



**Subject: Important Drug Warning: Risk of Malignancy Progression and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome) Associated with Zelboraf® (vemurafenib)**

August 2013

Dear Healthcare Professional,

Genentech, a member of the Roche Group, would like to inform you of the following:

**Summary**

***Progression of Malignancies Associated with RAS Mutation***

- Based on its mechanism of action, Zelboraf may cause progression of cancers associated with RAS mutations.
- Zelboraf should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

***Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome)***

- Cases of drug rash with eosinophilia and systemic symptoms (DRESS syndrome) have been reported with the use of Zelboraf.
- In patients who develop DRESS syndrome, Zelboraf treatment should be permanently discontinued.

Additional information about these risks is provided in the remainder of this letter.

***Further Information on the Safety Concern and the Recommendations***

• ***Risk of Progression of Malignancies Associated with RAS Mutation***

This risk is based on a single report from a literature article<sup>1</sup> about a 76-year-old male patient with stage IV melanoma in whom accelerated growth of a pre-existing NRAS-mutated chronic myelomonocytic leukemia was observed shortly after initiation of treatment with Zelboraf. It was observed that while Zelboraf caused regression of the patient's melanoma, it caused proliferation of the leukemic cells, which was dose-dependent and reversible. The proliferative effect of Zelboraf on the NRAS-mutant leukemia was also observed *in vitro* and was correlated with enhanced ERK signaling. These findings suggest that Zelboraf caused paradoxical activation of ERK signaling in the RAS-mutant leukemic cell population, which led to leukemic cell proliferation. The proliferative effect was reversed when Zelboraf was withdrawn. The causal

relationship of Zelboraf to the progression of the CMML was confirmed by multiple positive dechallenges and rechallenges, a positive dose-response relationship, biological plausibility, supportive experimental evidence, and supportive analogous evidence from preclinical models. Zelboraf should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

- ***Risk of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome)***

DRESS syndrome is a severe hypersensitivity drug reaction characterized by fever, skin rash, lymphadenopathy, hematologic abnormalities (eosinophilia, atypical lymphocytes), and internal organ involvement (liver, kidney) occurring 2-6 weeks after drug initiation. There is great variability in the clinical presentation of DRESS such that the diagnosis requires a degree of suspicion and clinical judgment. DRESS should be suspected in a patient receiving a drug treatment with a latency of 2-6 weeks and the following signs and symptoms: skin rash that is morbilliform or diffuse, confluent and infiltrative; fever, facial edema and enlarged lymph nodes. Hematologic abnormalities include eosinophilia >700/microL and/or atypical lymphocytosis. Organ involvement may include abnormal liver function tests (elevated transaminases), renal impairment, interstitial pneumonia and/or pleural effusion, and myocarditis. Although organ involvement is often asymptomatic, severe organ impairment may occur. Clinical management includes drug withdrawal and supportive measures.

The reported cases of DRESS syndrome seen with Zelboraf were characterized by rash, eosinophilia, and systemic involvement (e.g. fever, lymphadenopathy, elevated transaminases, and renal insufficiency). The typical time to onset was 7-25 days. No fatalities were reported. In the majority of patients, Zelboraf was discontinued, and some patients were treated with systemic steroids with corresponding improvement or resolution of symptoms. Zelboraf treatment should be permanently discontinued if a patient develops DRESS syndrome.

<sup>1</sup>Callahan MK, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. *N Engl J Med.* 2012 Dec 13;367(24):2316-21.

Roche is working closely with health authorities to update the product label.

Zelboraf is indicated for the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma. Zelboraf is not indicated for use in patients with wild-type BRAF melanoma.

### ***Call for Reporting***

Healthcare professionals should report any serious adverse events suspected to be associated with the use of Zelboraf to: Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or mailed, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

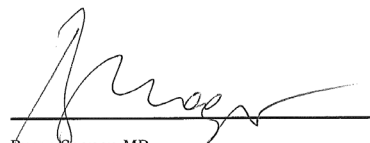
### ***Company Contact Point***

Should you have any questions regarding the use of Zelboraf, please feel free to contact us at: Genentech Medical Information/Communications Department at 1-800-821-8590.

The important safety information in this letter is not comprehensive. Please refer to the accompanying full Prescribing Information and Medication Guide.

Sincerely,

Genentech, a Member of the Roche Group



Bruce Cooper, MD

Senior Vice President, US Medical Affairs