Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med 2012;366:2171-9.

Supplementary Appendix

Supplement to: Sekulic A, Migden MR, Oro AE, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma

Contents

Collaborators

The authors wish to thank the following study investigators: Drs. Nicole Basset-Seguin, Juergen Becker, Stephen Bernard, M. Shane Chapman, Joseph Davies, Brigitte Dréno, David Fisher, Claus Garbe, Joel Gelfand, Anja Gesierich, Martin Gore, Omid Hamid, Christopher Lao, Laurent Mortier, Dedee Murrell, Thomas Olencki, Fernando Quevedo, Dirk Schadendorf, Luc Thomas, and Pierre Vereecken. The authors would like to thank Ling Fu, Cheryl V. Wong, Ron Firestein, and Chris Callahan for their contributions to the molecular analyses; Sravanthi Cheeti for contributions to the pharmacokinetic analysis; A. Barbara Mueller, Dawn Colburn, and Ivor Caro for contributions to clinical data analysis.

Through the Genentech-Curis collaboration, vismodegib was discovered by Genentech and was jointly validated by the parties through a series of preclinical studies. Genentech and Roche collaborated on the clinical development and commercialization of vismodegib.

SUPPLEMENTARY METHODS: TUMOR BIOPSIES IN THE LOCALLY ADVANCED BCC COHORT

Representative tumor biopsies were required for patients in the locally advanced basal-cell carcinoma cohort at baseline and either at the investigator's assessment of best response, if occurring prior to 24 weeks, or at 24 weeks, if patient was still in study and without evidence of progression. The sites, number, and technique of representative biopsies were determined by the investigator on the basis of the size and location of the accessible lesions. The protocol recommended that any areas suspicious for residual disease be biopsied, as well as areas which appeared to be free of disease. The protocol stated that at least one and up to five punch biopsies of at least 3 mm in size, or 14-gauge or larger core needle biopsies, as determined by the investigator, should be obtained. For large, accessible lesions in the skin and/or soft tissues, punch biopsies of 3 to 4 mm were strongly recommended to allow for optimal assessment of residual disease. Biopsies were fixed and paraffin embedded according to site standards and submitted to a central lab for processing and interpretation by an independent pathologist. Archival tumor tissue was also submitted for each patient. Per the statistical analysis plan, if the independent pathologist's interpretation of the baseline biopsy and archival tissue differed, the baseline biopsy result took precedence when determining efficacy-evaluability.

Supplementary Table 1. **Evaluation of Target Lesions by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0).**[1]

Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter
Progressive disease (PD)	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started

Reference

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.

Supplementary Table 2. **Sites of Metastatic Target Lesions.**

Site of lesion	Number of patients (%)
Lung	22 (66.7)
Lymph nodes	7 (21.2)
Other*	4 (12.1)
Mediastinum	3 (9.1)
Central nervous system	2 (6.1)
Liver	2 (6.1)
Forehead[†]	2 (6.1)
Neck	2 (6.1)
Bone	1 (3.0)
Skin/Soft tissue	1 (3.0)
Scalp[§]	1 (3.0)
Cheek[¶]	1 (3.0)

Note: patients may have had multiple sites of disease. Per protocol, patients with BCC tumors without externally visible disease but with radiographically measurable disease (e.g., tumor beneath skin graft) were considered as having metastatic BCC.

*Other includes: other soft tissue, spleen, kidney, axilla.

[†]Forehead tumors covered by skin graft/flap; one patient also had a lymph node target lesion.

[§]Scalp lesion in a patient who also had lung target lesions.

[¶]Subcutaneous tumor lateral to mandible.

Supplementary Table 3. **Reasons for Vismodegib Discontinuation.**

	mBCC (N=33)	**laBCC (N=71)**
Patients remaining on treatment* — no. (%)	19 (57.6)	32 (45.1)
Total vismodegib treatment discontinuations — no. (%)	14 (42.4)	39 (54.9)
Adverse event	1 (3.0)	11 (15.5)
Death	1 (3.0)	2 (2.8)
Lost to follow-up	2 (6.1)	1 (1.4)
Physician decision to discontinue therapy	2 (6.1)	1 (1.4)
Subject decision to discontinue therapy	2 (6.1)	18 (25.4)
Disease progression	6 (18.2)	5 (7.0)
Other	0 (0.0)	1 (1.4)

*As of data cutoff: November 26, 2010, nine months after last patient enrolled.

laBCC = locally advanced BCC; mBCC = metastatic BCC.

Supplementary Table 4. **Serious Adverse Events.**

	Any grade (N=104)	**Grade 5 (fatal) (N=104)**
- Any serious adverse events -	26 (25.0%)	7 (6.7%)
Death of unknown cause	3 (2.9%)	3 (2.9%)
Cardiac failure	2 (1.9%)	
Pneumonia	2 (1.9%)	
Pulmonary embolism	2 (1.9%)	
Acute myocardial infarction	1 (1.0%)	1 (1.0%)
Angina pectoris	1 (1.0%)	
Left ventricular dysfunction	1 (1.0%)	
Myocardial infarction	1 (1.0%)	
Restrictive cardiomyopathy	1 (1.0%)	
Eye hemorrhage	1 (1.0%)	
Aphagia	1 (1.0%)	
Gastrointestinal hemorrhage	1 (1.0%)	
Small intestinal obstruction	1 (1.0%)	
Cholestasis	1 (1.0%)	
Cellulitis	1 (1.0%)	
Viral meningitis	1 (1.0%)	
Urinary tract infection	1 (1.0%)	
Cervical vertebral fracture	1 (1.0%)	
Drug toxicity	1 (1.0%)	
Spinal compression fracture	1 (1.0%)	
Dehydration	1 (1.0%)	
Hypokalemia	1 (1.0%)	
Malignant melanoma	1 (1.0%)	
Metastatic malignant melanoma	1 (1.0%)	
Metastatic squamous cell carcinoma	1 (1.0%)	
Esophageal carcinoma	1 (1.0%)	
Sarcoma	1 (1.0%)	
Squamous cell carcinoma	1 (1.0%)	
Convulsion	1 (1.0%)	
Ischemic stroke	1 (1.0%)	1 (1.0%)
Meningeal disorder (“meningeal disease”)	1 (1.0%)	1 (1.0%)

Syncope	1 (1.0%)	
Renal failure	1 (1.0%)	
Pneumonia aspiration	1 (1.0%)	
Deep vein thrombosis	2 (1.9%)	
Hemorrhage	1 (1.0%)	
Hypovolemic shock	1 (1.0%)	1 (1.0%)
Orthostatic hypotension	1 (1.0%)	

Multiple occurrences of a specific adverse event for a patient were counted once.

Brief narratives of patients who had Grade 5 (fatal) adverse events are given below. In each case, the treating physician assessed the fatal adverse event as being unrelated to vismodegib.

1) A 59-year-old female with laBCC, hypertension, hypercholesterolemia, and two prior femoral−popliteal bypass operations experienced ischemic strokes on day 448 and day 452. Vismodegib was discontinued on day 452. A third ischemic stroke occurred on day 475. The patient died on day 514.

2) A 51-year-old male with laBCC, hypertension, and hypercholesterolemia experienced coughing and shortness of breath after a fall on day 535 for which he did not seek medical attention. He was found dead at home the following day; the cause of death was reported to be acute myocardial infarction.

3) A 72-year-old male with mBCC, autonomic neuropathy, hypotension, and paroxysmal atrial fibrillation died at home on day 350; the cause of death was unknown.

4) A 55-year-old female with laBCC and a history of renal deficiency was hospitalized on day 88 for diuretic intoxication, and on days 272 and 309

for hypokalemia, each related to diuretic use without prescription. On day 335, the patient died of an unknown cause. The investigator assessed diuretics to be a suspected cause of death.

5) A 56-year-old male with laBCC and a history of hypertension, concurrent cranial nerve palsies, arrhythmia (on flecainaide acetate), hypokalemia, hyponatremia, facial paralysis, brain swelling, and transient ischemic attacks was hospitalized for viral meningitis on day 73. He was again hospitalized for “meningeal disease” on day 113, at which time MRI scans revealed widespread leptomeningeal disease, cord edema, and an “extensive ongoing tumor of a perineural mechanism well posteriorly into the brainstem”. Vismodegib was discontinued on day 123. The patient died on day 124 due to “meningeal disease”; the physician reported that death was most likely due to progression of BCC and possibly concurrent illness.

6) An 89-year-old female with laBCC, aortic and mitral insufficiency, chronic atrial fibrillation, coronary heart disease, type 2 diabetes mellitus, and hypertension was hospitalized on day 67 for cardiac failure and pneumonia. Vismodegib was discontinued on day 67. On day 93, she was hospitalized for left ventricular systolic dysfunction and renal failure, and died on day 109 due to an unknown cause.

7) An 85-year-old male with laBCC and concurrent Alzheimer’s disease, arteritis, diabetes mellitus, hyperlipidemia, and ischemic cardiomyopathy, experienced hypovolemic shock on day 188, which resulted in the patient’s death the next day. The investigator assessed concurrent illness as another possible cause of death.

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1: Steady-state plasma vismodegib concentrations at approximately week 8. Concentrations of vismodegib were determined using a validated solid-phase extraction liquid chromatography–tandem mass spectrometry method.[1] All = All patients; laBCC = locally advanced basal-cell carcinoma patients; mBCC = metastatic basal-cell carcinoma patients.

Supplementary Figure 2: Hedgehog pathway activation in archival patient tumor samples and normal skin was assessed by relative expression levels of *GLI1* and *PTCH2*, as measured by qRT-PCR (see Methods). Data are normalized to *SMO* expression levels.

*Three control specimens below *GLI1* detection limit.

†One control specimen below *PTCH2* detection limit.

laBCC = locally advanced basal-cell carcinoma; mBCC = metastatic basal-cell carcinoma.

Supplementary Figure 3: Photos of patients with locally advanced basal-cell carcinoma (laBCC) treated with vismodegib.

Panel A: Seventy-one-year-old female with inoperable, extensive laBCC involving the scalp and invading into the central nervous system; no prior therapy had been given. Black areas represented exposed skull bone. Radiotherapy was considered contraindicated due to the massive involvement of tumor as well as recent history of brain abscess. No residual BCC was detected on sampling biopsies at week 24. This patient was assessed as a complete responder by independent review and to have stable disease by the investigator.

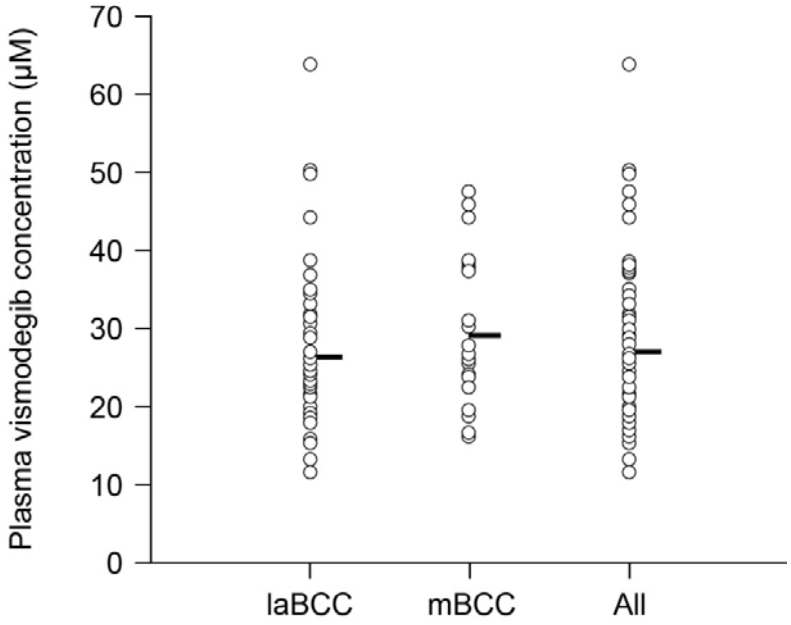
Panel B: Forty-six–year-old male with laBCC of the eyebrow and preauricular area. The patient had undergone multiple prior surgeries in other areas as well as topical imiquimod treatment. There was anticipated substantial morbidity and/or deformity from surgery. Radiotherapy was

considered contraindicated due to the risk of retinal damage and suspected Gorlin syndrome. At week 24, there was residual BCC observed in the eyebrow lesion but not the preauricular lesion. This patient was considered to have stable disease by independent assessment and to be a partial responder per investigator.

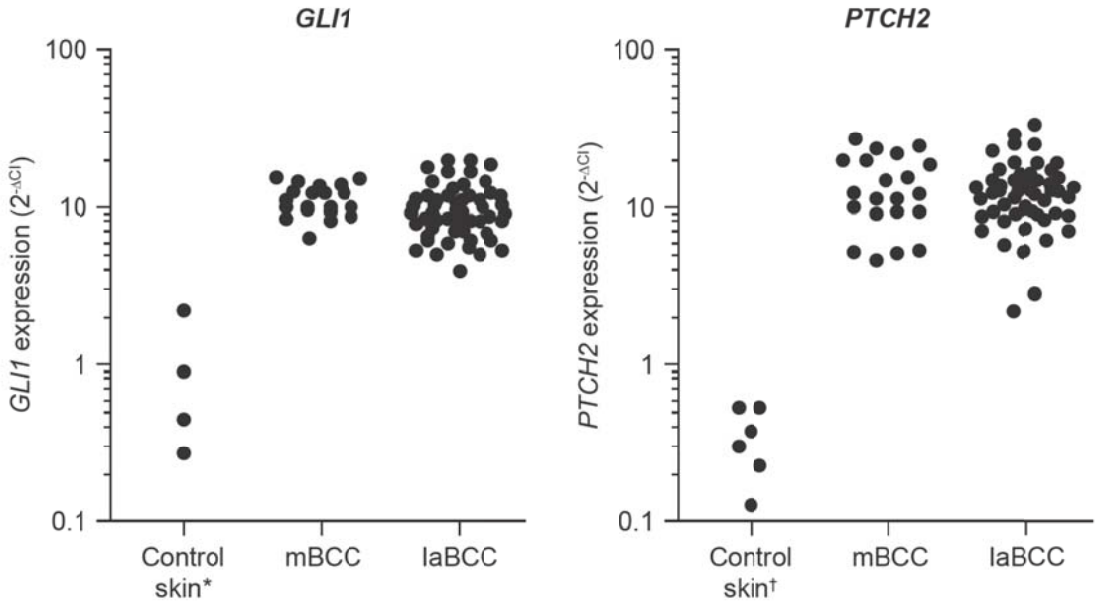
Reference

1. Ding X, Chou B, Graham RA, et al. Determination of GDC-0449, a small molecule inhibitor of the Hedgehog signaling pathway, in human plasma by solid phase extraction-liquid chromatographic-tandem mass spectrometry. J Chromatography B 2010;878:785-90.

Supplementary Figure 1



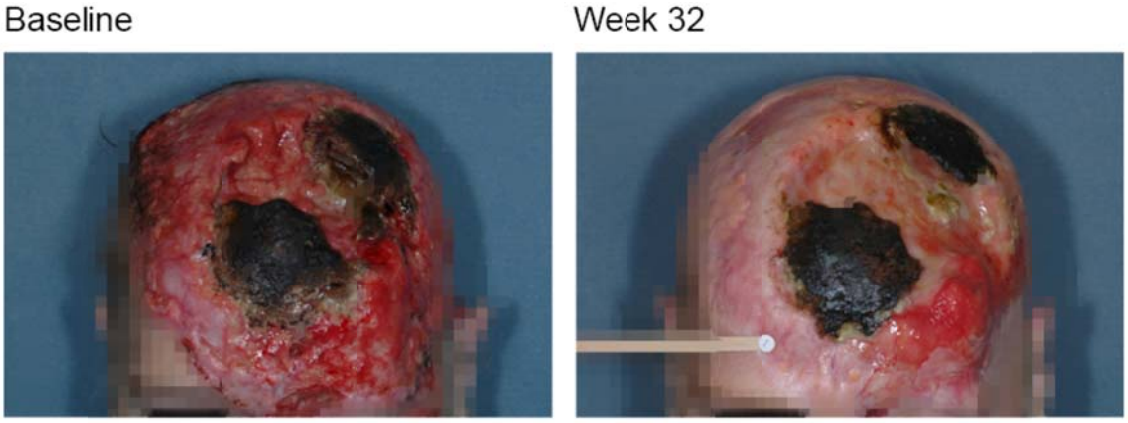
Supplementary Figure 2



Objective response did not appear to be associated with expression levels of *GLI1* and *PTCH2* markers in analyses comparing investigator- and/or independently-assessed response rates across tertiles of biomarker expression (data not shown).

Supplementary Figure 3

A



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