Treatment Interruptions and Erivedge

- Managing Adverse Reactions
- Data From the STEVIE Trial

Indication

Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation.

Boxed Warning

EMBRYO-FETAL TOXICITY

- **Erivedge can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Erivedge is embryotoxic, fetotoxic, and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations**
- **Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating Erivedge. Advise pregnant women of the potential risks to a fetus. Advise females of reproductive potential to use effective contraception during and after Erivedge**
- **Advise males of the potential risk of Erivedge exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential**

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Erivedge® (vismodegib) capsule

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- **Advise males of the potential risk of Erivedge exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential**
- Females of Reproductive Potential: Use contraception during therapy with Erivedge and for 24 months after the final dose
- Males: Use condoms, even after a vasectomy, to avoid potential drug exposure in pregnant partners and female partners of reproductive potential during and for 3 months after the final dose of Erivedge. Do not donate semen during and for 3 months after the final dose of Erivedge
- Blood Donation: Advise patients not to donate blood or blood products while receiving Erivedge and for 24 months after the final dose of Erivedge
- Advise female patients and female partners of male patients to contact their healthcare provider with a known or suspected pregnancy. Report pregnancies to Genentech at (888) 835-2555

Additional Important Safety Information

Severe Cutaneous Adverse Reactions

- Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with Erivedge. Permanently discontinue Erivedge in patients with these reactions

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Additional Important Safety Information (cont'd)

Premature Fusion of the Epiphyses

- Premature fusion of the epiphyses has been reported in pediatric patients exposed to Erivedge. In some cases, fusion progressed after drug discontinuation. Erivedge is not indicated for pediatric patients

Adverse Reactions

- The most common adverse reactions (≥10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia
- Amenorrhea can occur in females of reproductive potential. Reversibility of amenorrhea is unknown. In clinical trials, 30% of 10 pre-menopausal women developed amenorrhea while receiving Erivedge
- Grade 3 laboratory abnormalities observed in clinical trials were hyponatremia (4%), azotemia (2%), and hypokalemia (1%)
- Additionally, in a post-approval clinical trial conducted in 1232 patients with locally advanced or metastatic BCC treated with Erivedge, a subset of 29 patients had baseline values for blood creatine phosphokinase (CPK) reported. Within the subset of patients, 38% had a shift from baseline, including Grade 3 (3%) increased CPK. Grade 3 or 4 increased CPK occurred in 2.4% of the 453 patients across the entire study population with any CPK measurement
- Adverse reactions identified during post-approval use: drug-induced liver injury, Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms

Use in Specific Populations

Lactation

- No data are available regarding the presence of vismodegib in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Advise women that breastfeeding is not recommended during therapy with Erivedge and for 24 months after the final dose

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to Genentech at (888) 835-2555.

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Clinical trial information for ERIVANCE and STEVIE

	ERIVANCE (pivotal trial)[1-3]	STEVIE (post-approval study)[1,4-6†]
Overview	Phase II, single-arm, international, 2-cohort, open-label study	Single-arm, international, open-label, post-approval study to fulfill a European post-marketing commitment
Primary objective	Efficacy	Safety
Safety-evaluable patients (n)	104* (laBCC: n=71; mBCC: n=33)	1215* (laBCC: n=1119; mBCC: n=96)
Median age (range)	62 years (21-101)	72 years (18-101)
% White	100.0	72.4
% Male	61.0	57.1
Treatment	Oral Erivedge 150 mg daily until disease progression, intolerable toxicity, or withdrawal from study	Oral Erivedge 150 mg daily until disease progression, intolerable toxicity, or withdrawal from study
Median duration of treatment	10.2 months	8.6 months
Treatment interruptions	• **Up to 4-week treatment interruptions for intolerable adverse reactions (ARs) potentially related to Erivedge. Per PI, withhold treatment for up to 8 weeks for intolerable ARs until improvement or resolution** • **29 patients (27.9%) experienced ARs leading to treatment interruption**	• **Up to 8-week treatment interruptions for intolerable ARs potentially related to Erivedge or inability to swallow capsules** • **469 patients (38.6%) experienced ARs leading to treatment interruption**
Study limitations	Absence of a control arm	Absence of a control arm and lack of independent central review

Additional pooled safety population studies[3]

- Erivedge was administered as monotherapy at doses of ≥150 mg orally daily in 4 open-label, uncontrolled, dose-ranging or fixed single-dose clinical trials enrolling a total of 138 patients with advanced BCC
- Median age 61 years (range, 21 to 101 years), 100% White (including Hispanics), and 64% male
- Median duration of treatment was approximately 10 months (305 days; range, 0.7 to 36 months); 111 patients received Erivedge for 6 months or longer

Exploratory endpoint: treatment interruptions

Limitations: Because clinical trials are conducted under widely varying conditions, duration of treatment, number of treatment interruptions, and duration of treatment interruption observed in the clinical trial of a drug may not reflect actual clinical practice. This endpoint is exploratory and post-hoc, and no formal inferences can be drawn. Treatment interruption data are not exclusively a result of ARs. The patients captured do not include the total population who took treatment interruptions due to incomplete dosing information for some patients.

BCC=basal cell carcinoma; laBCC=locally advanced basal cell carcinoma; mBCC=metastatic basal cell carcinoma.
*Patients who received at least 1 dose of Erivedge.
†Results from the primary analysis of the total evaluable population (N=1215, data cutoff March 16, 2015).[6]

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Erivedge® (vismodegib) capsule

Erivedge Treatment May Entail Managing Intolerable Adverse Reactions (ARs)

1 Start patients on Erivedge 150 mg once daily

- Erivedge can be administered until disease progression or until unacceptable toxicity[3]
- In ERIVANCE, the pivotal trial for Erivedge, the first assessment of response was performed at 8 weeks[2]
- In a pooled analysis, the median time to onset of ARs ranged from 1.48 to 6.13 months[7]*

2 Educate patients about potential ARs from the start to help them understand what to expect

- ARs of any grade, including mild to moderate in severity (Grade 1 or 2), may affect the course of a patient's treatment
- The most common ARs (≥10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia[1-3]
  - All patients experienced ARs of some grade in ERIVANCE
- Patients may employ management strategies for ARs if necessary[3]

3 Withhold Erivedge for up to 8 weeks due to intolerable ARs until improvement or resolution

- Treatment interruptions prior to 8 weeks of continuous therapy were not studied[3]
- For ARs that become intolerable, treatment interruptions may be needed[3]
  - In STEVIE, 469 patients (38.6%) experienced ARs leading to treatment interruption[1†]
- Permanently discontinue Erivedge if patients experience severe cutaneous ARs, including Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms[3]
- If ARs recur and continue to be intolerable, additional treatment interruptions may be considered or initiated[3]
- At the point when ARs are no longer intolerable, continue treatment as indicated with appropriate management strategies as necessary[3]

*Median AR onset was not evaluable where incidence of AR occurrence was <50%.

†Results from the primary analysis of the total evaluable population (N=1215, data cutoff March 16, 2015).[6]

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Erivedge® (vismodegib) capsule

Treatment Interruptions Have Been Studied

Treatment interruptions were examined in a post-hoc analysis of the STEVIE trial at the time of the primary analysis.[1]

In the STEVIE trial, on the basis of dosing information collected from study medication pages, 283 patients (23.3%) of all 1,215 safety-evaluable patients were identified as having taken a treatment interruption. Greater than 50% of these patients took a treatment interruption as a result of an adverse reaction, but some took it for other reasons. This section of the study included information for the duration of treatment interruption and median duration of treatment that is represented below.[1*]

Limitations: Because clinical trials are conducted under widely varying conditions, duration of treatment, number of treatment interruptions, and duration of treatment interruption observed in the clinical trial of a drug may not reflect actual clinical practice. This endpoint is exploratory and post-hoc, and no formal inferences can be drawn. Treatment interruption data are not exclusively a result of adverse reactions. The patients captured do not include the total population who took treatment interruptions due to incomplete dosing information for some patients.

Number of treatment interruptions, median duration of breaks, and duration of treatment[1*†]

Number of treatment interruptions	Number of patients (safety evaluable)	Median length of interruption (days)	Median duration of treatment, including interruptions (months)
1	183	20.0[‡]	11.9
2	67	26.5[§]	15.5
≥3	33	15.0[¶]	21.2

*Methodology: The duration of treatment and interruptions are derived from dates and quantities of capsules recorded in medication pages, and therefore represent estimates based on available Case Report Form data.
†Results from the primary analysis of the total evaluable population (N=1,215, data cutoff March 16, 2015).[6]
‡Based on data from 155 interruptions.
§Based on data from 126 interruptions.
¶Based on data from 120 interruptions.

In ERIVANCE, the median duration of treatment was 10.2 months (range, 0.7 to 18.7 months), inclusive of laBCC and mBCC cohorts.[3]

Severe cutaneous adverse reactions were observed in postmarketing surveillance. Permanently discontinue Erivedge in patients with these reactions.[3]

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Patient Experience With a Spectrum of Treatment Interruption Breaks to Manage Adverse Reactions (ARs)

Withhold Erivedge for up to 8 weeks for intolerable ARs until improvement or resolution. Treatment durations shorter than 8 weeks prior to interruptions have not been studied.[3]

	Setting	Intolerable ARs	Number of interruptions*	Total days without treatment	Treatment duration (months)†
Chris, 38 years old[1]	ERIVANCE	Abdominal pain, nausea	1	2	9
Jason, 45 years old[1]	Clinical practice	Dysgeusia/ageusia	1	18	11
Stanley, 66 years old[1]	ERIVANCE	Muscle spasms	1	24	8.6
James, 79 years old[1]	ERIVANCE	Dysgeusia, musculoskeletal pain	3	79	11.7
Richard, 82 years old[1]	ERIVANCE	Abdominal pain, diarrhea	4	27	8.4
Tim, 56 years old[1]	Clinical practice	Muscle spasms	5	1-4 weeks	10.8

*In ERIVANCE, patients were allowed to interrupt drug treatment for reasons other than managing intolerable ARs.[1]

†In the ERIVANCE trial, the median duration of treatment was 10.2 months (range, 0.7 to 18.7 months), inclusive of laBCC and mBCC cohorts.[3]

ERIVANCE patient eligibility is based on study investigator assessment. Each case study shows results of treatment in a specific patient and was last verified at clinical data cutoff. Individual results may vary and are not reflective of mBCC patients. These cases are for general informational purposes only and are not intended to convey medical advice. You should use your independent medical judgment in the diagnosis and treatment of your patients.

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Prepare Your Patients for What to Expect Throughout the Duration of Their Treatment

Use this checklist with each of your patients taking Erivedge.

- [ ] Establish a treatment goal with your patients
- [ ] Check in to assess progress and review potential adverse reactions (ARs) and tolerability
- [ ] Document progress with photographs
- [ ] Manage common ARs by referencing the "Erivedge Management Strategies Guide for Most Common Adverse Reactions"
- [ ] Use treatment interruptions as necessary for appropriate ARs for up to 8 weeks
- [ ] Consider AR management strategies or treatment interruptions if ARs recur

For more information, visit Erivedge.com

References: 1. Data on file. Genentech, Inc. **2.** Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171-2179. **3.** Erivedge® (vismodegib) capsule Prescribing Information. Genentech, Inc. July 2020. **4.** Clinicaltrials.gov. STEVIE. A study of vismodegib in patients with locally advanced or metastatic basal cell carcinoma. https://clinicaltrials.gov/ct2/show/NCT01367665. Accessed August 7, 2020. **5.** Erivedge® (vismodegib) capsule European Medicines Agency Assessment Report. September 15, 2016. **6.** Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer*. 2017;86:334-348. **7.** Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021-1026.

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