Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma (BCC): 24-month update of the pivotal ERIVANCE BCC study

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Introduction

- Basal cell carcinoma (BCC) is the most common human malignancy[1]
  - Although most BCCs are amenable to surgery, a small subset progress to become locally advanced (la) or metastatic (m)[1]
  - Therapies for advanced basal cell carcinoma (aBCC) are limited[1]
- Abnormal Hedgehog (Hh) pathway signaling is a key driver in BCC pathogenesis[1,2]
- Vismodegib, a first-in-class small-molecule Hh pathway inhibitor,[3] is FDA approved for the treatment of adults with mBCC, or with laBCC that has recurred following surgery, or who are not candidates for surgery or radiation therapy

FDA, US Food and Drug Administration.

1. Sekulic A et al. N Engl J Med. 2012;366:2171-2179. 2. Macha MA et al. Cancer Manag Res. 2013;5:197-203.
3. LoRusso PM et al. Clin Cancer Res. 2011;17:2502-2511.

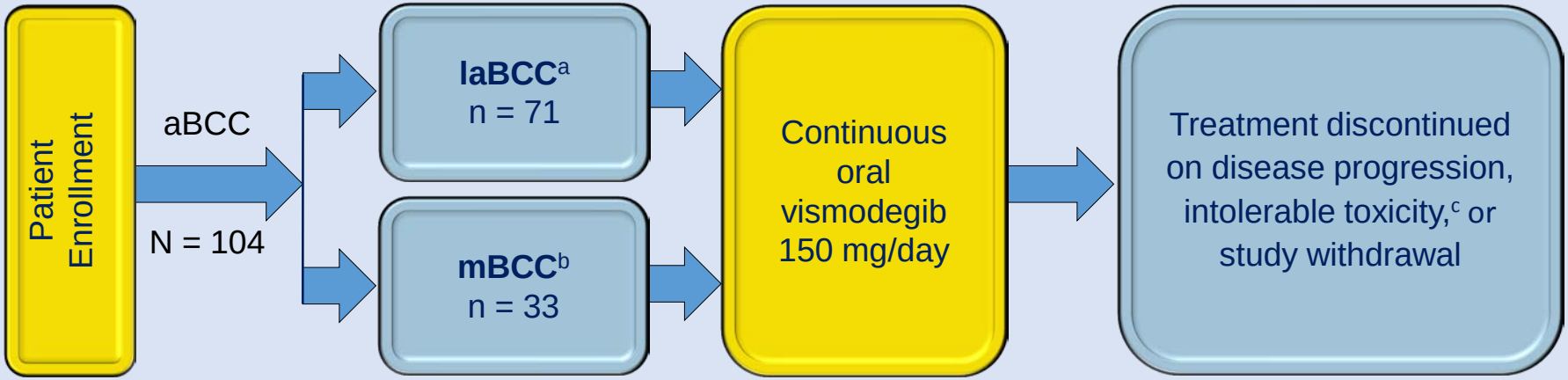
ERIVANCE BCC

- ERIVANCE BCC trial was an international, 2-cohort, nonrandomized study in which patients with laBCC or mBCC received 150 mg of oral vismodegib daily. Results from the primary analysis (26 Nov 2010) for the efficacy-evaluable population have been published.[1]
- Primary endpoint was objective response rate by independent review: 42.9% (laBCC patients) and 30.3% (mBCC patients).
  - Objective response rate by investigator review: 60.3% on laBCC patients and 45.5% in mBCC patients.
  - Median duration of response: By independent review: 7.6 months (both laBCC and mBCC) and by investigator review: 7.6 months (laBCC) and 12.9 months (mBCC)
- Here we present the safety and investigator-assessed efficacy results updated 24 months after the primary analysis (29 Nov 2012)

1. Sekulic A et al. N Engl J Med. 2012;366:2171-2179.

Study design

- **Primary end point:** ORR by independent review
- **Secondary end points:** investigator-assessed ORR, PFS, DOR, OS, and safety



ORR, objective response rate; PFS, progression-free survival; DOR, duration of response; OS, overall survival.
[a]Surgery inappropriate because of multiple recurrences, or substantial morbidity or deformity anticipated; radiotherapy also inappropriate.
[b]Radiographically measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.0.
[c]Four-week dose interruption allowed, if required, to manage toxicity.

Eligibility

- ≥18 years of age, adequate organ function, ECOG PS ≤2
- **laBCC:**
  - ≥1 lesion (longest diameter ≥10 mm) that was considered inoperable, or for which surgery was considered inappropriate because of (1) multiple previous recurrences and low likelihood of cure, or (2) substantial morbidity or deformity
  - Prior radiotherapy to ≥1 target lesion required, unless medically contraindicated or inappropriate
  - Further radiotherapy inappropriate
- **mBCC:**
  - Radiographically measurable disease per RECIST v1.0 (including nodal metastases)

ECOG PS, Eastern Cooperative Oncology Group performance status.
Sekulic A et al. N Engl J Med. 2012;366:2171-2179.

Baseline demographics

Variable	laBCC n = 63[a]	mBCC n = 33
Age, median (range), yr	62 (21-101)	62 (38-92)
Sex, n (%)		
Male	35 (55.6)	24 (72.7)
Female	28 (44.4)	9 (27.3)
Race, n (%)		
White	63 (100)	33 (100)
laBCC, n (%)		
Inoperable	24 (38.1)	
Surgery inappropriate	39 (61.9)	–
Multiple previous recurrences	16 (25.4)	
Significant morbidity/deformity likely	32 (50.8)	
Radiotherapy previously administered	13 (20.6)	
Radiotherapy inappropriate/contraindicated	50 (79.4)	

[a]Of 104 patients enrolled, 8 with laBCC were excluded from the efficacy analysis because the independent pathologist did not identify BCC in biopsies taken at baseline or at postbaseline biopsy.

Patient disposition

- At data cutoff, 14 (13.5%) patients continued to receive treatment, and 63 (60.6%) patients were in survival follow-up

Status	laBCC n = 71	mBCC n = 33	All Patients N = 104
Patients still on treatment, n (%)	**12 (16.9)**	**2 (6.1)**	**14 (13.5)**
Discontinued treatment, n (%)	**59 (83.1)**	**31 (93.9)**	**90 (86.5)**
Adverse event	16 (22.5)	5 (15.2)	21 (20.2)
Death	2 (2.8)	1 (3.0)	3 (2.9)
Lost to follow-up	2 (2.8)	1 (3.0)	3 (2.9)
Physician decision to discontinue	6 (8.5)	3 (9.1)	9 (8.7)
Patient decision to discontinue	21 (29.6)	4 (12.1)	25 (24.0)
Disease progression	11 (15.5)	16 (48.5)	27 (26.0)
Other	1 (1.4)	1 (3.0)	2 (1.9)

Data cutoff date: November 29, 2012. Percentages may not equal 100% due to rounding.

Exposure

- Median dose intensity (97%) was comparable to the primary analysis

Exposure	laBCC n = 71	mBCC n = 33	All Patients N = 104
Duration of treatment, mo			
Median	12.7	13.3	12.9
Range	(1.1-42.3)	(0.7-33.4)	(0.7-42.3)
Dose intensity, %			
Median	96.9	98.9	97.4
Range	(58.5-107.5)	(77.4-102.5)	(58.5-107.5)
Total cumulative dose, g			
Median	52.1	60.5	57.6
Range	(3.8-179.9)	(2.9-151.1)	(2.9-179.9)

Objective response

Investigator-Assessed Overall Response[a]	laBCC n = 63		mBCC n = 33		All Patients N = 96[d]
	24-month follow-up[b]	Primary analysis[1]	24-month follow-up[c]	Primary analysis[1]	24-month follow-up
Objective response[e], n (%)	38 (60.3)	38 (60.3)	16 (48.5)	15 (45.5)	54 (56.3)
Complete response, n (%)	20 (31.7)	20 (31.7)	0	0	20 (20.8)
Partial response, n (%)	18 (28.6)	18 (28.6)	16 (48.5)	15 (45.5)	34 (35.4)
95% CI for objective response	47.2-71.7	47-72	30.8-66.2	28-62	45.7-66.4
Stable disease, n (%)	15 (23.8)	15 (23.8)	14 (42.4)	15 (45.5)	29 (30.2)
Progressive disease, n (%)	6 (9.5)	6 (10)	2 (6.1)	2 (6)	8 (8.3)
Duration of response, months	Median (95% CI)	Median (range)	Median (95% CI)	Median (range)	Median (95% CI)
	26.2 (9.0-NE)	7.6 (2.1-11.1)	14.8 (5.5-17.0)	12.9 (1.9-12.9)	16.1 (9.5-26.2)

[a]Response defined as meeting either of the following criteria: ≥30% reduction in tumor size, confirmed by physical examination or radiography, or complete resolution of ulceration present at baseline; [b]Of 104 patients enrolled, 8 with laBCC were excluded from the efficacy analysis because the independent pathologist did not identify BCC in biopsies taken at baseline or at post baseline biopsy. Four patients were inevaluable for response; [c]One patient was inevaluable for response; [d]Five patients were inevaluable for response; [e]Objective response defined as a complete or partial response determined on 2 consecutive assessments ≥4 weeks apart.

1. Sekulic A et al. N Engl J Med. 2012;366:2171-2179.

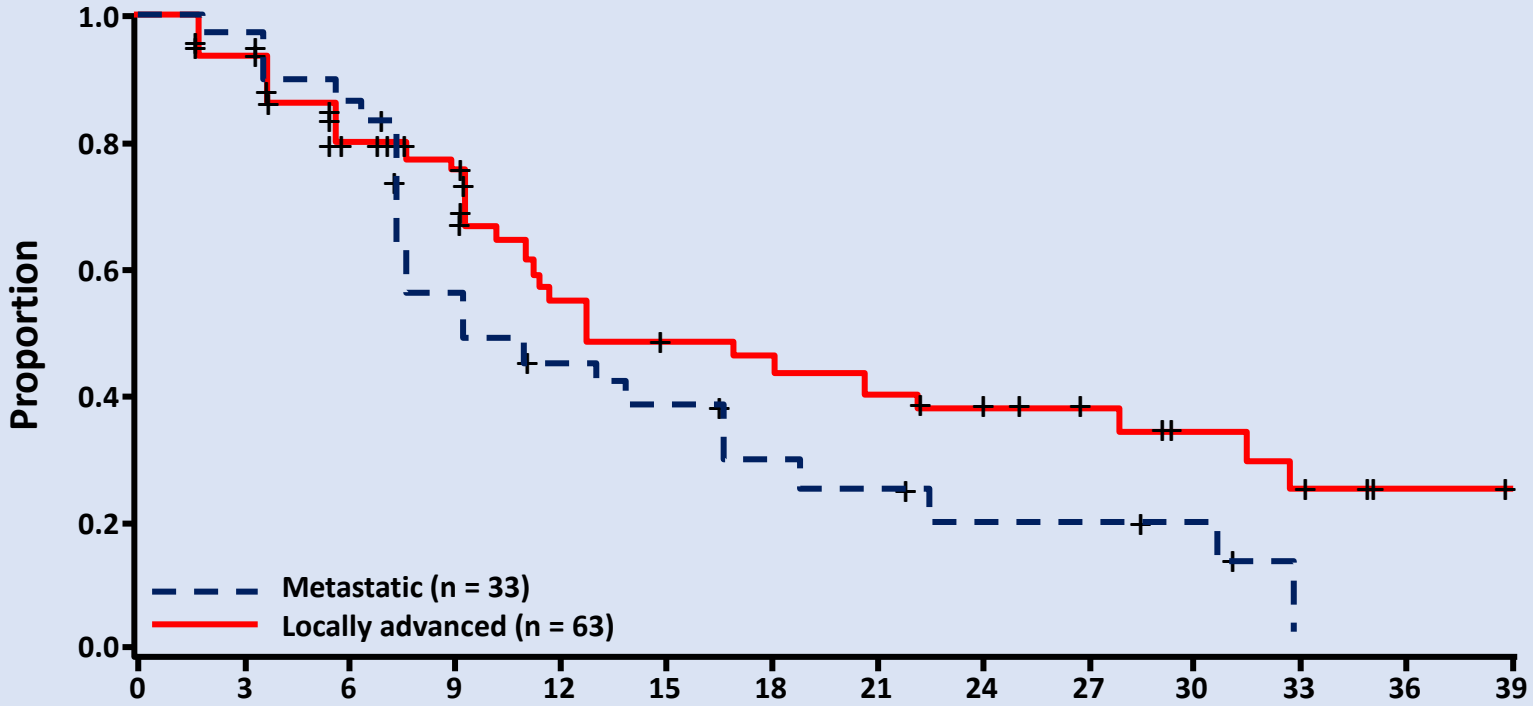
Progression-free survival and overall survival

Survival	laBCC n = 63	mBCC n = 33	All Patients N = 96
Progression-free survival, mo			
Median	12.9	9.3	12.8
Range	0.0+ – 38.8+	0.0+ – 32.8	0.0+ – 38.8+
Overall survival, mo			
Median	Not estimable	33.4	Not estimable
Range	2.4+ – 43.0+	6.7 – 40.2+	2.4+ – 43.0+

+ = censored value.

Progression-free survival

Kaplan-Meier plot of investigator -assessed progression-free survival (PFS INV)

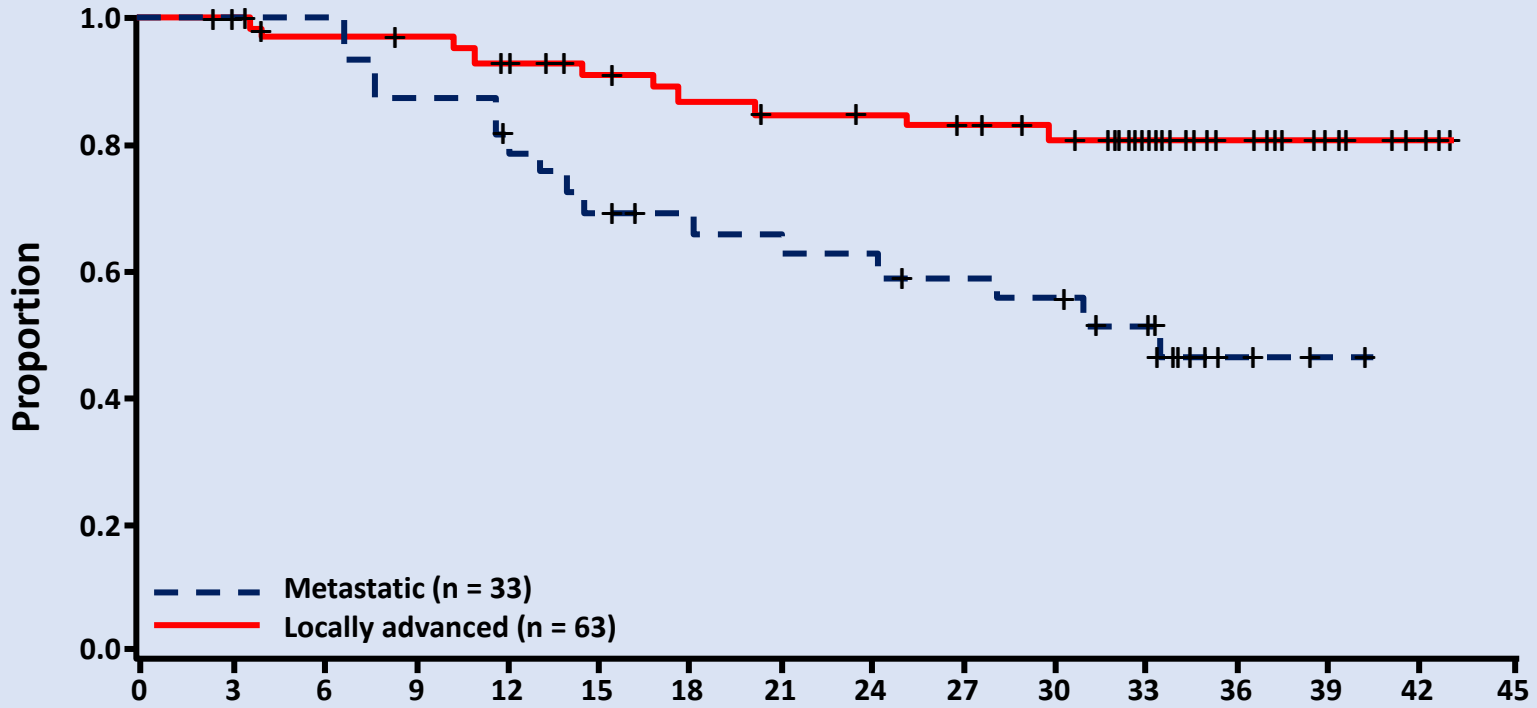


Number at Risk														
Metastatic	33	31	26	16	12	10	7	6	4	4	3	0	0	0
Locally advanced	63	55	42	38	24	19	17	16	13	10	7	5	1	0

INV, investigator.

Overall survival

Kaplan-Meier plot of investigator-assessed duration of survival



Number at Risk																
Metastatic	33	33	33	29	25	22	20	18	18	16	15	12	3	1	0	0
Locally advanced	63	61	57	55	52	48	45	43	41	39	35	25	15	7	3	0

NE, not estimable.

Adverse events in >10% of patients by maximum grade

Adverse Event[a], n (%)	NCI CTCAE Grade (N = 104)					
	Total	1	2	3	4	5
Any adverse event	104† (100)	9 (8.7)	39 (37.5)	35 (33.7)	13 (12.5)	7 (6.7)
Muscle spasms	74 (71.2)	46 (44.2)	22 (21.2)	6 (5.8)	0	0
Alopecia	68 (65.4)	48 (46.2)	20 (19.2)	0	0	0
Dysgeusia	57 (54.8)	31 (29.8)	26 (25.0)	0	0	0
Weight decreased	54 (51.9)	29 (27.9)	17 (16.3)	8 (7.7)	0	0
Fatigue	45 (43.3)	33 (31.7)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Decreased appetite	28 (26.9)	18 (17.3)	7 (6.7)	3 (2.9)	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	4 (3.8)	1 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	0	0
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	0	0	0
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	0	0	0

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[a]Medical Dictionary for Regulatory Activities preferred term. †One patient had one ungraded AE

Serious adverse events (occurring in ≥2 patients)

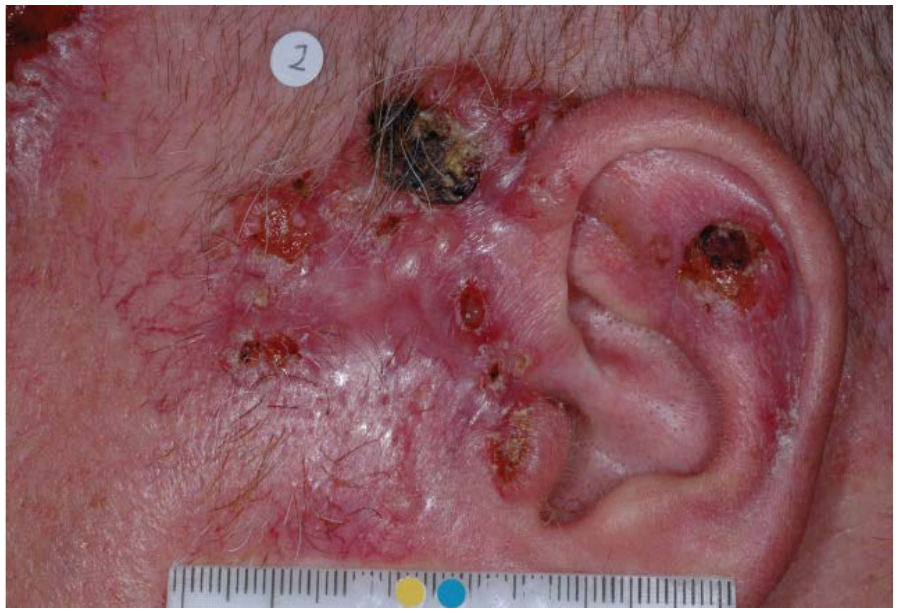
Serious Adverse Event, n (%)	All Patients N = 104
Any	36 (34.6)
Syncope	4 (3.8)
Hip fracture	3 (2.9)
Death	3 (2.9)
Pneumonia	3 (2.9)
Cardiac failure	2 (1.9)
Gastrointestinal hemorrhage	2 (1.9)
Cellulitis	2 (1.9)
Squamous cell carcinoma	2 (1.9)
Pulmonary embolism	2 (1.9)
Deep vein thrombosis	2 (1.9)

Deaths

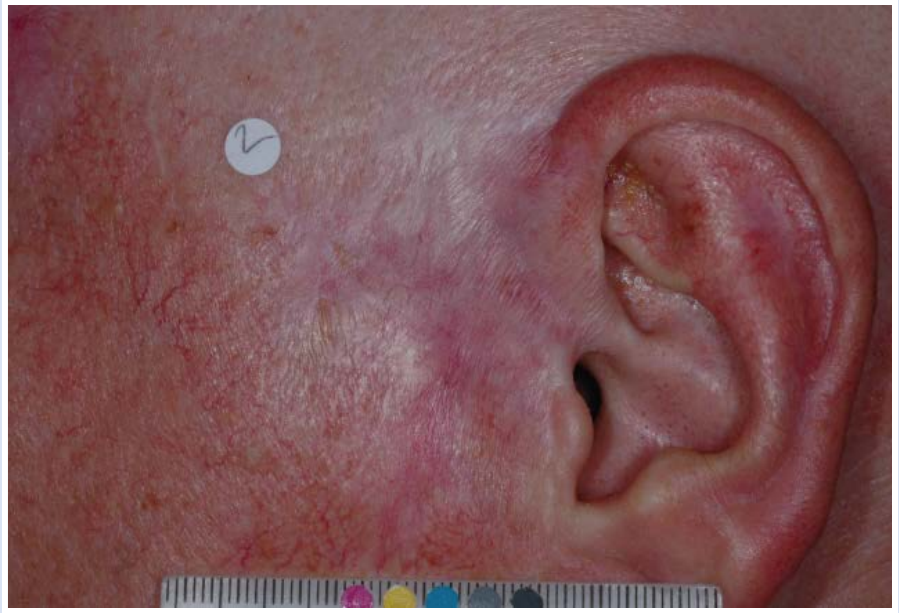
- In the update period following the primary analysis, 13 additional deaths were reported, leading to a total count of 29 deaths
- These occurred during survival follow-up (while the patients were not receiving study drug) and were not considered to be related to vismodegib

	laBCC n = 71	mBCC n = 33	All Patients N = 104
Deaths (total), n (%)	13 (18.3)	16 (48.5)	29 (27.9)
Death while on study drug	5 (7.0)	1 (3.0)	6 (5.8)
Death during survival follow-up	8 (11.3)	15 (45.5)	23 (22.1)
Cause of death, n (%)			
Disease progression	4 (5.6)	12 (36.4)	16 (15.4)
Adverse event	6 (8.5)	1 (3.0)	7 (6.7)
Melanoma or metastatic melanoma	2 (2.8)	0	2 (1.9)
General failure to thrive	0	1 (3.0)	1 (1.0)
Other	1 (1.4)	2 (6.1)	3 (2.9)

Response after long-term vismodegib treatment



Screening



Week 104

Conclusions

- Vismodegib is the first approved Hedgehog pathway inhibitor
- With longer duration of follow-up, median duration of response approximately tripled in the laBCC cohort compared with the primary analysis
- The safety profile of vismodegib remained consistent with that reported in the primary analysis