
The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma



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Background: The hedgehog pathway inhibitor sonidegib demonstrated meaningful tumor shrinkage in more than 90% of patients with locally advanced basal cell carcinoma (BCC) or metastatic BCC in the BCC Outcomes with LDE225 Treatment study.

Objective: This report provides long-term follow-up data collected up to 12 months after the last patient was randomized.

Methods: In this multicenter, randomized, double-blind phase II study, patients were randomized 1:2 to sonidegib 200 or 800 mg. The primary end point was objective response rate assessed by central review.

Results: Objective response rates in the 200- and 800-mg arms were 57.6% and 43.8% in locally advanced BCC and 7.7% and 17.4% in metastatic BCC, respectively. Among the 94 patients with locally advanced BCC who responded, only 18 progressed or died and more than 50% had responses lasting longer than 6 months. In addition, 4 of 5 responders with metastatic BCC maintained an objective response. Grade 3/4 adverse events and those leading to discontinuation were less frequent with sonidegib 200 versus 800 mg (38.0% vs 59.3%; 27.8% vs 37.3%, respectively).

Limitations: No placebo or comparator arms were used because sonidegib demonstrated efficacy in advanced BCC in a phase I study, and the hedgehog pathway inhibitor vismodegib was not yet approved.

Conclusion: With longer follow-up, sonidegib demonstrated sustained tumor responses in patients with advanced BCC. (J Am Acad Dermatol 2016;75:113-25.)

Key words: advanced basal cell carcinoma; Basal Cell Carcinoma Outcomes with LDE225 Treatment study; hedgehog pathway inhibitor; locally advanced basal cell carcinoma; metastatic basal cell carcinoma; sonidegib.

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Basal cell carcinoma (BCC), the most commonly diagnosed cancer,^{1,2} is associated with aberrant activation of hedgehog signaling caused by sporadic mutations in the pathway components patched (>85% of cases) and smoothened ($\approx 10\%$).³⁻⁵ The vast majority of BCCs are effectively treated with topical therapy, surgery, and/or radiotherapy,⁶⁻⁸ but in a minority (<1%) of patients, BCCs can become advanced and difficult to treat.⁹ For patients with advanced BCC, including those with locally advanced BCC (laBCC) who may have multiple, large, neglected, poorly defined, aggressive, and/or recurrent lesions that are not amenable to surgery/radiation and those with metastatic BCC (mBCC), treatment options are limited^{1,10} and include the oral hedgehog pathway inhibitors (HPIs) sonidegib

and vismodegib,¹¹⁻¹⁷ more conventional chemotherapy, radiation (mBCC), or a clinical trial.⁶⁻⁸

Sonidegib (LDE225) is an oral HPI that selectively targets the pathway activator smoothened, thereby inhibiting hedgehog pathway signaling.^{18,19} Sonidegib (200 mg) was approved for use in patients with advanced BCC^{11,12} or laBCC^{13,14} who are not amenable to curative surgery/radiotherapy based on the meaningful, durable tumor responses observed in the BCC Outcomes with LDE225 Treatment (BOLT) study.²⁰ The primary end point, objective response rate (ORR), was met in both treatment arms at the time of the primary analysis (June 28, 2013, cutoff).²⁰ Updated safety and efficacy data from the 12-month analysis (December 31, 2013, cutoff) are presented.

CAPSULE SUMMARY

- Hedgehog pathway inhibition is one of the few treatment options available for patients with advanced basal cell carcinoma.
- Sonidegib provides meaningful tumor shrinkage and durable responses in patients with advanced basal cell carcinoma.
- Sonidegib may offer a promising new treatment option for this difficult-to-treat patient population.

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Supplemental tables and figures are available at <http://www.jaad.org>.

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