and the potential use of immune checkpoint blockade for MCC?

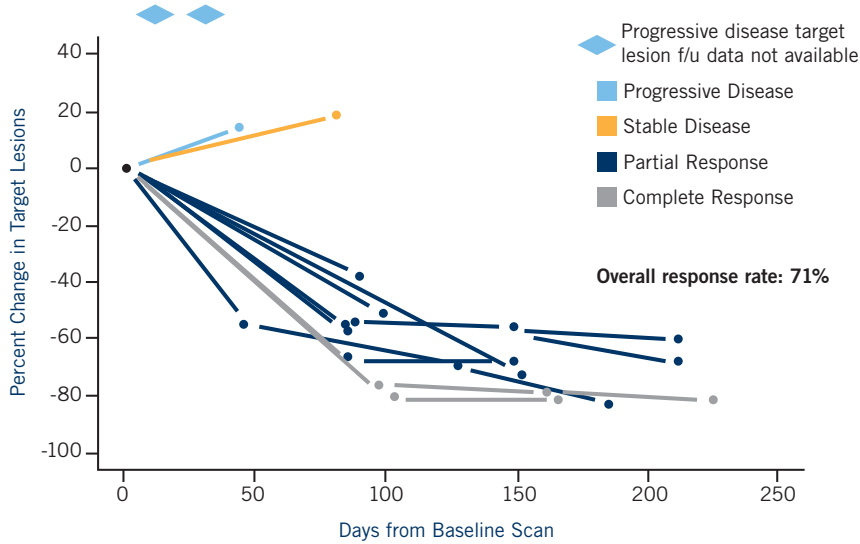
DR LIPSON: MCC is a rare but deadly skin cancer that is often associated with the Merkel cell polyomavirus and sun exposure. Despite appropriate first-line treatment, the cancer often recurs either locally or in another location. Because of the association with the virus and the belief that the immune milieu is active, we undertook a study to assess the association between the presence of the virus in the tumor and expression of

PD-L1. The study demonstrated that patients whose tumors expressed PD-L1 experienced a longer overall survival than those with PD-L1-negative tumors (Lipson 2013).

This suggests that enhancing the immune response with a checkpoint inhibitor could boost the ability of the immune system to destroy the tumor. Currently anti-PD-1/anti-PD-L1 antibodies are being explored for patients with unresectable or metastatic MCC, and we have observed some good responses (Nghiem 2015; [3.1]).

3.1

Phase II Trial of the Activity of Pembrolizumab as First Systemic Therapy for Advanced Merkel Cell Carcinoma



With permission from Nghiem P et al. *Proc ECC* 2015;**Abstract 22LBA**.

Tracks 3-4

DR LOVE: Your group recently reported on the safety of ipilimumab in patients with advanced melanoma and preexisting hepatitis B or C. Would you discuss those results?

DR LIPSON: Studies of immune checkpoint blockade have generally excluded patients with any immunologic comorbidity. One of the potential side effects of administering checkpoint inhibitors is autoimmune hepatitis. We published a case series last year evaluating the effect of using ipilimumab in patients with preexisting hepatitis B or C.

Our results showed that in these patients, viral hepatitis was stable. Patients tolerated the agent well, and the rates of liver function test abnormalities were similar to those of a normal population (Ravi 2014). It was a small study, but it does suggest that in patients with underlying viral hepatitis, ipilimumab can be safely used with close monitoring.

DR LOVE: Would you also discuss your work evaluating the administration of ipilimumab in patients who had undergone kidney or liver transplantation?

DR LIPSON: We studied the safety and efficacy of ipilimumab in 2 patients with metastatic melanoma who had previously undergone kidney transplantation and found that neither of the patients' renal allografts was affected by this therapy (Lipson 2014a). Both of the patients demonstrated an antitumor response to ipilimumab.

The other report was of a patient with a liver transplant who received ipilimumab therapy and who also did not experience rejection of the allograft (Morales 2015). These reports suggest that these patients who are immunosuppressed can still experience responses to checkpoint inhibitors. I would emphasize that these are small trials, however. We cannot conclude that checkpoint blockade is safe across the board in patients with kidney and liver transplants. It is important to have a conversation with your patient about the potential risks.

Track 5

DR LOVE: Another interesting area of research that you have been involved with is the use of circulating tumor DNA (ctDNA) to monitor tumor burden in patients with melanoma who are receiving treatment with checkpoint inhibitors. Would you discuss that work?

DR LIPSON: This study addresses a common issue in patients receiving checkpoint blockade therapy. In a small but meaningful percent of patients, tumors may seem to enlarge or appear anew before regressing. So the question was, how can you accurately predict a response to a checkpoint inhibitor early in the course of therapy?

The study evaluated patients with melanoma receiving checkpoint blockade agents who had mutations that were detectable in the peripheral blood. The levels of ctDNA were analyzed during therapy. In general, levels of ctDNA correlated with what the radiologic scans were demonstrating. Patients who were experiencing both radiologic and clinical disease progression had rising levels of ctDNA.

Interestingly, a patient who had undergone a biopsy of a soft-tissue lesion experienced a huge spike in the level of ctDNA, which stayed elevated for several weeks. So a perturbation in the tumor environment through a needle biopsy released a large bolus of tumor into circulation. Another woman who was receiving ipilimumab for locally advanced unresectable melanoma with neck lymphadenopathy showed disease progression by clinical evaluation. However, her ctDNA dropped to an undetectable level midway through her therapy, which was an early indicator that she was going to respond. She did eventually experience a complete response (Lipson 2014b). ■

SELECT PUBLICATIONS

Lipson EJ et al. **Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma.** *J Clin Oncol* 2014a;32(19):e69-71.

Lipson EJ et al. **Circulating tumor DNA analysis as a real-time method for monitoring tumor burden in melanoma patients undergoing treatment with immune checkpoint blockade.** *J Immunother Cancer* 2014b;2(1):42.

Lipson EJ et al. **PD-L1 expression in the Merkel cell carcinoma microenvironment: Association with inflammation, Merkel cell polyomavirus and overall survival.** *Cancer Immunol Res* 2013;1(1):54-63.

Morales RE et al. **Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation.** *J Immunother Cancer* 2015;3:22.

Ravi S et al. **Ipilimumab administration for advanced melanoma in patients with pre-existing hepatitis B or C infection: A multicenter, retrospective case series.** *J Immunother Cancer* 2014;2(1):33.