Objectives

- Describe the Hedgehog pathway and explore its role in basal cell carcinoma
- Identify patient populations who should not receive vismodegib
- Explore the clinical trials with vismodegib for the treatment of basal cell carcinoma

Vismodegib

- FDA approval: January, 2012
- Erivedge™: Approved in adults for the treatment of metastatic basal cell carcinoma (mBCC) or locally advanced (la) BCC that has recurred following surgery, or in patients who are not candidates for surgery, and not candidates for radiation.
- Also known as GDC-0449 (in clinical trials)
- Hedgehog pathway inhibitor (first-in-class)

Basal Cell Carcinoma (BCC)

- 8 out of 10 skin cancers are BCCs
- 3.5 million basal & squamous cell skin cancers diagnosed per year
  - Most are BCC
- Risk factors include
  - UV light exposure
  - Fair skin
  - Older age
  - Male gender (2x as likely)
  - Chemical exposure (arsenic), radiation exposure
  - Prior skin cancer
  - Prolonged or severe skin inflammation or injury

Basal Cell Carcinoma

- BCCs are slow growing
- Treatment is typically surgery or radiation therapy
- BCCs rarely reach advanced stage
- Median survival (mBCC): 8 months
- BCCs are associated with mutations in the Hedgehog signaling pathway

The Hedgehog (Hh) Pathway

- The Hh pathway regulates cell growth and differentiation development and controls epithelial and mesenchymal interactions in embryogenesis
  - Hh signaling is necessary for internal organ, midline, limb hematopoietic, and neurologic structure development
  - Malfunctions in Hh signaling may lead to cranial malformations, limb abnormalities, and improper organ development
- In healthy adults, the role of the Hh pathway is generally limited
  - Hair growth
  - Spermatogenesis
  - Damaged tissue repair
Hh Pathway and BCC

- Mammalian ligand homologues:
  - Sonic Hh
  - Indian Hh
  - Desert Hh

- Mutations in BCC allow the Hh ligand to bind to and inactivate the tumor-suppressor protein, patched homologue 1 (PTCH1)
- Smoothened homologue (SMO), the PTCH1 protein receptor then transmits downstream signaling
- SMO signaling activates transcription factors, resulting in basal cell proliferations
- Vismodegib selectively binds to SMO and inhibits the downstream signaling

Vismodegib

- **Dosing and Administration**
  - Oral: 150 mg once daily
  - Continue treatment until disease progression or unacceptable toxicity
  - May be administered with or without food
  - Missed dose: Do not make up; resume with the next scheduled dose
  - Available through specialty pharmacies

Key Warnings

- Contraindications: None
- **Boxed Warning:**
  - May result in embryo-fetal death or severe birth defects
  - Embryotoxic and teratogenic in animal reproduction studies
  - Severe midline defects, missing digits, other irreversible malformations
  - Verify pregnancy status prior to treatment; initiate highly effective contraception prior to 1st dose; continue for 7 mo after treatment
  - Advise patients (female & male) of these risks
  - Blood donations: Patients should not donate blood or blood products during and for at least 7 months after treatment
  - FDA medication guide

Effects in Pregnancy

- Teratogenic in rats at 1/5 of corresponding human dose (lethal at corresponding doses)
  - Craniofacial anomalies, open perineum, absent or fused digits
- Report exposures during pregnancy to the Genentech adverse event line (1-888-835-2555)
  - Encourage participation in Eviredge pregnancy pharmacovigilance program for direct exposures or exposure via seminal fluid
- Patients of reproductive potential
  - Females: Highly effective contraception (failure rate <1%) during and for 7 months after last dose
  - Males: Condoms with spermicide (even after vasectomy) during and for 2 months after last dose

Adverse Reactions

- Muscle spasm (72%) 
- Alopecia (65%)
- Abnormal taste (55%; taste loss 11%)
- Weight loss (45%)
- Fatigue (40%)
- Nausea (30%); Vomiting (14%)
- Amenorrhea (30%)
- Diarrhea (29%)
- Appetite decreased (25%)
- Constipation (21%)
- Arthralgia (16%)

Pharmacokinetics

- Oral Bioavailability: ~32%; not affected by food
- T max (150 mg): 2.4 days (± 2.2 days)
- Protein Binding: >99% to albumin and alpha-1-acid glycoprotein (AAG)
  - AAG binding is saturable
  - Increasing doses (270 or 540 mg) did not result in higher plasma concentrations
  - Vd: 16.4 to 26.6 L
  - T1/2: 10–14 days
  - Single dose: 12 days; Continuous daily dosing: 4 days
- Metabolism: Oxidation, glucuronidation, and pyrimidine ring cleavage
  - >99% of circulating components are parent drug
- Elimination: Primarily hepatic (Feces: 82%; Urine: 4.4%)
  - Mostly unchanged drug


Drug Interactions

- Vismodegib levels may be increased by:
  - P-glycoprotein (P-gp) inhibitors (clarithromycin, erythromycin, azithromycin)
- Vismodegib levels may be decreased by:
  - Antacids
  - H2-antagonists
  - Proton pump inhibitors
  - P-gp inducers

Evredge™ prescribing information, 2012

Clinical Studies

- Phase I study in BCC:
  - Open label, multicenter 2 stage study to evaluate safety and efficacy of vismodegib
  - 33 patients with laBCC or mBCC
  - 18 with mBCC; 15 with laBCC
- 3 dose levels: Oral
  - 150mg/day [n=17], 270 mg/day [n=15], and 540 mg/day [n=1]
- No dose limiting toxicities
- Overall response
  - mBCC: 50%
  - laBCC: 60%
- Complete response: 2; Partial response: 16; Stable disease: 11; Disease progression: 4
- Median duration of response: 8.8 months (and ongoing)

Von Hoff, NEJM, 2009

Clinical Studies

- Phase II study in BCC
  - Multicenter, 2-cohort, non randomized study
  - 150 mg orally once daily until disease progression
  - Primary endpoint: Overall Response Rate (ORR) by independent review (IRF); Secondary endpoints: Response duration; response (by investigator; INV), and safety
  - 104 patients enrolled (71 laBCC and 33 mBCC)
  - laBCC: ORR by IRF: 43% (95% CI, 31-56%); ORR by INV: 60% (95% CI, 47-72%)
  - mBCC: ORR by IRF: 30% (95% CI, 16-48%); ORR by INV: 46% (95% CI, 28-62%)
  - Safety: ADRs ≥30%: muscle spasm, alopecia, taste disturbance, weight loss and fatigue
  - Serious ADRs: 25%; 4% were considered treatment-related
  - Duration of response – not reported in the abstract

Sekulic, Melanoma Research, 2011

Place in Therapy

- NCCN Guidelines: Panel recommends clinical trial (preferred) or vismodegib for
  - Residual BCC (after surgery or radiation therapy)
  - Metastatic BCC
- UpToDate: Systemic treatment of advanced cutaneous squamous and BCCs:
  - Suggest vismodegib for metastatic or locally advanced BCC which is not amenable to surgery or radiation therapy

NCCN Basal Cell and Squamous Cell Skin Cancers, v.2.2012; UpToDate: Systemic treatment of advanced cutaneous squamous and BCCs

References

- Vismodegib is a first-line treatment agent for early-stage basal cell skin carcinoma.
  A. True
  B. False
Question 2

- The appropriate dose of vismodegib is:
  A. 960 mg orally twice daily until disease progression or unacceptable toxicity
  B. 150 mg orally once daily until disease progression or unacceptable toxicity
  C. 150 mg orally twice daily until disease progression or unacceptable toxicity
  D. 300 mg orally once daily until disease progression or unacceptable toxicity

Question 3

- Common adverse events associated with vismodegib include:
  A. Fatigue, squamous cell skin cancer, and alopecia
  B. Abnormal taste, fatigue, alopecia
  C. Hypertension, headache, QT prolongation

Question 4

- Hedgehog mutations associated with basal cell carcinoma can activate the Hedgehog pathway
  A. True
  B. False

Question 5

- Patients should NOT donate blood during vismodegib treatment
  A. True
  B. False