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Efficacy of sonidegib in histologic subtypes of advanced basal cell carcinoma: Results from the final analysis of the randomized phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) trial at 42 months

To the Editor: Basal cell carcinoma (BCC) is the most common cancer worldwide.[1] Major histologic subtypes of BCC include nonaggressive (nodular and superficial) and aggressive forms (morpheaform, infiltrative, micronodular, and basosquamous).[1] Locally advanced BCC and metastatic BCC can cause extensive tissue destruction, limiting effective treatment options.[1]

Sonidegib, a Hedgehog pathway inhibitor selectively targeting Smoothened, is approved in the United States for the treatment of adult patients with recurrent locally advanced BCC after surgery or radiation therapy or those who are not candidates for surgery or radiation therapy.[2] Here we examine the long-term efficacy of sonidegib 200 and 800 mg once daily across histologic subtypes of BCC at 42 months.

Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT; NCT01327053) is an international, randomized, double-blind, phase 2 study with patients randomized 1:2 to sonidegib 200 or 800 mg once daily. The primary endpoint was objective response rate (ORR) by central review. Key secondary endpoints included duration of response, time to tumor response, progression-free survival, and overall survival. Tumor evaluations and ORR were assessed per BCC-modified Response Criteria In Solid Tumors (mRECIST) for locally advanced BCC and RECIST version 1.1 for metastatic BCC.[3] Tumor evaluations were conducted at baseline, weeks 5 and 9, every 8 weeks during the first year, and every 12 weeks thereafter.

Overall, 230 patients enrolled; 36 (15.7%) with metastatic BCC and 194 (84.3%) with locally advanced BCC (aggressive, 112 of 194 [57.7%]; nonaggressive, 82 of 194 [42.3%]). The ORRs at 42 months for patients with aggressive and nonaggressive locally advanced BCC were 59.5% (22 of 37) and 51.7% (15 of 29) for 200 mg and 45.3% (34 of 75) and 47.2% (25 of 53) for 800 mg, respectively. Among patients with metastatic BCC, ORRs were 7.7% (200 mg) and 17.4% (800 mg).

Highest ORRs were in infiltrative (200 mg, 51.6% [16 of 31]; 800 mg, 36.8% [21 of 57]) and morpheaform (200 mg, 50.0% [3 of 6]; 800 mg, 75.0% [6 of 8]) for aggressive subtypes. Approximately 50% of patients with nonaggressive subtypes in each group achieved objective response (Table I). Median duration of response for patients with nodular subtype was not estimable and was 15.7 months (95% confidence interval, 7.4-26.4 months) for 200 mg and 800 mg, respectively (Table II).

Patients with infiltrative locally advanced BCC receiving 800 mg had a longer median progression-free survival but lower ORR vs patients receiving 200 mg, highlighting that this analysis was underpowered to determine differences between treatment groups within a histologic subtype.

Subtypes with more enrolled patients generally demonstrated ORRs similar to those observed in the entire population, suggesting a consistent response to sonidegib across histologic subtypes. Comparably, BCC histopathologic subtype did not appear to influence overall tumor response to vismodegib over 12 to 24 weeks.[4]

Limitations of this study include the small patient sample size and the exclusion of patients with

Table I. Best overall response in patients with aggressive and nonaggressive subtypes of advanced basal cell carcinoma treated with sonidegib

	Sonidegib 200 mg				Sonidegib 800 mg			
	Aggressive		Nonaggressive		Aggressive		Nonaggressive	
Best overall response*	Infiltrative (n = 31)	Morpheaform (n = 6)	Nodular (n = 28)	Superficial (n = 10)	Infiltrative (n = 57)	Morpheaform (n = 8)	Nodular (n = 42)	Superficial (n = 25)
Complete response	1 (3.2)	0	2 (7.1)	0	0	1 (12.5)	0	1 (4.0)
Partial response	15 (48.4)	3 (50.0)	11 (39.3)	5 (50.0)	21 (36.8)	5 (62.5)	20 (47.6)	12 (48.0)
Stable disease	12 (38.7)	2 (33.3)	12 (42.9)	5 (50.0)	24 (42.1)	2 (25.0)	17 (40.5)	8 (32.0)
Progressive disease	1 (3.2)	0	0	0	1 (1.8)	0	0	0
Unknown	2 (6.5)	1 (16.7)	3 (10.7)	0	11 (19.3)	0	5 (11.9)	4 (16.0)
Overall response rate†	16 (51.6)	3 (50.0)	13 (46.4)	5 (50.0)	21 (36.8)	6 (75.0)	20 (47.6)	13 (52.0)

*Data are shown as number (%).
†Calculated as complete response + partial response.

Table II. Response characteristics in patients with histologic subtypes of advanced basal cell carcinoma

Characteristic*	Sonidegib 200 mg	Sonidegib 800 mg
TTR, mo		
Infiltrative	4.7 (1.9-6.6)	3.7 (1.9-5.5)
Morpheaform	3.7 (1.2-5.7)	3.7 (1.3-5.6)
Nodular	3.9 (2.1-4.2)	3.8 (1.9-7.4)
Superficial	5.6 (1.9-9.3)	3.9 (1.8-5.6)
DOR, mo		
Infiltrative	12.9 (NE)	23.7 (NE)
Morpheaform	NE	NE
Nodular	NE	15.7 (7.4-26.4)
Superficial	NE	29.6 (NE)
PFS, mo		
Infiltrative	16.9 (11.0-39.6)	29.3 (NE)
Morpheaform	NE	18.3 (NE)
Nodular	24.7 (NE)	19.2 (13.2-30.5)
Superficial	NE	24.9 (NE)

DOR, Duration of response; *NE*, not estimable; *PFS*, progression-free survival; *TTR*, time to tumor response.
*Data are presented as the median (95% confidence interval).

recurrent disease previously treated with a Hedgehog inhibitor.

The 42-month results from the BOLT study demonstrate long-term positive responses for patients with aggressive and nonaggressive histologic subtypes of advanced BCC. These results are similar to those at 6 and 30 months.[3,5] Future investigations may clarify whether differences within subtypes remain consistent in larger populations.

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Association between halo nevi and melanoma in adults: A multicenter retrospective case series

To the Editor: The halo nevus is thought to be of little concern in children. In adults, however, a new-onset halo nevus has been suggested to be a harbinger of melanoma either within the halo nevus or at distant cutaneous or noncutaneous sites, according to case reports and small case series.[1,2] Multiple widely used dermatologic reference texts[3,4] and online references (eg, UpToDate.com, DermNetNZ.org) advocate extensive melanoma screening in adults with new-onset halo nevus, including full cutaneous, oral, ophthalmic, and vaginal examinations, despite limited evidence supporting an association between halo nevus and melanoma. We aimed to further investigate the association between new-onset halo nevus and melanoma in adults by evaluating the incidence of melanoma in the year after a new halo nevus diagnosis.

A multicenter retrospective chart review of clinical and histopathologic records at 8 university hospitals identified 879 patients in whom 888 halo nevi were diagnosed at aged 18 years or older (Brigham and Women's Hospital [n = 80], Massachusetts General Hospital [n = 166], New York University [n = 7], Northwestern University [n = 36], Oregon Health & Science University [n = 103], University of Pennsylvania [n = 27], Huntsman Cancer Institute and the University of Utah [n = 364], and Yale University [n = 96]). Ethical approval was obtained from each university's institutional review board. Patients being treated with immunotherapy for melanoma were excluded.

Mean age at halo nevus diagnosis was 36.3 years (standard deviation 13.2 years) (Table I). Clinical records review identified 95 occurrences of melanoma in these 879 patients. Only 9 halo nevi were diagnosed within 1 year before melanoma diagnosis, representing a melanoma incidence rate of 0.01 (95% confidence interval 0.004-0.017) per person per year. All 9 of these melanomas represented primary cutaneous melanoma; there were no occurrences of primary noncutaneous melanoma, metastatic melanoma, or melanoma within the incident halo nevus. None of these 9 patients presented with multiple halo nevi. The remaining 86 melanoma