Brand Name: Erivedge

Generic Name: Vismodegib

Manufacturer [1]: Genentech, Inc.

Drug Class: hedgehog pathway inhibitor [1, 2, 3]

Uses:

Labeled Uses [1, 2, 3, 4, 5]:

Used for the treatment of metastatic basal cell carcinoma, locally advanced basal cell carcinoma that has recurred after surgery. It is also used for patients that are not candidates for surgery or radiation.

Mechanism of Action [1, 2 ,3, 4, 5]:

Basal cell cancer is associated with mutations in Hedgehog pathway components. Hedgehog regulates cell growth and differentiation in embryogenesis; while generally not active in adult tissue, Hedgehog mutations associated with basal cell cancer can activate the pathway resulting in unrestricted proliferation of skin basal cells. Vismodegib is a selective Hedgehog pathway inhibitor which binds to and inhibits Smoothened homologue (SMO), the transmembrane protein involved in Hedgehog signal transduction.

Pharmacokinetics [1, 2, 3, 4, 5]:

Absorption:

T_{max}	Not reported
V_d	16.4-26.6 L
$t_{½}$ Single dose	12 days
$t_{½}$ Continuous Daily Dosing	4 days
Clearance	Not reported
Protein binding	>99%
Bioavailability	31.8%

Metabolism: Greater than 98% of the total circulating drug-related components are the parent drug. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5.

Elimination: Vismodegib and its metabolites are eliminated primarily by the hepatic route with 82% of the administered dose recovered in the feces and 4.4% recovered in urine. The estimated elimination half-life ($t_{1/2}$) of vismodegib is 4 days after continuous once-daily dosing and 12 days after a single dose.

Efficacy:

Tang, Jean, Julian Mackay-Wiggan, et al. "Inhibiting the Hedgehog Pathway in Patients with the Basal-Cell Nevus Syndrome." ***New England Journal of Medicine*****. 366. (2012): 2180-88. Web. 4 Sep. 2012.**

Study Design: Multicenter, double-blind, randomized, placebo-controlled, parallel-group design study

Description of Study: *Methods*: 42 patients with the basal-cell nevus syndrome were enrolled at three clinical centers from September 2009 through January 2011. After providing written informed consent, patients were randomly assigned, in a 2:1 ratio, to receive oral vismodegib at a dose of 150 mg daily or placebo for a planned 18 months. The primary statistical end point was the comparative rate of appearance of new basal-cell carcinomas that were eligible for surgical resection— those with a diameter of 3 mm or greater on the nose or periorbital skin, 5 mm or greater elsewhere on the face, or 9 mm or greater on the trunk or limbs (excluding the leg below the knees, which was not monitored). Secondary end points included a reduction in the rate of appearance, reduction in size of existing surgically eligible basal-cell carcinomas, duration of the effect against basal-cell carcinoma, change in hedgehog target-gene expression in basal-cell carcinomas, and between-group differences in adverse events. Tumor response was assessed per-protocol by examining the skin at study visits, monthly for the first 3 months, every other month for the next 6 months, and every 3 months for the final 9 months of the 18-month study period. Basal-cell carcinoma lesions were identified clinically, calipers were used to measure the longest diameter, and clinical photos from previous visits were used to ensure consistency of clinical examination. The principal investigator trained all study dermatologists and participated in early study visits to ensure consistent assessments of surgically eligible basal-cell carcinomas. One patient was discontinued from participation because of clinical worsening of disease.

Limitations: The study drug was provided by Genentech and the study was partially funded by Genentech as well. Very few patients actually completed the study because of side effects of the medication. This also means that unblinding was very likely in this study due to side effects. Most surgically eligible basal-cell carcinomas also regrew once the drug was stopped.

Conclusion: Vismodegib significantly reduced the rate of appearance of new surgically eligible basal-cell carcinomas among patients with the basal-cell nevus syndrome. Vismodegib also reduced the size of existing surgically eligible carcinomas, even to the point of clinical resolution. Overall, the findings confirm the essential role of the hedgehog pathway in basal-cell carcinomas and indicate that vismodegib is efficacious in

preventing and treating basal-cell carcinomas in patients with the basal-cell nevus syndrome.

Sekulic, Aleksandar , Michael Migden, et al. "Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma." ***New England Journal of Medicine*****. 366. (2012): 2171-79. Web. 4 Sep. 2012.**

Study Design: Multicenter, non-blinded, non-randomized non-controlled study

Description of Study: *Methods*: A control group was not used in this study, because of the small patient population, the historical absence of spontaneous responses, and the lack of available effective therapies. The continuous dosing schedule of 150 mg of vismodegib once daily was chosen on the basis of the pharmacokinetic properties characterized. Six patients received vismodegib until disease progression, unacceptable toxic effects, or discontinuation of the study. Dose interruption for up to 4 weeks was allowed in order for patients to recover from toxic effects.

The primary end point was the objective response rate as assessed by independent review. For metastatic basal-cell carcinoma, the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.07 was used. A standard end point for locally advanced basal-cell carcinoma did not exist when this study was designed, response was defined as a decrease of 30% or more in the externally visible or radiographic dimension (if applicable) or complete resolution of ulceration (if present at baseline). The investigators and independent reviewers were instructed to include residual scarring when measuring the externally visible dimension. Responses had to be confirmed at least 4 weeks after initial documentation. Progressive disease was defined as an increase of 20% or more in the externally visible or radiographic dimension (if applicable), new ulceration, or a new lesion. For patients with multiple target lesions, the sum of the longest diameters was used to determine response and progression.

Limitations: Genentech supported this study and provided the study drug. This study was non-blinded and non-controlled which enhances the possibility of bias and threatens the validity of study conclusions.

Conclusion: On the basis of the efficacy observed in this study, the trial was designed to evaluate the efficacy and safety of vismodegib in patients with advanced basal-cell carcinoma. The study met the protocol-defined primary end point, as measured by the independently assessed tumor response. The majority of patients in both cohorts had tumor shrinkage in response to vismodegib. In addition, 54% of patients with locally advanced basal-cell carcinoma had no residual disease in biopsy specimens obtained during treatment with vismodegib. Furthermore, photographs of patients and comments from treating physicians suggest that the response may have been underestimated for some patients with locally advanced basal-cell carcinoma, such as those with tumor regression and residual scarring, since scarring was included in the measurement of the externally visible dimension.

LoRusso, Patricia, Charles Rudin, et al. "Phase I Trial of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Refractory, Locally Advanced or Metastatic Solid Tumors ." *Clinical Cancer Research*. 17. (2011): 2502. Web. 4 Sep. 2012.

Study Design: Multicenter, open-label, two stage phase I trial

Description of Study: *Methods*: A total of 68 patients enrolled in the study at three centers. Stage 1 was a dose escalation stage, designed to estimate the MTD of GDC-0449. Patients received a single oral dose of GDC-0449 on day 1, followed by daily administration at the same dose beginning on day 8; 7 patients received 150 mg/d, 9 received 270 mg/d, and 4 received 540 mg/d. Patients with dose-limiting toxicities, other intolerable side effects, disease progression, or who did not benefit from treatment, as decided by the investigator, were discontinued from treatment.

Stage 2 included an expansion cohort of 12 patients with solid tumors (none of whom had advanced BCC) who began continuous daily dosing at 150 mg/d on day 1, to further assess the safety profile, pharmacokinetics, and pharmacodynamics of GDC-0449. After a study amendment, two further cohorts were added: a cohort of 16 patients (including with advanced BCC), to investigate pharmacokinetic properties of a new GDC-0449 formulation at 150 mg/d; and a cohort of 20 patients with advanced BCC (treated at 150 or 270 mg/d), to evaluate safety and efficacy, based on encouraging response of 2 patients in stage 1 with advanced BCC. Patients in stage 2 were treated until disease progression, occurrence of intolerable side effects, or study withdrawal.

Limitations: P. LoRusso received research funding from Genentech, is on Genentech's speakers bureau (compensated) and has participated in Genentech Advisory Boards (compensated); C. Rudin has been a paid consultant to Genentech (not on projects related to Hedgehog inhibitors); G. Weiss is an investigator on hedgehog pathway inhibitor studies for Genentech and Infinity; D. Von Hoff received a grant to his institution for the phase I trial of GDC-0449; J. Reddy, I. Chang, W. Darbonne, R. Graham, K. Zerivitz, and J. Low are employees of Genentech, a member of the Roche Group, and shareholders of Roche. The other authors report no conflicts of interest.

Conclusion: GDC-0449 has an acceptable safety profile, however phase I trials do not assess the efficacy of study drugs.

Contraindications[1,2,3,4,5]:

specific contraindications have not been determined

Precautions[1,2,3,4,5]:

Blood donation: Advise patients to not donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose of vismodegib.

Amenorrhea: Amenorrhea has been observed in clinical trials in females of reproductive potential. Reversibility of amenorrhea is unknown.

Renal function impairment: The safety and effectiveness of vismodegib have not been established in patients with renal impairment.

Hepatic function impairment: The safety and effectiveness of vismodegib have not been established in patients with hepatic impairment.

Carcinogenesis: Carcinogenicity studies with vismodegib have not been conducted. Pilomatricoma (a benign cutaneous neoplasm) was observed in rats administered oral vismodegib for 26 weeks at 100 mg/kg/day (approximately 0.8 times the systemic exposure (area under the curve [AUC]) in patients at the recommended human dose).

Mutagenesis: vismodegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human chromosomal aberration assay in human peripheral blood lymphocytes or in the in vivo rat bone marrow micronucleus assay.

Fertility impairment: Studies to assess the potential of vismodegib to affect fertility have not been conducted; however, data from repeat-dose toxicology studies in rats and dogs indicate that male and female reproductive function and fertility may be impaired in patients receiving vismodegib. In a 26-week toxicology study in rats, a relative decrease in percent motile sperm was observed at 15 mg/kg/day or more (approximately 0.3 or more times the AUC in patients at the recommended human dose). In dogs, increased numbers of degenerating germ cells and hypospermia were observed in young animals administered oral vismodegib for 4 weeks at 50 mg/kg/day or more (approximately 2 or more times the AUC in patients at the recommended human dose). No corresponding findings were observed in sexually mature dogs at similar doses in 13- and 26-week toxicology studies. A decrease in the number of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks at 100 mg/kg/day (approximately 0.8 times the AUC in patients at the recommended human dose)

Children: The safety and effectiveness of vismodegib have not been established in pediatric patients.

Elderly: Clinical studies did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger patients.

Adverse Effects:

Dermatologic:

Alopecia (63.8%)

Endocrine metabolic:

Weight loss (44.9%)

Gastrointestinal:

Constipation (21%)
Decrease in appetite (25.4%)
Diarrhea, All grades (29%)
Loss of taste (10.9%)
Nausea, All grades (30.4%)
Taste sense altered (55.1%)
Vomiting (13.8%)

Musculoskeletal:

Arthralgia (15.9%)
Skeletal muscle spasm (71.7%)

Other:

Fatigue (39.9%)

Amenorrhea:

In clinical trials, a total of 30% premenopausal women developed amenorrhea while receiving vismodegib.

Lab test abnormalities:

Treatment-emergent grade 3 laboratory abnormalities observed in clinical trials were hyponatremia (4%), hypokalemia (1%), and azotemia (2%).

Drug Interactions[1,2,3,4,5]:

Cytochrome P450 system:

CYP inhibition is not predicted to alter vismodegib systemic exposure.

Vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19, and the transporter BCRP.

Drugs that affect gastric pH:

Drugs that alter the pH of the upper GI tract (eg, proton pump inhibitors [eg, omeprazole], H_2-receptor antagonists [eg, famotidine], antacids [eg, magnesium hydroxide]) may alter the solubility of vismodegib and reduce its bioavailability. The effect on efficacy of vismodegib is unknown.

P-glycoprotein inhibitors:

Vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp). Coadministration of vismodegib with drugs that inhibit P-gp (eg, clarithromycin, erythromycin, azithromycin, amiodarone, atorvastatin) may increase vismodegib systemic exposure and incidence of adverse reactions.

Dosing/Administration[1,2,3,4,5]:

General dosing considerations:

Determine pregnancy status within 7 days prior to initiation of vismodegib in childbearing female patients.

Adults:

150 mg once daily until disease progression or unacceptable toxicity.[1]

Children:

Safety and effectiveness have not been established.

Renal Impairment:

Has not been studied

Hepatic Impairment:

Has not been studied

Use in special circumstances:

Overdosage [(4)]:

There is no information on overdosage in humans. In clinical trials, vismodegib was administered at 540 mg orally once daily; exposure did not increase above 540 mg daily.

Pregnancy [(4)]:

Category D. Vismodegib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal exposures lower than the human exposures at the recommended dosage of 150 mg/day. Vismodegib is embryolethal in rats at exposures within the range achieved at the recommended human dose. If vismodegib is used during pregnancy, or if the patient becomes pregnant while taking this drug (or, for a male patient, if his female partner is exposed to drug), the patient should be educated on the potential hazard to the embryo or fetus.

Lactation [(4)]:

It is not known whether vismodegib is excreted in human breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants from vismodegib, decide whether to discontinue breast-feeding or the drug, taking into account the importance of the drug to the mother

Conclusion:

The quality of life for patients who have recurrent basal-cell carcinoma can be severely diminished by the need for frequent, repetitive, scarring surgical procedures. Other than Vismodegib, no pharmacologic therapy has been shown to be consistently efficacious for basal-cell carcinomas. Vismodegib has been shown to be efficacious at preventing new basal cell carcinoma growths and has been shown to have an acceptable safety profile. Adverse events, such as alopecia, fatigue and weight loss are a concern with this medication as most patients seem to experience moderate to severe side effects. Lack of sustained effectiveness is also a concern once medication has been discontinued. However, since it is the only medication that has consistently been shown to be effective, it may be a good option for recurrent or severe basal-cell carcinoma.

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