INTERVIEW

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Dr Sekulic is Assistant Professor of Dermatology at Mayo Clinic in Scottsdale, Arizona.

Tracks 1-16

Select Excerpts from the Interview

Track 6

DR LOVE: What treatment options are currently available for patients with basal cell carcinoma (BCC) of the skin that requires systemic therapy?

DR SEKULIC: At this point, treatment options include the use of targeted inhibitors of the so-called hedgehog signaling pathway. This has been an

exciting area of progress in research during the past decade, as it illustrates the true "bench-to-bedside" transition — a pathway was identified that is involved in virtually all cases of BCC, and the agent was developed to specifically target a member of that pathway called smoothened homolog (SMO).

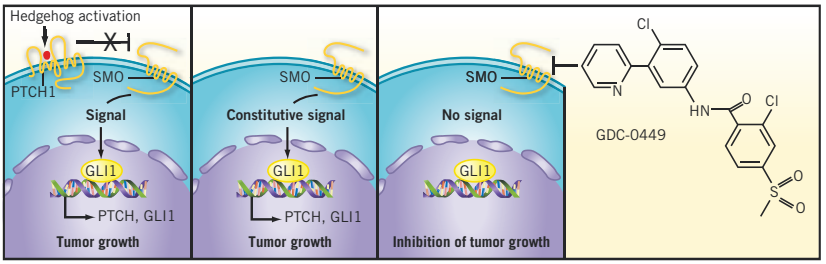
DR LOVE: Would you discuss what the hedgehog pathway is and what kind of agents are available to inhibit it?

DR SEKULIC: The hedgehog signaling pathway relies on SMO, an active protein, which is normally repressed by a protein called patched homolog. When patched is not inhibiting SMO, SMO induces the proliferation of cells. In basal cell nevus syndrome, or Gorlin-Goltz syndrome, patients have mutations or loss of the patched gene, thus losing the repression of SMO and resulting in continual activity and the proliferation of cells. The pathways are important in development, and they also seem to play an important role in so-called stem cell compartments of some tissues, such as epithelial tissues, hair follicles and so on.

Cyclopamine is an inhibitor of SMO, which is an active member of the hedgehog signaling pathway. The identification of hedgehog pathway activity in BCC led to efforts to attempt to use cyclopamine for treatment. Synthetic analogs of cyclopamine are now being developed, the most advanced of which is GDC-0449, which is now known as vismodegib (Von Hoff 2009; [3.1]).

3.1

Mechanism of Action of Vismodegib (GDC-0449), a Small-Molecule Inhibitor of Smoothened Homolog (SMO)



Track 7

DR LOVE: What kind of side effects and complications have been observed with vismodegib?

DR SEKULIC: Vismodegib is a small-molecule synthetic derivative of cyclopamine that is administered orally once a day. The side effects observed in the Phase I trial and published in *The New England Journal of Medicine* include hair loss, taste alterations, muscle cramping and weight loss, which may or may not be secondary to the taste alterations (Von Hoff 2009; [3.2]).

The Phase I trial was initially set up to accommodate patients with various advanced types of cancer, and drastic responses were observed in patients with BCC, leading to an expansion cohort of 33 patients. Eighteen of the 33 patients experienced objective responses, 11 maintained stable disease and four experienced progressive disease.

Out of the 18 responders, two complete responses were observed (Von Hoff 2009; [3.2]). The duration of response is still not clear, however. In some of the patients the responses continued for a couple of years, but this question must be answered in the long term.

3.2

Phase I Efficacy and Safety of Vismodegib (GDC-0449) in Advanced Cutaneous Basal Cell Carcinoma (N = 33)

Treatment outcomes	n	Percent
Objective response	18	55%
Complete response	2	6%
Partial response	16	48%
Stable disease	11	33%
Progressive disease	4	12%

Adverse events (AE) summary: No dose-limiting toxic effects or Grade 5 events were observed during the study period. A single Grade 4 AE (asymptomatic hyponatremia) occurred. Eight Grade 3 AEs deemed to be possibly related to vismodegib were reported in six patients, including four with fatigue, two with hyponatremia, one with muscle spasm and one with atrial fibrillation.

Von Hoff DD et al. *N Engl J Med* 2009;361(12):1164-72.

Track 9

DR LOVE: What other trials of vismodegib are ongoing?

DR SEKULIC: A Phase II trial has accrued, and the goal of the trial is to evaluate overall response rates in patients with locally advanced or metastatic BCC, similar to the population that was studied in the Phase I study of vismodegib. Another trial is evaluating operable BCC with treatment for three months in one cohort compared to a cohort of patients who receive treatment for three months and are then observed for six months. At the end of the three-month treatment in cohort one and at the end of the observation period after treatment in the second cohort, the original tumor is removed. The questions being asked are, is there a clearance of the tumor, and what is the durability of response after the drug is stopped? ■

SELECT PUBLICATIONS

Kasiske BL et al. **Cancer after kidney transplantation in the United States.** *Am J Transplant* 2004;4(6):905-13.

Von Hoff DD et al. **Inhibition of the hedgehog pathway in advanced basal-cell carcinoma.** *N Engl J Med* 2009;361(12):1164-72.