INTERVIEW

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Tracks 1-16

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: How often do you see patients with metastatic basal cell carcinoma? Also, what is your clinical experience in terms of when these patients end up seeking treatment?

DR PAVLICK: I have been in practice for more than 15 years and had not seen one of these patients until recently, when an agent was developed for metastatic basal cell carcinoma. I recently opened a clinical trial that was enrolling patients with metastatic basal cell cancer, and now I have 6 patients with basal cell carcinoma.

Most cases of metastatic basal cell carcinoma that I treat are in patients who did not see a doctor until it was too late. Public awareness and education are lacking, and a lot of patients with basal cell carcinoma are in denial. Some patients believe if they observe a

lesion and do nothing it will disappear. They often state that they had a lesion for years that worsened over time, in some cases resulting in lymph node involvement.

I had a patient who had a large basal cell carcinoma on her leg, and it continued to grow until she sought treatment. She had to have an above-the-knee amputation because the margins of the tumor could not be cleanly resected.

She fared well for a couple of years but then developed lung metastases and a large pelvic mass that was obstructing her ureter and required a nephrostomy tube. The patient also developed diffuse basal cell carcinomas all over the rest of her body.

DR LOVE: What treatment did she receive?

DR PAVLICK: Multiple hedgehog inhibitors are being investigated for the treatment of basal cell carcinoma. Vismodegib is FDA approved, but others are in the investigational stage. She was enrolled on a clinical trial with an investigational hedgehog inhibitor called erismodegib (LDE225). She experienced a 50% reduction in her disease volume, which has lasted for almost a year.

DR LOVE: What side effects did she experience on erismodegib?

DR PAVLICK: Although these hedgehog inhibitors are orally administered, they are not easy to tolerate and have side effects similar to BRAF inhibitors. The patient experienced a significant alteration in taste. She also lost her hair and had to wear a wig. She has experienced intermittent muscle cramps, which is another big complaint with these agents. However, those seem to have resolved with time.

Tracks 5-7

DR LOVE: Would you discuss the mechanism of action and efficacy of vismodegib in basal cell carcinoma?

DR PAVLICK: Basal cell carcinomas harbor a genetic alteration in the hedgehog pathway. The protein Smoothened transduces an antiapoptotic signal to the nucleus, allowing these cells to proliferate. The hedgehog inhibitor vismodegib works by inhibiting Smoothened, thus preventing cells from proliferating.

A Phase II study for patients with locally advanced or metastatic disease led to the approval of vismodegib (Sekulic 2012). Response rates in both groups were similar and in the 40% to 60% range with a time to disease progression longer than 9 months (3.1).

DR LOVE: What are your thoughts on the change in taste and muscle cramps that patients experience while receiving vismodegib?

DR PAVLICK: The change in taste is bothersome. Patients report an inability to taste or that food tastes like metal. A few patients consider coming off treatment before the holidays so they can enjoy holiday food and then go back on treatment afterward. Once the drug is discontinued, taste sensation is restored.

The other major side effect is muscle cramps, which often wake patients at night. We've tried administering quinine, lorazepam or magnesium and checking patients' electrolyte levels, but they are difficult to manage. I had a patient who had to come off therapy because the leg muscle cramps were excruciating. The reason patients develop these side effects is not understood. Almost everyone to whom I've administered a hedgehog inhibitor has also developed significant alopecia.

DR LOVE: Would you consider administering vismodegib in the neoadjuvant setting for basal cell carcinoma?

DR PAVLICK: Neoadjuvant therapy with vismodegib is being investigated, especially for large basal cell carcinomas, to shrink the tumor and make surgery easier (Ally 2013; Chang 2013; [3.2]). I believe it is clearly beneficial, especially in older patients who may not be amenable to wide resections, to downsize the tumor and subsequently allow a more limited resection to be performed.

3.1

ERIVANCE BCC: Updated 18-Month Analysis of a Phase II Trial of Vismodegib in Locally Advanced or Metastatic Basal Cell Carcinoma (BCC)

Efficacy	Metastatic BCC (n = 33)	Locally advanced BCC (n = 63)
Objective response rate	48.5%	60.3%
Median progression-free survival	9.3 months	12.9 months
Median overall survival	30.9 months	NE
Select adverse events (n = 104)*	Any grade	Grade 3 or 4
Muscle spasms	71.2%	5.8%
Alopecia	65.4%	0%
Dysgeusia	54.8%	0%
Decrease in weight	51%	6.7%
Fatigue	42.3%	4.8%
Diarrhea	26.9%	2.9%
Ageusia/hypogeusia	11.5%/10.6%	0%/0%

NE = not estimable; * Occurring in ≥10% of patients

Sekulic A et al. *Proc ASCO* 2013;**Abstract 9037**.

3.2

Vismodegib as Neoadjuvant Treatment Prior to Surgery for Basal Cell Carcinomas (BCCs)

Single-arm study of neoadjuvant vismodegib prior to Mohs micrographic surgery (N = 5)

- Reduction in surgical defect size: 38%
- Reduction in tumor from baseline: 46%
- No BCCs in 3 tumors, residual BCC in 1, equivocal diagnosis in 3
- No recurrence after median of 3 months of follow-up

Ally M et al. *Proc American Academy of Dermatology* 2013;**Abstract S018**.

Track 12

DR LOVE: What are some of the common misconceptions about metastatic melanoma?

DR PAVLICK: One common misconception among patients is that a BRAF mutation is genetically transmitted. I clearly explain to patients that this is an intrinsic mutation within the tumor that would not be genetically transmitted to members of their family. Because melanoma is not a common cancer, one of the misconceptions that some of the

community oncologists have is that if a patient has a BRAF mutation, he or she should always receive a BRAF inhibitor up front. This should not be the "knee-jerk" response.

DR LOVE: A recent paper entitled "Which drug, and when, for patients with BRAF mutant melanoma?" was published in *Lancet Oncology* (Jang 2013). The authors contend that for a patient with BRAF-mutant melanoma who has nonbulky, asymptomatic disease and a normal LDH level, immunotherapy should be considered first followed by a BRAF inhibitor upon disease progression. What are your thoughts?

DR PAVLICK: I agree with the authors. The one drug class that we know of that provides patients with the possibility of a durable complete response is immunotherapy. For patients with low-volume or indolent disease who have a normal LDH level and are fit and asymptomatic, even for those with a BRAF mutation, many of us will argue that immunotherapy should be administered first. This offers the patient a possibility of a complete and durable response. If the patient has BRAF-mutant disease, a BRAF inhibitor would be the next choice and the disease should respond.

Track 15

DR LOVE: In what situations do you consider chemotherapy for metastatic melanoma, and what are your thoughts on the recent study that evaluated *nab* paclitaxel versus dacarbazine (1.4, page 7)?

DR PAVLICK: If I had to choose a taxane to administer to a patient with metastatic melanoma, I would pick *nab* paclitaxel. I believe it's easier to administer, and I find it to be well tolerated despite the possibility of neurotoxicity. On a recent trial of *nab* paclitaxel versus dacarbazine for previously untreated metastatic melanoma, *nab* paclitaxel was a bit more efficacious than dacarbazine. Even though these agents are not the main focus of research right now in melanoma, that doesn't mean we don't have appropriate settings in which to administer them.

One such setting is for a patient with BRAF wild-type melanoma who doesn't experience a response to ipilimumab or anti-PD-1 on a clinical trial. If you have no other clinical trial options for such a patient, what are you going to do? It's hard to tell a patient, "Sorry, there's nothing left for you," so we'd treat with chemotherapy in that setting.

I consulted with such a patient this week. This patient had received ipilimumab a year ago and experienced a partial response. We observed him, and eventually his disease began to progress.

He received 4 additional doses of ipilimumab but did not experience a response, so he now has explosive disease with significant intraluminal tumors throughout his gastrointestinal tract and requires a blood transfusion every 2 weeks. I explained to him that we'd be unable to get him on a clinical trial because of his active bleeding and that we needed to try to slow the disease down. I explained that chemotherapy could at least control his disease and, we would hope, open future treatment options and that given his rapidly progressing disease I'd like to try *nab* paclitaxel and carboplatin. ■

SELECT PUBLICATIONS

Chang AL et al. **Surgical excision after neoadjuvant therapy with vismodegib for a locally advanced basal cell carcinoma and resistant basal carcinomas in Gorlin syndrome.** *JAMA Dermatol* 2013;149(5):639-41.

Jang S, Atkins MB. **Which drug, and when, for patients with BRAF-mutant melanoma?** *Lancet Oncol* 2013;14(2):e60-9.