Targeted Therapy Comes to BCC: Hedgehog Inhibitors

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Disclosures

• Genentech:
  • Prior
  • Consultant, Speaker’s Bureau, & Advisory Board
  • Industry sponsored clinical trials
  • Planning
  • Completion at Mayo Clinic Florida, Investigator initiated vismodegib research support via Saint Louis University, funding via Genentech,

• I am a Mohs Surgeon and routinely manage BCCs surgically.
Outline:

• Part I: History of Drug Development & January 2012 FDA Approval of vismodegib for “laBCC” and mBCC.
  • Efficacy and Adverse Events

• Part II: Since 2012, what have we learned.
  • Neo adjuvant, alternate dosing regimens, drug resistance, cSCCs emerge during tx, long term safety

• Part III: Sonidegib FDA approval 2015 for laBCC

• Part IV: Case Presentations
Attention spans

Consumer Insights, Microsoft Canada
We know human attention is dwindling

12 seconds
The average human attention span in 2000.

8 seconds
The average human attention span in 2013.

9 seconds
The average attention span of a goldfish.
HHIs and BCC

• Hedgehog inhibitor, binds to smoothened, blocking cell proliferation
• FDA approved vismodegib January 2012 for locally advanced BCC (laBCC) and metastatic BCC (mBCC), sonidegib in 2015 for laBCC
• It works, at times impressively, but not always
• Durability of response is unknown
• Embryotoxic and teratogenic
• Side effects are very common, muscle cramps (70%), altered or loss of taste (50%) and hair loss (50%)
• Drug resistance can develop & SCCs can emerge during treatment
• Neoadjuvant role reported, modest improvement (30%) reduced Mohs surgery wound’s surgical size
• Ideal dosing and duration of therapy is being studied (MIKIE Trial)
• Other Hedge Hog Inhibitors in the pipeline
• For some patients, impactful, a game changer…laBCC and BCNS
• Any questions?
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  • Efficacy and Adverse Events

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• Part IV: Case Presentations
1950s: Idaho

1970s: Drosophila labs

Cyclops

Corn lilies: cyclopamine

Hedgehog pathway/Embryogenesis
Hedgehog Pathway (Hh)

- Important **regulator** of growth & development in embryogenesis

- *Dormant* during adulthood (Ptch=tumor suppressor)

- **Inappropriate activation** in many cancers: BCC, medulloblastoma, pancreatic, prostate, ovarian, colon, sarcomas, etc.

Mechanism of Action

Expert Opin. Drug Discov. (2014) 9(8)
Molecular Pathways: Novel Approaches for Improved Therapeutic Targeting of Hedgehog Signaling in Cancer Stem Cells

Verline Justilien and Alan P. Fields

Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma

Aleksandar Sekulic, M.D., Ph.D., Michael R. Migden, M.D., Anthony E. Oro, M.D., Ph.D., Luc Dirix, M.D., Ph.D., Karl D. Lewis, M.D., John D. Hainsworth, M.D., James A. Solomon, M.D., Ph.D., Simon Yoo, M.D., Sarah T. Arron, M.D., Ph.D., Philip A. Friedlander, M.D., Ph.D., Ellen Marmur, M.D., Charles M. Rudin, M.D., Ph.D., Anne Lynn S. Chang, M.D., Jennifer A. Low, M.D., Ph.D., Howard M. Mackey, Ph.D., Robert L. Yauch, Ph.D., Richard A. Graham, Ph.D., Josina C. Reddy, M.D., Ph.D., and Axel Hauschild, M.D.

Erivance: Pivotal Phase 2 Study

• International, single-arm, open label

• 2 cohorts (n=104):
  • mBCC (n=33)
  • laBCC (n=71) (recurrent tumors, non-surgical or XRT candidates)

• Median Age: 62 years

• Male: 61%, Female 39%

• 21% of patients = Basal Cell Nevus Syndrome (BCNS/Gorlins)

• Vismodegib 150mg PO QD

• Treated until disease progression (+20% size, new ulceration, new lesions), unacceptable toxicities, or end of study

Erivance Phase 2 Study

• 1° end-point: objective response rate (ORR)
  • mBCC: RECIST guidelines (Response Evaluation Criteria in Solid Tumors), ↓ 30% radiographically SLD (Sum Longest Diameter)
  • laBCC: ↓ 30% visible tumor or resolution of ulceration

• Complete Response: ORR and Negative Biopsy
  • laBCC 21%, 0% mBCC

• Partial Response: ORR and Positive Biopsy
  • laBCC 22%, 30% mBCC

Maximum Tumor Shrinkage in the Two Cohorts.

**Table II. Phase II trial of vismodegib in locally advanced (laBCC) and metastatic (mBCC) basal cell carcinoma.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>mBCC (n = 33)</th>
<th>laBCC (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>10 (30.3%)</td>
<td>27 (42.9%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (30.3%)</td>
<td>14 (22.2%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>13 (20.6%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>21 (63.6%)</td>
<td>24 (38.1%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (3.0%)</td>
<td>8 (12.7%)</td>
</tr>
<tr>
<td>Unable to be evaluated</td>
<td>1 (3.0%)</td>
<td>4 (6.3%)</td>
</tr>
</tbody>
</table>

Erivance Phase 2 Study

- Median duration of therapy: 9.7 months
- Median duration of response: 7.6 months

- Adverse Events: Majority Grade 1/2
  - Muscle cramps 68%
  - Alopecia 63%
  - Dysgeusia 51%

Serious Adverse Events (n=26, 25%)

- 7 fatal (mBCC=1, laBCC=6)
- Patients with multiple comorbidities
- Relationship to drug unknown

Vismodegib

• January 2012 FDA approved for:
  1. Adults, metastatic BCC (mBCC)
  2. Adults, locally advanced BCC (laBCC)
     • >1 cm that recurred following surgery
     • or who are not candidates for surgery
     • & who are not candidates for radiation

Black Box Warning: Embryotoxic and Teratogenic

• Women:
  • Verify pregnancy status within 7 days prior to starting therapy
  • Effective contraception (2 forms, barrier and highly effective method), during and 9 months after last dose

• Men
  • Secreted in semen
  • Condom use recommended, even after vasectomy
  • During and 3 months after last dose; avoid sperm donation

• Lactation: unknown risk, advise patient

• Blood donation: 9 months after last dose
Inhibiting the Hh Pathway in Patients w/ Basal-Cell Nevus (Gorlin) Syndrome

- 2nd Phase 2 trial, n=41
- Randomized, double-blind, placebo-controlled
- Vismo 150mg vs placebo
- Significant clinical benefit found & placebo arm stopped

New BCCs: 2 vs 25/year
Decreased size -77% vs -22%

Inhibiting the Hh Pathway in Patients w/ Basal-Cell Nevus (Gorlin) Syndrome

• 54% (14/26) of patients discontinued drug due to adverse events
• Majority Grade 1/2
• Upon ceasing drug
  • Dysgesia & muscle cramps ceased at 1 month
  • Hair regrowth noted at 3 months

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• Part II: Since 2012, what have we learned:
  • *Neo adjuvant, drug resistance, cSCCs emerge during tx, long term safety, alternate dosing regimens*

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• Part IV: Case Presentations
Literature
Fig. 1. Clinical pictures at baseline (a), 4 weeks after the end of the conservative treatment of the microinvasive SCC of the right cheek (b), and after 16 weeks of oral treatment with vismodegib (c).
Vismodegib and SCC

Orouji, A et al BJD 2014 Jan 21
Vismodegib and Keratoacanthomas

JAMA Dermatol 2013;149:242-3
Two Different Scenarios of Squamous Cell Carcinoma Within Advanced Basal Cell Carcinomas
Cases Illustrating the Importance of Serial Biopsy During Vismodegib Usage

Gefei A. Zhu, BS; Uma Sundram, MD, PhD; Anne Lynn S. Chang, MD

1. Collision tumor, delayed detection after BCC regresses

2. Dedifferentiation of BCC later in course of therapy

*JAMA Dermatol.* doi:10.1001/jamadermatol.2014.583
Published online April 16, 2014.
SCC Initial Presence or Emergence

• Thoroughly evaluate your patient at the time of presentation. Biopsy lesions!
• Ideally manage SCCs prior to tx
• Monitor closely during treatment.
• Repeat biopsy for areas of non-response or progression during treatment.
BCC Tumor Regrowth While On Drug: Resistance can Develop

Chang AL, Oro AE  Arch Dermatolo 2012;148:1324-5
BCCs: New or Regrowth during or after tx:

- **New during tx:** 21% (6/28) of patients developed new BCCs while on vismo

- **Regrowth after tx:** overall 5% (36/690)
  - Avg time: 55-62 weeks

Chang AL, Oro AE. Arch Dermatolo 2012;148:1324-5
Amenorrhea secondary to a vismodegib-induced blockade of follicle-stimulating hormone–receptor activation

John Strasswimmer, M.D., Ph.D., a,b,c Benjamin Latimer, B.S., c and Steven Ory, M.D. d,e

a Melanoma and Cutaneous Oncology Program, Lynn Cancer Institute, Boca Raton Regional Hospital, Boca Raton; b Department of Biochemistry, Florida Atlantic University, Boca Raton; c Dermatology Associates of the Palm Beaches, Delray Beach; d,g IVF Florida, Margate; and e Department of Obstetrics and Gynecology, Florida International University, Miami, Florida

Fertility and Sterility; 2014, May 30.
Other Adverse Events

• Elevated INR, on Coumadin, 3 wks after tx
• Hypersensitivity reaction, 3wks after tx, psoriasis (ustekinumab) and other agents
• Cholestatic injury, concomitant aspirin and naproxen use
Neoadjuvant + Surgery

Neoadjuvant + Mohs Surgery

- Reduced surgical defect: 31%
- If used at least 3 months

Neoadjuvant + XRT

Case Report/Case Series

Concurrent Vismodegib and Radiotherapy for Recurrent, Advanced Basal Cell Carcinoma

Erqi L. Pollom, MD; Timothy T. Bui, BS; Anne Lynn S. Chang, MD; A. Dimitrios Colevas, MD; Wendy Y. Hara, MD

JAMA Dermatol. doi:10.1001/jamadermatol.2015.0326
Published online April 15, 2015.
Neoadjuvant + XRT

Induction Hedgehog pathway inhibition followed by combined modality radiotherapy for basal cell carcinoma

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³Department of Dermatology, University of California San Francisco, San Francisco, CA

Neoadjuvant + XRT

Compassionate use of vismodegib and adjuvant radiotherapy in the treatment of multiple locally advanced and inoperable basal cell carcinomas and squamous cell carcinomas of the skin

Fig 1. Vismodegib therapy. Multiple basal cell carcinomas and squamous cell carcinomas before treatment.

Fig 2. Vismodegib therapy. Multiple basal cell carcinomas and squamous cell carcinomas after treatment and localized radiotherapy (left zygoma).

Gathings RM, Orscheln CS, Huang WW. Letter: JAAD April 2014
Vismodegib for Periocular and Orbital Basal Cell Carcinoma

Harmeet S. Gill, MD, FRCSC; Eve E. Moscato, MD; Anne Lynn S. Chang, MD; Seaver Soon, MD; Rona Z. Silkiss, MD

Figure. Case 5

A. Right lower eyelid basal cell carcinoma pre-vismodegib treatment. B. Lesion at 3 months posttreatment.

Vismodegib for Locally Advanced Basal Cell Carcinoma in a Heart Transplant Patient

A. Five biopsy specimens along the border and within nasal flaps were consistent with basal cell carcinoma (BCC) on histopathologic analysis. B. Partial tumor response confirmed by histopathologic analysis with site A free of tumor and site B remaining positive for BCC.

Cusack et al JAMA Dermatol 2015;151:70-2. (Drexel University)
A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma

Howard Sofen, MD, a Kenneth G. Gross, MD, b Leonard H. Goldberg, MD, FRCP, c Harry Sharata, MD, PhD, d Tiffani K. Hamilton, MD, e Barbara Egbert, MD, f,g Benjamin Lyons, PhD, h Jeannie Hou, MD, h and Ivor Caro, MD h

Los Angeles, San Diego, Palo Alto, and South San Francisco, California; Houston, Texas; Madison, Wisconsin; and Atlanta, Georgia
### Cohort 1 (n = 24): Assessment of CHC
**Lesion sites:** Scalp/head/neck and cape area

- **D1**
- **PK sample (Week 9)**
- **12 weeks Tx**
- **30 d F/U**
- **Mohs surgery***

### Cohort 2 (n = 25): Assessment of CHC durability
**Lesion sites:** Scalp/head/neck and trunk/limbs

- **D1**
- **PK sample (Week 9)**
- **12 weeks Tx**
- **24 weeks observation**
- **30 d F/U**
- **Mohs surgery***

### Cohort 3 (n = 25): Assessment of CHC
**Lesion sites:** Scalp/head/neck and trunk/limbs

- **D1**
- **PK sample (Week**
- **8 weeks Tx**
- **4 weeks no Tx**
- **8 weeks Tx**
- **30 d F/U**
- **Mohs surgery***

Complete histologic clearance:

- **42%**
- **16%**
- **44%**
Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC

Aleksandar Sekulic, MD, a Michael R. Migden, MD, b Karl Lewis, MD, c John D. Hainsworth, MD, d
James A. Solomon, MD, PhD, e,f,g Simon Yoo, MD, h Sarah T. Arron, MD, PhD, i
Philip A. Friedlander, MD, PhD, j,k Ellen Marmur, MD, k Charles M. Rudin, MD, PhD, l
Anne Lynn S. Chang, MD, m Luc Dirix, MD, PhD, n Jeannic Hou, MD, o Huibin Yue, PhD, o
and Axel Hauschild, MD, p on behalf of the ERIVANCE BCC investigators

Scottsdale, Arizona; Houston, Texas; Denver, Colorado; Nashville, Tennessee; Ormond Beach and Orlando, Florida; Urbana and Evanston, Illinois; San Francisco, Palo Alto, and South San Francisco, California; Boston, Massachusetts; New York, New York; Baltimore, Maryland; Antwerp, Belgium; and Kiel, Germany

**Results:** After 12 months of additional follow-up, median duration of exposure to vismodegib was 12.9 months. Objective response rate increased from 30.3% to 33.3% in patients with metastatic disease, and from 42.9% to 47.6% in patients with the locally advanced form. Median duration of response in patients with locally advanced BCC increased from 7.6 to 9.5 months. No new safety signals emerged with extended treatment duration.

**Limitations:** Limitations include low prevalence of advanced BCC and challenges of designing a study with heterogenous manifestations.

**Conclusion:** The 12-month update of the study confirms the efficacy and safety of vismodegib in management of advanced BCC. (J Am Acad Dermatol 2015;72:1021-6.)

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Greb, Rainer Kurzfeld, Brigitte Dröge, Laurent Mortier, Paolo A Ascierto, Lisa Llorens, Caroline Dutuit, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Galliot, Reinhard Dummer, Kate Fiflo, D Scott Ernst, Sarah Williams, Alberto Fidipaldo, Ioannis Xyris, Johan Hansen

Summary
Background: The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal cell carcinoma and is approved for treatment of patients with advanced basal cell carcinoma for whom surgery is inappropriate. STEVIE was designed to assess the safety of vismodegib in a situation similar to routine practice, with a long follow-up.

Methods: In this multicentre, open-label trial, adult patients with histologically confirmed locally advanced basal cell carcinoma or metastatic basal cell carcinoma were recruited from regional referral centres or specialist clinics. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function. Patients with locally advanced basal cell carcinoma had to have been deemed ineligible for surgery. All patients received 150 mg oral vismodegib capsules once a day on a continuous basis in 28-day cycles. The primary objective was safety (incidence of adverse events until disease progression or unacceptable toxic effects), with assessments on day 1 of each treatment cycle (28 days) by principal investigator and coinvestigators at the site. Efficacy variables were assessed as secondary endpoints. The safety evaluable population included all patients who received at least one dose of study drug. Patients with histologically confirmed basal cell carcinoma who received at least one dose of study drug were included in the efficacy analysis. An interim analysis was pre-planned after 500 patients achieved 1 year of follow-up. This trial is registered with ClinicalTrials.gov, number NCT01367665. The study is still ongoing.

Findings: Between June 30, 2011, and Nov 6, 2014, we enrolled 1227 patients. At clinical cutoff (Nov 6, 2013), 499 patients (416 with locally advanced basal cell carcinoma and 31 with metastatic basal cell carcinoma) had received study drug and had the potential to be followed up for 12 months or longer. Treatment was discontinued in 406 (80%) patients: 180 (36%) had adverse events, 10 (14%) had progressive disease, and 51 (10%) requested to stop treatment. Median duration of Vismodegib exposure was 36.4 weeks (IQR 17.7–62.6). Adverse events happened in 491 (98%) patients; the most common were muscle spasms (317 [64%]), alopecia (307 [62%]), dysgeusia (269 [54%]), weight loss (162 [32%]), asthenia (141 [28%]), decreased appetite (126 [25%]), nausea (112 [22%]), diarrhea (83 [17%]), fatigue (59 [11%]), and rash (59 [11%]). Most adverse events were grade 1 or 2. We recorded serious adverse events in 108 (22%) of 499 patients. Of the 31 patients who died, 21 were the result of adverse events. As assessed by investigators, 302 (66.7%, 62–1–71–0) of 453 patients with locally advanced basal cell carcinoma had an overall response (153 complete responses and 149 partial responses); 11 (57.9%; 29–2–57–7) of 29 patients with metastatic basal cell carcinoma had an overall response (two complete responses, nine partial responses).

Interpretation: This study assessed the use of vismodegib in a setting representative of routine clinical practice for patients with advanced basal cell carcinoma. Our results show that treatment with vismodegib adds a novel therapeutic modality from which patients with advanced basal cell carcinoma can benefit substantially.

### STEVIE Trial: Long-term Safety and Efficacy


<table>
<thead>
<tr>
<th></th>
<th>All patients (n=482*)</th>
<th>Patients with locally advanced basal cell carcinoma (n=453)</th>
<th>Patients with metastatic basal cell carcinoma (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>155 (32%)</td>
<td>153 (34%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Partial</td>
<td>158 (33%)</td>
<td>149 (33%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>128 (27%)</td>
<td>118 (26%)</td>
<td>10 (34%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (3%)</td>
<td>11 (2%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Missing/not evaluable</td>
<td>26 (5%)</td>
<td>22 (5%)</td>
<td>4 (14%)</td>
</tr>
</tbody>
</table>

Data are n (%). *Excludes patients without histologically confirmed disease (n=3) and without measurable disease (n=14).

**Table 4:** Best response to treatment
**STEVIE Trial: Long-term Safety and Efficacy**

Table 3: Incidence of treatment-emergent adverse events according to duration of vismodegib exposure (≥12 months vs <12 months; n=499)

<table>
<thead>
<tr>
<th>All TEAEs</th>
<th>≥12 months’ exposure (n=185)</th>
<th>Grade 3–5 TEAEs</th>
<th>≥12 months’ exposure (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>184 (99%)</td>
<td>84 (45%)</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>148 (80%)</td>
<td>17 (9%)</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>153 (83%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>130 (70%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>82 (44%)</td>
<td>14 (8%)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>65 (35%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52 (28%)</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Ageusia</td>
<td>37 (20%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (16%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (23%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>51 (28%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%). For the most common treatment-emergent adverse events (TEAEs) of any grade, event occurring in 10% or more of patients are reported. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version (version 4.0).

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>85 (17%)</td>
<td>191 (38%)</td>
<td>170 (34%)</td>
<td>23 (5%)</td>
<td>21 (4%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>165 (33%)</td>
<td>114 (23%)</td>
<td>38 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>178 (36%)</td>
<td>127 (25%)</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>156 (31%)</td>
<td>102 (20%)</td>
<td>11 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>76 (15%)</td>
<td>51 (10%)</td>
<td>12 (2%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>76 (15%)</td>
<td>39 (8%)</td>
<td>11 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>72 (14%)</td>
<td>71 (14%)</td>
<td>17 (3%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>64 (13%)</td>
<td>16 (3%)</td>
<td>3 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>59 (12%)</td>
<td>20 (4%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ageusia</td>
<td>55 (11%)</td>
<td>46 (9%)</td>
<td>10 (2%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50 (10%)</td>
<td>18 (4%)</td>
<td>11 (2%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n (%). Treatment-emergent adverse events were defined as occurring between the first administration of study drug and 30 days after the last administration of study drug, inclusive. Patients were counted only once with each preferred term for the most severe case of that preferred term.

Table 2: Most common treatment-emergent adverse events in ≥10% patients by severity (n=499)
MIKIE: A Randomized, Double-Blind, Regimen-Controlled, Phase 2 Study to Assess the Efficacy and Safety of Two Different Vismodegib Regimens in Patients With Multiple Basal Cell Carcinomas

**INTRODUCTION**

Background: Vismodegib is an oral, selective, ATP-competitive inhibitor of the mammalian target of rapamycin (mTOR). In a randomized Phase 2 study, vismodegib was well tolerated and demonstrated antitumor activity in patients with advanced basal cell carcinoma (BCC). This study compared the antitumor activity and toxicity of two different vismodegib regimens in patients with multiple BCC.

**OBJECTIVES**

- Primary objective: To evaluate the antitumor activity of vismodegib in patients with multiple BCC.
- Secondary objectives: To evaluate the safety and tolerability of vismodegib in patients with multiple BCC.

**METHODS**

- Study design: Randomized, double-blind, regimens-controlled, Phase 2 study.
- Eligibility criteria: Patients with multiple BCC, age 18 or older, and ECOG performance status of 0 or 1.
- Randomization: Patients were randomized to one of two regimens: 250 mg daily for 2 weeks followed by 2 weeks off, or 250 mg daily for 2 weeks, then 2 weeks every other week, for a total of 12 weeks.

**RESULTS**

- Tumor response: Differences in tumor response were not statistically significant between the two regimens.
- Safety and tolerability: The most common adverse events were fatigue, nausea, and diarrhea.

**CONCLUSIONS**

- Vismodegib is well tolerated and demonstrates antitumor activity in patients with multiple BCC.
- The two regimens tested were not statistically different in terms of tumor response.

**REFERENCES**

1. ClinicalTrials.gov Identifier: NCT01676334

**ACKNOWLEDGMENTS**

The authors thank the patients and the study team for their participation in the study.
Figure 1. Study design.

Patients with multiple BCCs (n = 229) stratified according to:
• Gorlin syndrome (Y/N)
• Region (EU vs Americas)
• Immunosuppression (Y/N)

BCC, basal cell carcinoma; EU, European Union; R, randomized.

MIKIE Trial: Rogers et al. Poster 9509 at ASCO June 2016

Presented at the 2016 American Society of Clinical Oncology Annual Meeting; June 3-7, 2016, Chicago, IL, USA
MIKIE Trial: Rogers et al. Poster 9509 at ASCO June 2016

Figure 2. Mean percentage relative reduction in the number of clinically evident BCCs.

Presented at the 2016 American Society of Clinical Oncology Annual Meeting; June 3-7, 2016, Chicago, IL, USA
## Table 3. Primary and Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm A (n = 116)</th>
<th>Treatment arm B (n = 113)</th>
<th>Difference (arm A to arm B) [95% CI]*</th>
<th>Treatment arm P-value (from ANCOVA)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean relative reduction from baseline in total number of BCC lesions at EOT, %</td>
<td>62.7</td>
<td>54.0</td>
<td>-8.9% [-23.0 to 5.2]</td>
<td>Model A: 0.2132 Model B: 0.2443</td>
</tr>
<tr>
<td>Relative reduction in total size of 3 target BCCs, %</td>
<td>82.9</td>
<td>68.8</td>
<td>-15.2 [-27.4 to -3.0]</td>
<td>0.0146</td>
</tr>
<tr>
<td>Proportion of patients with at least 50% reduction in total number of BCCs from baseline at EOT, n (%)</td>
<td>76 (65.5)</td>
<td>57 (50.4)</td>
<td>-15.1% [-27.7 to -2.4]</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Number of patients without new BCC lesions at EOT compared with baseline, n (%)</td>
<td>72 (76.6)</td>
<td>64 (74.4)</td>
<td>-2.2% [-14.8 to 10.4]</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Presented at the 2016 American Society of Clinical Oncology Annual Meeting; June 3-7, 2016, Chicago, IL, USA
### Table 4. Most Common TEAEs, Occurring in ≥10% of Patients

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Treatment arm A (n = 114)</th>
<th>Treatment arm B (n = 113)</th>
<th>Total (N = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>113 (99.1)</td>
<td>110 (97.3)</td>
<td>223 (98.2)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>83 (72.8)</td>
<td>93 (82.3)</td>
<td>176 (77.5)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>75 (65.8)</td>
<td>75 (66.4)</td>
<td>150 (66.1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>72 (63.2)</td>
<td>73 (64.6)</td>
<td>145 (63.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (21.1)</td>
<td>26 (23.0)</td>
<td>50 (22.0)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>24 (21.1)</td>
<td>21 (18.6)</td>
<td>45 (19.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21 (18.4)</td>
<td>17 (15.0)</td>
<td>38 (16.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (17.5)</td>
<td>18 (15.9)</td>
<td>38 (16.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (20.2)</td>
<td>14 (12.4)</td>
<td>37 (16.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15 (13.2)</td>
<td>20 (17.7)</td>
<td>35 (15.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (15.8)</td>
<td>16 (14.2)</td>
<td>34 (15.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>18 (15.8)</td>
<td>12 (10.6)</td>
<td>30 (13.2)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>14 (12.3)</td>
<td>13 (11.5)</td>
<td>27 (11.9)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase level increase</td>
<td>11 (9.6)</td>
<td>15 (13.3)</td>
<td>26 (11.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (9.6)</td>
<td>12 (10.6)</td>
<td>23 (10.1)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event.

**Presented at the 2016 American Society of Clinical Oncology Annual Meeting; June 3-7, 2016, Chicago, IL, USA**
Outline:

• Part I: History of Drug Development & January 2012 FDA Approval of vismodegib for “laBCC and mBCC”.
  • Efficacy and Adverse Events

• Part II: Since 2012, what have we learned.
  • Neo adjuvant, alternate dosing regimens, drug resistance, cSCCs emerge during tx, long term safety

• **Part III: Sonidegib FDA approval 2015 for laBCC**

• Part IV: Case Presentations
Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial

Michael R Migden, Alexander Guminski, Ralf Gutzmer, Luc Dirix, Karl D Lewis, Patrick Combemale, Robert M Herd, Ragini Kudchadkar, Uwe Trefzer, Sven Gogov, Celine Pallaud, Tingting Yi, Manisha Mone, Martin Kaatz, Carmen Loquai, Alexander J Stratigos, Hans-Joachim Schulze, Ruth Plummer, Anne Lynn S Chang, Frank Cornélis, John T Lear, Dalila Sellami, Reinhard Dummer

200 mg qd

800 mg qd
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

Reinhard Dummer, MD, Alexander Guminski, MD, PhD, Ralf Guterm, MD, Luc Dirix, MD, Karl D. Lewis, MD, Patrick Combemale, MD, Robert M. Herd, MD, Martin Kaatz, MD, Carmen Loquai, MD, Alexander J. Stratigos, MD, Hans-Joachim Schulze, MD, Ruth Plummer, MD, Sven Gogov, MD, Celine Pallaud, PhD, Tingting Yi, PhD, Manisha Mone, PhD, Anne Lynn S. Chang, MD, Frank Cornélius, MD, Ragini Kudchadkar, MD, Uwe Trefzer, MD, John T. Lear, MD, Dalila Sellami, MD, and Michael R. Migden, MD

Zürich and Basel, Switzerland; Sydney, Australia; Hannover, Jena, Gera, Mainz, Münster, and Berlin, Germany; Antwerp and Brussels, Belgium; Aurora, Colorado; Lyon, France; Glasgow, Newcastle upon Tyne, and Manchester, United Kingdom; Athens, Greece; East Hanover, New Jersey; Redwood City, California; Atlanta, Georgia; and Houston, Texas

A: Partial Response

B: Stable Disease

C: Partial Response

D: Partial Response

| Patients with mBCC | Sonidegib 200 mg once daily | | Sonidegib 800 mg once daily | |
|-------------------|----------------------------|------------------|------------------|
| Time to tumor response | Primary Analysis | 12-mo Analysis | Primary Analysis | 12-mo Analysis |
| Median (95% CI), mo | Per central review | 4.6 (1.8-7.4) | 1.8 (NE) | 1.0 (1.0-2.1) | 1.0 (1.0-2.1) |
|                    | Per investigator review | 1.0 (0.9-3.7) | 1.0 (0.9-3.7) | 2.7 (1.0-5.6) | 2.7 (1.0-5.6) |
| Duration of response | Events/responders, n/n; median (95% CI), mo | | | |
|                    | Per central review | 0/2; not reached | 0/1; not reached | 1/4; 8.3 (NE) | 1/4; not reached |
|                    | Per investigator review | 0/3; not reached | 1/3; 17.7 (NE) | 1/8; 10.2 (NE) | 3/8; 10.2 (NE) |
| Progression-free survival | Events/ n; median (95% CI), mo | | | |
|                    | Per central review | 4; 13.1 (5.6-13.1) | 6; 13.1 (5.6-16.9) | 10; 7.6 (6.2-11.1) | 11; 11.1 (NE) |
|                    | Per investigator review | 7; 13.1 (9.2-16.6) | 8; 13.1 (9.2-18.6) | 6; 13.3 (NE) | 10; 14.3 (11.1-20.2) |

### Table 1. Efficacy of sonidegib by treatment arm

<table>
<thead>
<tr>
<th>Patients with IaBCC</th>
<th>Sonidegib 200 mg once daily</th>
<th>Sonidegib 800 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Analysis</td>
<td>12-mo Analysis</td>
</tr>
<tr>
<td>Time to tumor response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  Median (95% CI), mo | 3.9 (3.6-4.2) | 4.0 (3.8-5.6) | 3.7 (2.6-3.8) | 3.8 (3.7-5.5) |
| Per central review | 1.9 (1.8-3.7) | 2.5 (1.9-3.7) | 1.9 (1.2-2.0) | 1.9 (1.4-2.0) |
| Per investigator review | | | | |
| Duration of response |  
  Events/responders, n/n; median (95% CI), mo | 4/31; not reached | 7/38; not reached | 3/45; not reached | 11/56; 15.7 (NE) |
| Per central review | 10/43; 20.2 (10.1-20.2) | 14/47; 20.2 (NE) | 10/73; not reached | 17/74; 19.8 (15.7-20.5) |
| Per investigator review | | | | |
| Progression-free survival |  
  Events, n; median (95% CI), mo | 7; not reached | 11; 22.1 (NE) | 10; not reached | 22; 21.5 (NE) |
| Per central review | 15; 16.6 (13.7-22.0) | 19; 22.0 (NE) | 17; not reached | 26; 21.5 (NE) |
| Per investigator review | | | | |
Characterization and Management of Hedgehog Pathway Inhibitor-Related Adverse Events in Patients With Advanced Basal Cell Carcinoma

MARIO E. LACOUTURE, Brigitte Dréno, PAOLO ANTONIO ASCIERTO, REINHARD DUMMER, NICOLE BASSET-SEGUIN, KATE FIFE, SCOTT ERNST, LISA LICITRA, ROGERIO I. NEVES, KETTY PERIS, SUSANA PUIG, JONAS SOKOLOF, ALEKSANDAR SEKULIC, AXEL HAUSCHILD, RAINDER KUNSTFELD

Memorial Sloan Kettering Cancer Center, New York, New York, USA; Department of Dermatology, Hôtel Dieu University Hospital, Nantes, France; Istituto Nazionale Tumori Fondazione, G Pascale, Naples, Italy; University of Zurich Hospital, Zurich, Switzerland; Université Paris 7 and Hôpital Saint-Louis, Paris, France; Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, United Kingdom; Western University London Regional Cancer Program, London, Ontario, Canada; Fondazione IRCCS, Istituto Tumori, Milan, Italy; Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA; Catholic University of Rome, Rome, Italy; Dermatology Department, Hospital Clinic, University of Barcelona, Institut d’Investigaciones Biomediques August Pi i Sunyer, Barcelona, Spain; Mayo Clinic, Scottsdale, Arizona, USA; Department of Dermatology, University of Kiel, Kiel, Germany; Medical University of Vienna, Vienna, Austria

Key Words. Adverse events • Management • Vismodegib • Sonidegib • Advanced basal cell carcinoma • Hedgehog pathway

Lacouture M et al. The Oncologist August 2016
Alopecia
↓ Dermal papillae function/hair growth
Tx: Minoxidil 5% b.i.d.

Dysgeusia/Ageusia
↓ Bitter/sweet responsivity
↓ Taste buds
Tx: Nutrition consult

Muscle Spasms
↓ Myogenic factors
↓ Injury recovery
Tx: Amlodipine 10 mg/day

Weight Loss
↑ Glucose uptake in muscle/brown adipocytes
Tx: Nutrition consult

Figure 1. Adverse events associated with hedgehog pathway inhibitors [19, 21, 26, 29].
Abbreviations: b.i.d., twice daily; Tx, treatment.
Outline:

• Part I: History of Drug Development & January 2012 FDA Approval of vismodegib for “laBCC and mBCC”.
  • Efficacy and Adverse Events

• Part II: Since 2012, what have we learned.
  • Neo adjuvant, alternate dosing regimens, drug resistance, cSCCs emerge during tx, long term safety

• Part III: Sonidegib FDA approval 2015 for laBCC

• **Part IV: Case Presentations**
Summary: HHIs and BCC

- Hedgehog inhibitor, binds to Smo, blocking cell proliferation
- Vismodegib: FDA approved 2012 for locally advanced BCC (laBCC) and metastatic BCC (mBCC), Sonidegib: 2015 laBCC
- Embryotoxic and teratogenic
- It works, at times impressively, but not always.
- Durability is unknown and unpredictable.
- Side effects are common, muscle cramps, altered or loss of taste and hair loss
- Resistance can develop & SCCs can emerge during treatment
- Neoadjuvant role reported, Surgery and XRT
- Ideal dosing and duration of therapy is being studied further
- For some and select patients, quite impactful…
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Response predictivity</th>
<th>Response clinically [clinicaltrials.gov NCT id</th>
<th>% with complete responses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>Decreased proliferation, tumor growth and metastasis</td>
<td>NCT0150666A: recruiting patients</td>
<td>25% (TGA)</td>
<td>(10, 79)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Decreased collagen invasion in primary tumors and in vivo</td>
<td>NCT01105296: recruiting</td>
<td>77% (TGA)</td>
<td>(7)</td>
</tr>
<tr>
<td>Breast</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>25% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Decreased cell proliferation and survival</td>
<td>NCT0150666A: recruiting</td>
<td>77% (TGA)</td>
<td>(40, 78, 79)</td>
</tr>
</tbody>
</table>

**Abbreviations**: LAC, lung adenocarcinoma; LSCC, lung squamous cell carcinoma; GCCC, small cell lung cancer; TGA, The Cancer Genome Atlas.

Non-Surgical Treatment Modalities
Acknowledgements: Research Team at Saint Louis University (SLU)

- Rosemary King, PA-C
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  - Dr. Timur Galperin
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- Mohs Fellows
  - Dr. Jordan Slutsky
- Biostatistician
  - Eric Armbrecht, Ph.D.