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Randomized, Double-Blind Study of Sonidegib (LDE225) in Patients With Advanced Basal Cell Carcinoma

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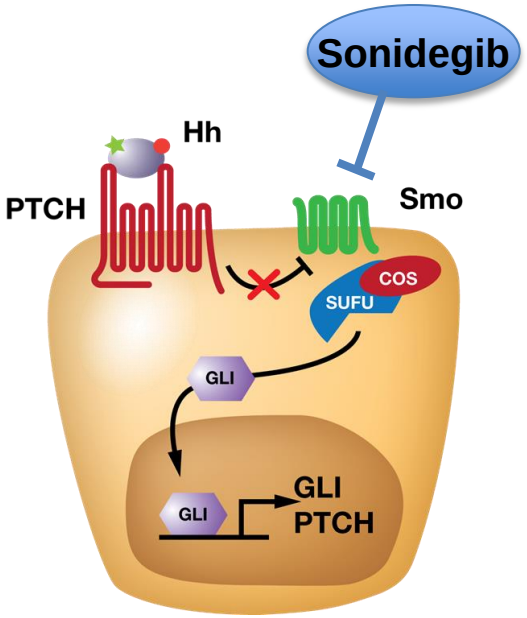
Disclosures

- I have served as a consultant/advisor and have received honoraria and research funding from Novartis, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Roche, and Amgen

Background

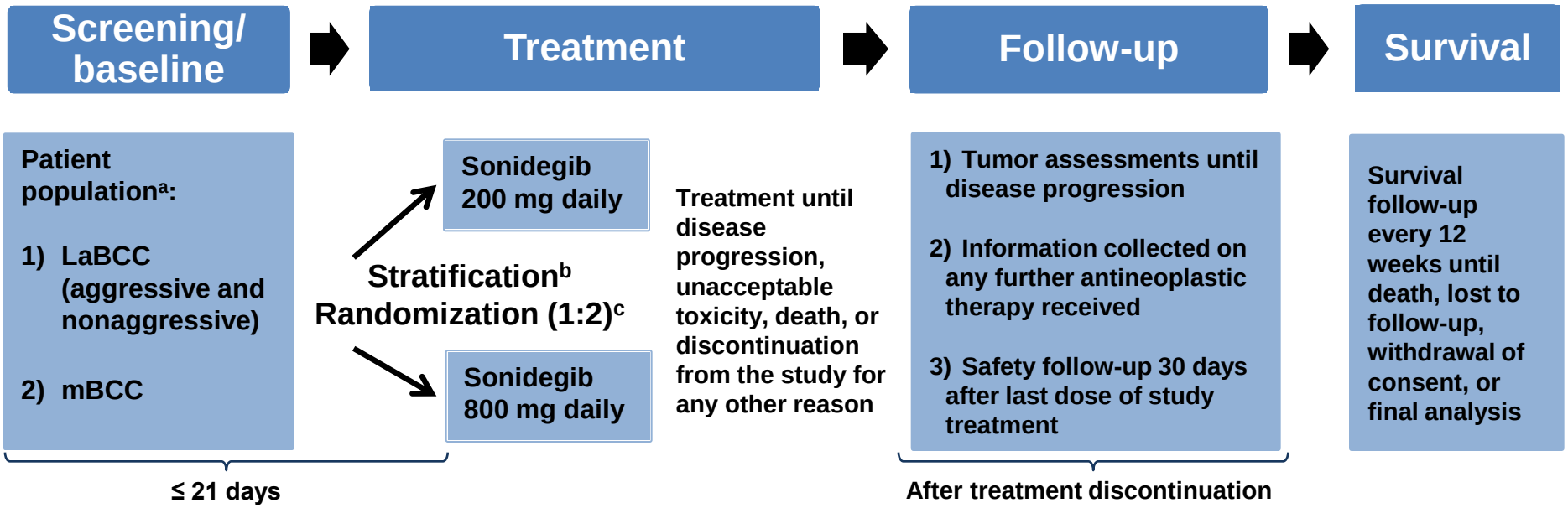


- Basal cell carcinoma (BCC) is among the most commonly diagnosed human cancers[1-3]
- Treatment options for patients with locally advanced BCC (LaBCC) or metastatic BCC (mBCC) are limited[1-4]
- Most sporadic BCCs (≈ 95%) have mutations in the hedgehog (Hh) pathway components patched (PTCH; > 85%) or smoothened (SMO; ≈ 10%)[5,6]
  - Expression of glioma-associated oncogene homolog 1 (*GLI1*) is a marker for Hh pathway activation
- The BOLT phase 2 study of 2 dosages of sonidegib (LDE225; selective SMO inhibitor[7]) in patients with advanced BCC (NCT01327053) met its primary endpoint of objective response rate (ORR) ≥ 30% after a median follow-up of 13.9 months[8]
- Associations of *GLI1* expression with clinical outcome as of the primary analysis[8] and updated 12-month efficacy and safety data are presented here

BOLT; Basal cell carcinoma Outcomes with LDE225 Treatment trial; COS, conserved ortholog set; SUFU, suppressor of fused.

1. NCCN Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancers. V2.2014. http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. 2. Basal cell carcinoma, squamous cell carcinoma (and related lesions) a guide to clinical management in Australia. Cancer Council Australia and Australian Cancer Network, Sydney. 2008. 3. Trakatelli M, et al. *Eur J Dermatol*. 2014;24:312-329. 4. Erivedge (vismodegib) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2012. 5. Scales SJ. *Trends Pharmacol Sci.* 2009;30:303-312. 6. Epstein EH. *Nat Rev Cancer*. 2008;8:743-754. 7. Pan S, et al. *ACS Med Chem Lett*. 2010;1:130-134. 8. Migden MR, et al. *J Clin Oncol.* 2014;32(5 suppl) [abstract 9009a].

BOLT Study Design



[a] Patients with prior treatment with sonidegib or other Hh pathway inhibitors were excluded.
[b] Stratification based on stage, disease histology for LaBCC patients (nonaggressive vs aggressive), and geographic region.
[c] Doses chosen based on data from the phase 1 study.[1] Sonidegib 200 mg once daily was the lowest dose level tested with evidence of antitumor activity; sonidegib 800 mg once daily was the highest well-tolerated, biologically active dose.

1. Rodon J, et al. *Clin Cancer Res*. 2014;20:1900-1909.

- **Primary analysis:** data collected up to 6 months after the last patient randomization date (data cutoff, June 28, 2013; median follow-up, 13.9 months)
- **12-month analysis:** data collected up to 12 months after the last patient randomization date (data cutoff, December 31, 2013; median follow-up, 20.0 months)

Endpoints

Primary	**ORR** → best overall confirmed response of CR or PR by central review according to mRECIST (LaBCC) or RECIST 1.1[1] (mBCC)[a]
Key secondary	**DOR and CR rate** by central review according to mRECIST (LaBCC) or RECIST 1.1[1] (mBCC)
Other secondary	ORR and DOR by investigator review; PFS and TTR by central and investigator review; overall survival and safety
Exploratory	Change in *GLI1* expression in tumor tissue and associations with clinical response and safety

mRECIST integrates:

- **MRI according to RECIST 1.1[1]**
- **Standard and annotated color photography using WHO criteria[2]**
- **Histology in multiple biopsies based on lesion surface area**

CR, complete response; DOR, duration of response; *GLI1*, glioma-associated oncogene homolog 1; LaBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; mRECIST, modified RECIST; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response; WHO, World Health Organization.

[a] Point estimates to meet or exceed 30% (with lower bound of 95% CI > 20%) in either treatment arm.

1. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45:228-247. 2. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, Switzerland: World Health Organization; 1979.

Stringent Response Criteria for LaBCC

MRI[a]	Photograph[b]	Histology	Composite Overall Response per mRECIST[c]
CR	CR	Negative	CR[d]
	PR (scar/fibrosis only) or SD (scar/fibrosis only)		
	NA		
NA	CR		
	PR (scar/fibrosis only) or SD (scar/fibrosis only)		
PR	CR	Negative	PR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)		
SD	CR		
	PR (scar/fibrosis only) or SD (scar/fibrosis only)		
CR	PR		
PR			
SD			
NA			
PR	NA		
CR	SD	Negative	SD
PR			
CR	SD	Positive or UNK	
	SD (scar/fibrosis only)		
PR	SD		
	SD (scar/fibrosis only)		

CR, complete response; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.
[a] Measurability by central review per RECIST 1.1. [b] PR was defined as ≥ 50% decrease in the sum of products of perpendicular diameters from baseline. PD was defined as ≥ 25% increase in the sum of products of perpendicular diameters from the lowest point. [c] An independent review committee reread all available histology reports for LaBCC to determine a composite response. [d] Confirmed CRs required multiple punch biopsy samples per lesion.

Baseline Demographics and Disease Characteristics

Sonidegib Dose (daily)	200 mg (n = 79)	800 mg (n = 151)
Median age (range), years	67 (25-92)	65 (24-93)
Age ≥ 65 years, %	60	52
Male, %	61	64
ECOG performance status, %		
0	63	63
1	24	29
2	10	7
Unknown	3	1
Aggressive histology/cytology (predominant), %	51	50
Metastasis, %	18	15
≥ 2 lesions at baseline, %	62	62
Prior antineoplastic therapy, %		
Surgery	76	84
Radiotherapy	24	33

ECOG, Eastern Cooperative Oncology Group.

- **Tumor burden at baseline was extensive:** the median sum (range) of target lesions by central review was 12.1 cm^2 (0.7-639.3 cm^2) in patients with LaBCC per WHO criteria by photo and 4.9 cm (1.5-15.8 cm) in patients with mBCC per RECIST 1.1 by MRI or computed tomography

Patient Exposure and Disposition

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 151)	
Analysis	**Primary[a]**	**12-Month[b]**	**Primary[a]**	**12-Month[b]**
Median duration of exposure (range), months	8.9 (1.3-21.4)	11.0 (1.3-27.8)	6.5 (0.3-19.1)	6.6 (0.3-27.8)
Treatment ongoing, %	49	27	30	19
Treatment discontinued, %	51	73	69	80
Primary reasons for discontinuation, %				
Adverse event	20	25	32	34
Progressive disease[c]	19	29	4	10
Patient decision[d]	6	9	19	19
Physician decision[d]	4	9	7	7
Lost to follow-up	1	1	3	3
Death	0	0	3	3
Noncompliance	0	0	2	3
Protocol deviation	0	0	1	1

[a] Data cutoff, June 28, 2013; median follow-up,13.9 months.
[b] Data cutoff, December 31, 2013; median follow-up, 20.0 months.
[c] More patients in the 200-mg arm were able to stay on treatment until disease progression due to improved tolerability.
[d] Reasons for withdrawal either by patient or physician were mostly due to adverse event.

- Shorter median exposure in the 800-mg arm was attributed to early discontinuation of patients as a result of adverse events

Efficacy in LaBCC

Sonidegib Dose (daily)	200 mg (n = 66)		800 mg (n = 128)	
Analysis of All Randomized Patients by Central Review	Primary[a]	12-Month[b]	Primary[a]	12-Month[b]
ORR (95% CI), %	47 (35-60)	58 (45-70)	35 (27-44)	44 (35-53)
CR, %[c]	3	5	0	2
PR, %[c]	44	53	35	42
Disease control (CR+PR+SD) rate, %	91	91	78	81
TTR, median (95% CI), mo (responders only)	3.9 (3.6-4.2)	4.0 (3.8-5.6)	3.7 (2.6-3.8)	3.8 (3.7-5.5)
DOR, n/N[d] KM median (95% CI), mo KM 12-mo event-free probability (95% CI), %	4/31 NE 66 (26-88)	7/38 NE 62 (33-82)	3/45 NE 83 (54-94)	11/56 15.7 (NE) 72 (50-85)
PFS, n[d] KM median (95% CI), mo KM 12-mo event-free probability (95% CI), %	7 NE 84 (65-93)	11 22.1 (NE) 82 (67-91)	10 NE 86 (73-93)	22 21.5 (NE) 80 (67-89)

CR, complete response; DOR, duration of response; KM, Kaplan-Meier estimate; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to tumor response.

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Efficacy in mBCC

Sonidegib Dose (daily)	200 mg (n = 13)		800 mg (n = 23)	
Analysis of All Randomized Patients by Central Review	Primary[a]	12-Month[b]	Primary[a]	12-Month[b]
ORR (95% CI), %	15 (2-45)	8 (0-36)[c]	17 (5-39)	17 (5-39)
CR, %[d]	0	0	0	0
PR, %[d]	15	8[c]	17	17
Disease control (CR+PR+SD) rate, %	92	92	83	91
TTR, median (95% CI), mo (responders only)	4.6 (1.8-7.4)	1.8 (NE)	1.0 (1.0-2.1)	1.0 (1.0-2.1)
DOR, n/N[e] KM median (95% CI), mo KM 12-mo event-free probability (95% CI), %	0/2 NE NE	0/1 NE 100 (NE)	1/4 8.3 (NE) 0 (NE)	1/4 NE NE
PFS, n[e] KM median (95% CI), mo KM 12-mo event-free probability (95% CI), %	4 13.1 (5.6-13.1) 65 (25-87)	6 13.1 (5.6-16.9) 59 (23-83)	10 7.6 (6.2-11.1) 16 (1-48)	11 11.1 (NE) 42 (18-65)

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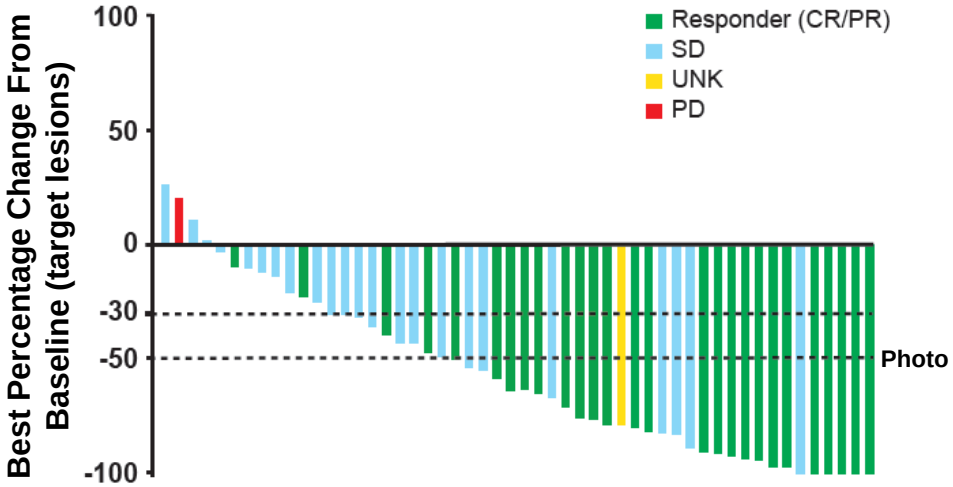
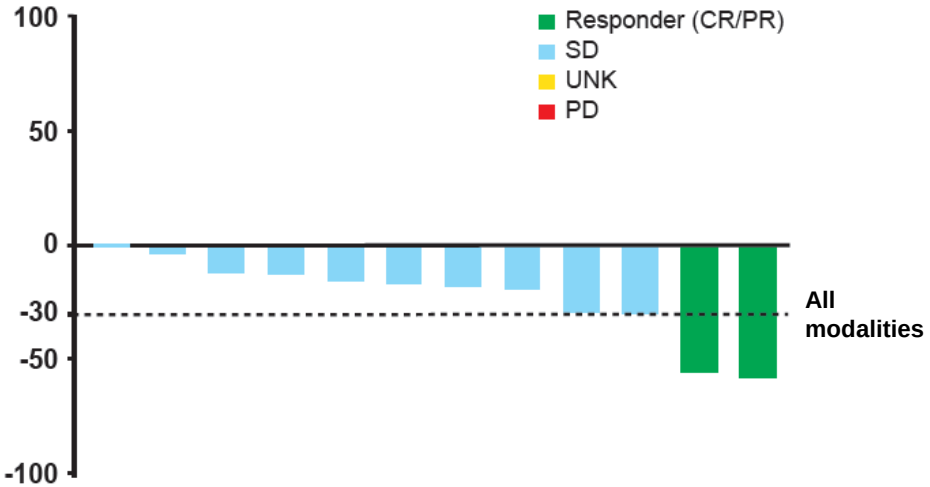
Best Percentage Change in Target Lesions (Primary Analysis)

Central Review

LaBCC (photograph only)
Sonidegib 200 mg QD (n = 52)



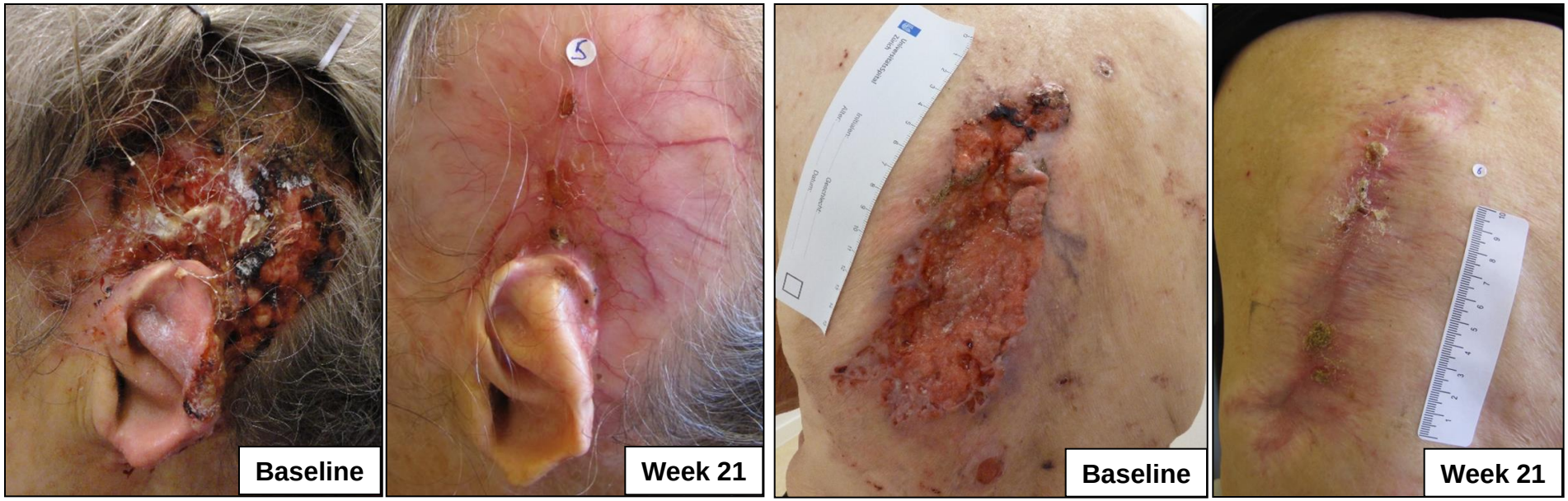
mBCC
Sonidegib 200 mg QD (n = 12)



Sonidegib Dose (daily)	200 mg		800 mg	
	LaBCC	mBCC	LaBCC	mBCC
Decrease in best percentage change from baseline, %	92	92	90	84
Increase or no change in best percentage change from baseline, %	8	8	10	16

CR, complete response; LaBCC, locally advanced BCC; mBCC, metastatic BCC; PD, progressive disease; PR, partial response; QD, once-daily; SD, stable disease; UNK, unknown.

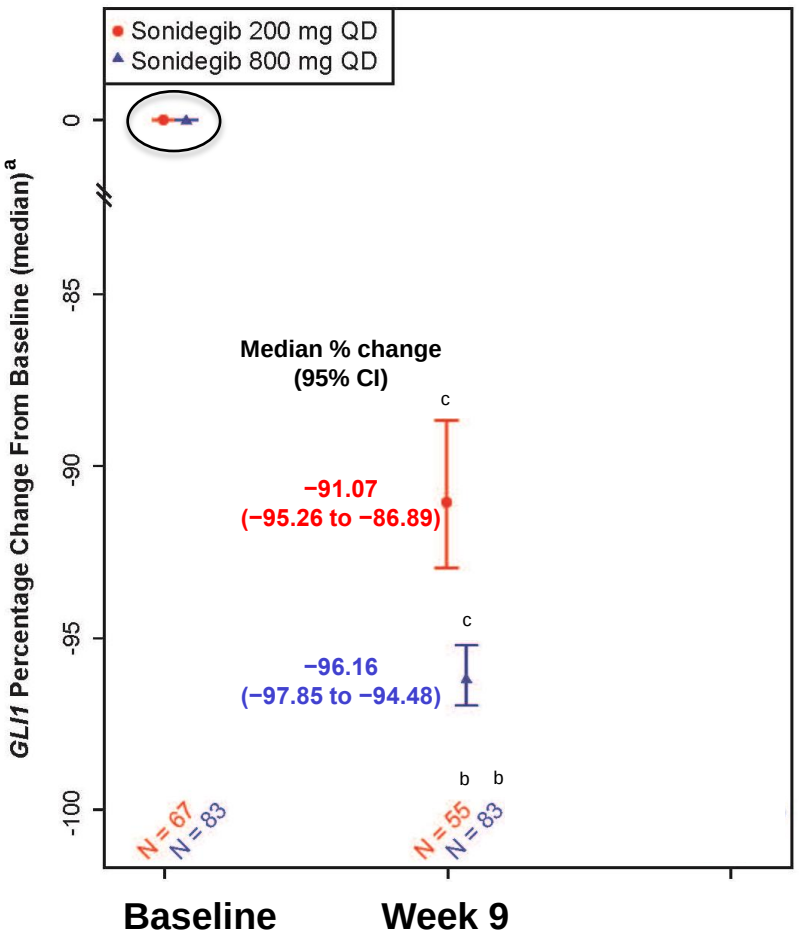
Response in Patient Treated With Sonidegib 800 mg



Photographs provided by R. Dummer, Zürich, Switzerland.

- Patient with aggressive LaBCC treated with sonidegib 800 mg achieved an overall response of PR by central and investigator review

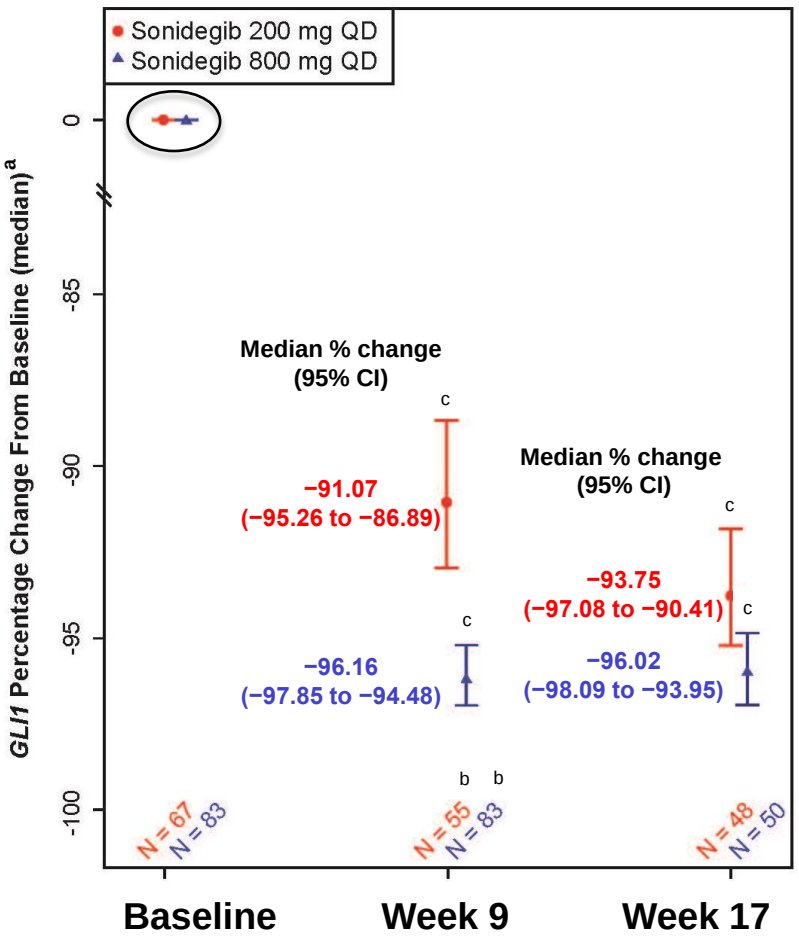
Percentage Change in *GLI1* Levels by Dose



- *GLI1* expression was analyzed by qRT-PCR in tumor tissue collected at baseline, week 9, and week 17
- *GLI1* baseline levels were similar in patients with LaBCC and those with mBCC and in patients receiving sonidegib 200 mg and those receiving 800 mg
- Longitudinal analyses showed a substantial reduction in *GLI1* levels from baseline at weeks 9 and 17 (range of median percentage change, −91% to −96%)
  - No notable differences were seen between weeks 9 and 17
  - Results were similar with both doses
- *GLI1* reductions from baseline were similar in patients with LaBCC and those with mBCC in analyses adjusted for dose, BCC subtype, and multiple testing

GLI1, glioma-associated oncogene homolog 1; qRT-PCR, quantitative reverse transcription polymerase chain reaction.
[a] Samples were histologically tested prior to *GLI1* measurement to confirm the presence of tumor. [b] $P = .11$ for 800 mg vs 200 mg, with adjustment for multiple testing at the biomarker level (unadjusted $P = .03$). [c] Unadjusted $P < .0001$ vs baseline.
N = patients with valid biomarker samples.

Percentage Change in *GLI1* Levels by Dose



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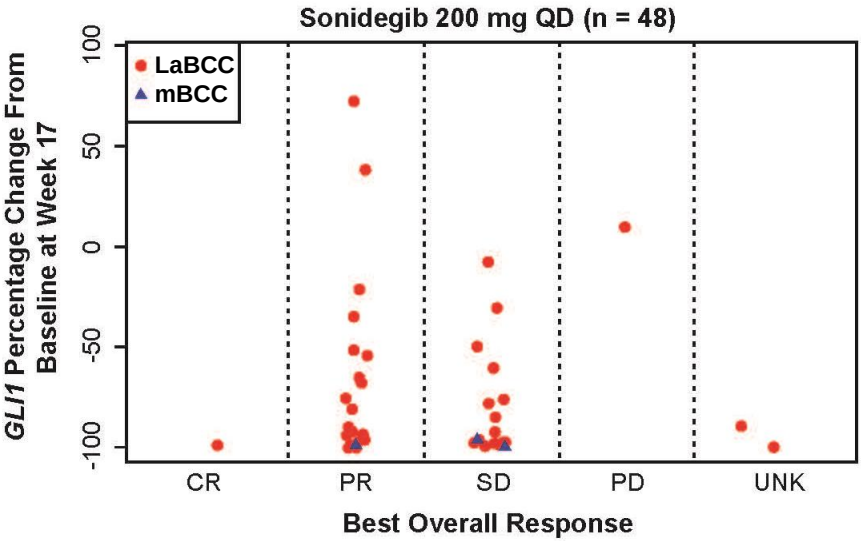
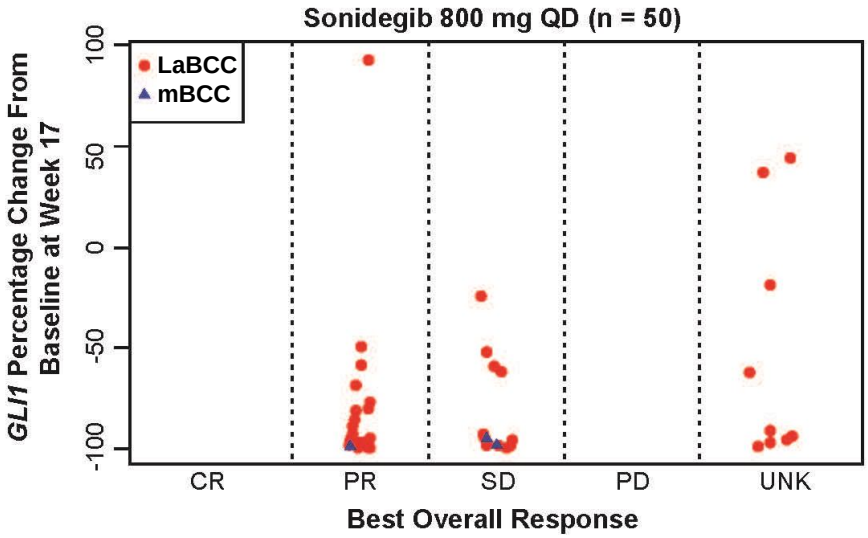
[a] Samples were histologically tested prior to *GLI1* measurement to confirm the presence of tumor. [b] $P = .11$ for 800 mg vs 200 mg, with adjustment for multiple testing at the biomarker level (unadjusted $P = .03$). [c] Unadjusted $P < .0001$ vs baseline.
N = patients with valid biomarker samples.

Association of *GLI1* and Response (Primary Analysis)

- Patients with disease control (CR, PR, or SD) had substantial reductions in *GLI1* levels from baseline with both doses of sonidegib; results were similar at weeks 9 and 17





Best Overall Response (Week 17)	Sonidegib 200 mg QD		Sonidegib 800 mg QD	
	N	Median % Change (95% CI)	N	Median % Change (95% CI)
CR	1	−99.47	0	–
PR	23	−90.79 (−95.49 to −64.40)	26	−96.96 (−98.80 to −85.84)
SD	21	−96.58 (−98.13 to −76.51)	15	−96.07 (−99.31 to −62.11)
PD	1	+10.19	0	–
UNK	2	−94.24 (−99.83 to −88.66)	9	−91.81 (−97.48 to 34.72)

CR, complete response; *GLI1*, glioma-associated oncogene homolog 1; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; UNK, unknown.

Adverse Events

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
AEs in ≥ 20% of Patients, Any Grade, %; Grade 3/4, %[a]	Primary[b]	12-Month[c]	Primary[b]	12-Month[c]
All AEs	95; 30	98; 38	100; 56	100; 59
Muscle spasms	49; 3	52; 3	67; 5	69; 5
Alopecia	43; 1	49; 0	55; 0	57; 0
Dysgeusia	38; 0	41; 0	59; 1	60; 0
Nausea	33; 1	35; 1	45; 3	47; 3
CK increased	29; 6	30; 6	37; 13	37; 13
Fatigue	29; 0	29; 0	36; 2	36; 2
Weight decreased	27; 1	29; 3	38; 5	42; 6
Diarrhea	24; 0	30; 1	22; 0	23; 0
Appetite decreased	19; 0	23; 0	31; 4	32; 4
Myalgia	19; 0	19; 0	26; 2	26; 2
Vomiting	6; 1	8; 1	26; 1	27; 1

AE, adverse event; CK, creatine kinase.

[a] Safety was assessed throughout treatment until 30 days following the last dose. AEs were assessed according to Common Terminology Criteria for Adverse Events v4.03.

[b] Data cutoff, June 28, 2013; median follow-up, 13.9 months.

[c] Data cutoff, December 31, 2013; median follow-up, 20.0 months.

Muscle-Related Adverse Events

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
AEs in ≥ 20% of Patients, Any Grade, %; Grade 3/4, %[a]	Primary[b]	12-Month[c]	Primary[b]	12-Month[c]
All AEs	95; 30	98; 38	100; 56	100; 59
Muscle spasms	49; 3	52; 3	67; 5	69; 5
Alopecia	43; 1	49; 0	55; 0	57; 0
Dysgeusia	38; 0	41; 0	59; 1	60; 0
Nausea	33; 1	35; 1	45; 3	47; 3
CK increased	29; 6	30; 6	37; 13	37; 13
Fatigue	29; 0	29; 0	36; 2	36; 2
Weight decreased	27; 1	29; 3	38; 5	42; 6
Diarrhea	24; 0	30; 1	22; 0	23; 0
Appetite decreased	19; 0	23; 0	31; 4	32; 4
Myalgia	19; 0	19; 0	26; 2	26; 2
Vomiting	6; 1	8; 1	26; 1	27; 1

AE, adverse event; CK, creatine kinase.

[a] Safety was assessed throughout treatment until 30 days following the last dose. AEs were assessed according to Common Terminology Criteria for Adverse Events v4.03.

[b] Data cutoff, June 28, 2013; median follow-up, 13.9 months.

[c] Data cutoff, December 31, 2013; median follow-up, 20.0 months.

Gastrointestinal/Taste-Related Adverse Events

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
AEs in ≥ 20% of Patients, Any Grade, %; Grade 3/4, %[a]	Primary[b]	12-Month[c]	Primary[b]	12-Month[c]
All AEs	95; 30	98; 38	100; 56	100; 59
Muscle spasms	49; 3	52; 3	67; 5	69; 5
Alopecia	43; 1	49; 0	55; 0	57; 0
Dysgeusia	38; 0	41; 0	59; 1	60; 0
Nausea	33; 1	35; 1	45; 3	47; 3
CK increased	29; 6	30; 6	37; 13	37; 13
Fatigue	29; 0	29; 0	36; 2	36; 2
Weight decreased	27; 1	29; 3	38; 5	42; 6
Diarrhea	24; 0	30; 1	22; 0	23; 0
Appetite decreased	19; 0	23; 0	31; 4	32; 4
Myalgia	19; 0	19; 0	26; 2	26; 2
Vomiting	6; 1	8; 1	26; 1	27; 1

AE, adverse event; CK, creatine kinase.

[a] Safety was assessed throughout treatment until 30 days following the last dose. AEs were assessed according to Common Terminology Criteria for Adverse Events v4.03.

[b] Data cutoff, June 28, 2013; median follow-up, 13.9 months.

[c] Data cutoff, December 31, 2013; median follow-up, 20.0 months.

Other Adverse Events of Interest

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
AEs in ≥ 20% of Patients, Any Grade, %; Grade 3/4, %[a]	Primary[b]	12-Month[c]	Primary[b]	12-Month[c]
All AEs	95; 30	98; 38	100; 56	100; 59
Muscle spasms	49; 3	52; 3	67; 5	69; 5
Alopecia	43; 1	49; 0	55; 0	57; 0
Dysgeusia	38; 0	41; 0	59; 1	60; 0
Nausea	33; 1	35; 1	45; 3	47; 3
CK increased	29; 6	30; 6	37; 13	37; 13
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AE, adverse event; CK, creatine kinase.

[a] Safety was assessed throughout treatment until 30 days following the last dose. AEs were assessed according to Common Terminology Criteria for Adverse Events v4.03.

[b] Data cutoff, June 28, 2013; median follow-up, 13.9 months.

[c] Data cutoff, December 31, 2013; median follow-up, 20.0 months.

Serious Adverse Events and On-Treatment Deaths

Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
Analysis	**Primary[a]**	**12-Month[b]**	**Primary[a]**	**12-Month[b]**
Serious AEs (all grades) in ≥ 1% of patients overall, %				
Rhabdomyolysis	1	1	3	3
CK increased	1	1	2	3
Pneumonia	1	1	1	1
Syncope	1	1	1	1
Vomiting	0	0	3	3
Anemia	0	0	2	2
Nausea	0	0	2	2
Dehydration	0	1	1	1
Deaths on-treatment (within 30 days of last dose), n (%)				
Disease progression/study indication[c]	0	0	2 (1)	2 (1)
Cardiac related[d]	0	0	2 (1)	3 (2)
Sepsis[e]	0	0	0	1 (1)
Respiratory arrest[f]	0	0	0	1 (1)

[a] Data cutoff, June 28, 2013; median follow-up, 13.9 months. [b] Data cutoff, December 31, 2013; median follow-up, 20.0 months. [c] Both patients had mBCC; deaths occurred on study days 16 and 38. [d] Patients with LaBCC died on study days 18, 196, and 349 of cardiac failure, cardiac death, and cardiac arrest, respectively; these patients had preexisting confounding conditions at baseline. [e] Patient with mBCC died on study day 391. [f] Patient with mBCC died on study day 433.

- An independent safety review and adjudication committee on muscle toxicity defined rhabdomyolysis as CK levels > 10 × baseline (or upper limit of normal [ULN] if baseline was not available) plus a 1.5-fold increase in serum creatinine from the baseline level (or ULN)—based on this definition, ***none of the reported cases of rhabdomyolysis were confirmed***

Conclusions

- The BOLT study met its primary endpoint (ORR) for both treatment arms
- With an additional 6 months of follow-up, sonidegib continued to exhibit sustained, clinically meaningful responses in patients with advanced BCC
- GLI1 levels were reduced from baseline in patients with disease control
- Sonidegib has acceptable safety and tolerability; no new safety concerns emerged with longer follow-up
- Maintenance or improvement in quality of life was reported by most patients with advanced BCC treated with sonidegib (Dummer et al. ESMO 2014 [poster 1125P])
- Sonidegib is a promising new treatment option for patients with advanced BCC; the 200-mg dose has been selected for future use based on its more favorable benefit-risk profile

Acknowledgments

- Patients and their families
- Global study investigators, their clinical teams, and study site staff
- Study steering committee: Reinhard Dummer, Michael Migden, Alex Guminski, Ralf Gutzmer, John Lear
- Study independent data monitoring committee: Mark Pittelkow, Jürgen Becker, Stephen George
- Study efficacy independent review committee: Vernon Sondak, James Grichnik, Lawrence Schwartz
- Muscle safety review and adjudication committee: Robert Rosenson, Vinay Chaudhry, Paul Thompson
- Novartis clinical study personnel