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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zelboraf® (vemurafenib tablets – Genentech/Daiichi Sankyo)

TAC REVIEW DATE: 06/18/2019

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated for the following indications:

1. Erdheim-Chester disease, for treatment of patients with the *BRAF V600* mutation; AND
2. Melanoma, for treatment of unresectable or metastatic disease with *BRAF V600E* mutation as detected by a Food and Drug Administration (FDA)-approved test (Note that Cotellic® (cobimetinib tablets) is a MEK inhibitor that is indicated to be given in combination with Zelboraf in a similar patient population with melanoma);[1] AND

Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Disease Overview

Mutations in the BRAF gene are common in several types of cancer.[2] The BRAF protein is normally switched on and off in response to signals that control cell growth and development; however, mutations cause the BRAF protein to be continuously active. This over activity may contribute to the growth of cancers by allowing abnormal cells to grow and divide uncontrollably. The V600E mutation is the most common *BRAF* gene mutation identified in cancers, particularly in melanoma.

ECD is a rare non-Langerhans histiocytosis. There is a *BRAF V600* mutation estimated in between 38% and 100% of patients with ECD.[8] Although multiple systems may be affected, clinical findings most often exhibit in the CNS or as bone pain.

Guidelines

Prior to approval of Zelboraf guidelines for ECD (2014) list Zelboraf as a first- or second-line treatment option.[8] The National Comprehensive Cancer Network (NCCN) also supports use of Mekinst in multiple cancers.

FDA-Approved Indications

- Melanoma: Guidelines (version 2.2019 – March 12, 2019) recommend BRAF + MEK inhibitor combinations (e.g., Zelboraf + Cotellic, Tafinlar + Mekinist, Braftovi + Mektovi) for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a V600 activating mutation.[3] While combination BRAF/MEK inhibition is preferred, NCCN notes that if contraindicated, monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) are recommended options, particularly for patients who are not appropriate candidates for checkpoint immunotherapy. Tafinlar + Mekinist is also recommended in guidelines as adjuvant therapy (including for nodal recurrance) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection.

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Other Uses With Supportive Evidence

- Colon Cancer: NCCN guidelines for colon cancer (version 2.2019 – May 15, 2019) recommend BRAF/MEK inhibitor combinations for *BRAF V600E*-mutated disease.[4] For primary treatment (following adjuvant chemotherapy) or as subsequent use, Zelboraf + ironotecan + Erbitux (cetuximab IV infusion) or Vectibix (panitumumab IV infusion) is a recommended treatment option. Subsequent use of either Braftovi + Mektovi or Tafinlar + Mekinist are also treatment options recommended in combination with Erbiux or Vectibix.
- Hairy Cell Leukemia: NCCN guidelines for hairy cell leukemia (version 3.2019 – January 31, 2019) state that a purine analog (e.g., cladribine, Nipent) is recommended as initial therapy.[4] Zelboraf ± rituximab is listed as an option for patients with relapsed or refractory disease following one of these regimens.
- Non-Small Cell Lung Cancer: NCCN guidelines for NSCLC (version 4.2019 – April 29, 2019) list Tafinlar + Mekinist as a first-line therapy for tumors with a *BRAF* mutation.[5] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.
- Thyroid Cancer: NCCN guidelines for thyroid cancer (version 1.2019 – May 28, 2019) list Tafinlar and Zelboraf as treatment options for iodine-refractory differentiated thyroid cancer with a *BRAF V600E* mutation.[6] This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zelboraf. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zelboraf is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Erdheim-Chester Disease (ECD).** Approve for 3 years if the patient has *BRAF V600* mutation-positive disease.

2. **Melanoma.** Approve Zelboraf for 3 years if the patient meets BOTH of the following (A and B):
   A) The patient has unresectable, advanced, or metastatic melanoma; AND
   B) The patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

3. **Colon or Rectal Cancer.** Approve for 3 years if the patient meets the following (A, B, and C):
   A) The patient has *BRAF V600E* mutation-positive disease; AND
   B) The patient has previously received a chemotherapy regimen for colon or rectal cancer.
   NOTE: This includes previous adjuvant use of chemotherapy. Examples of previous chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin); AND

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C) The agent is prescribed as part of a combination regimen for colon or rectal cancer. NOTE: examples of combination regimens include: Zelboraf/ironotecan/Erbitux (cetuximab IV infusion), Zelboraf/ironotecan/Vectibix (panitumumab IV infusion). .

4. Hairy Cell Leukemia. Approve for 3 years if the patient meets BOTH of the following conditions (A and B):
- **A)** The patient has relapsed/refractory hairy cell leukemia; AND
- **B)** The patient has tried at least one other therapy for hairy cell leukemia (e.g., cladribine, Nipent™ [pentostatin injection], rituximab injection, Intron® A [interferon alpha-2b injection]).

5. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient has *BRAF V600E* mutation-positive disease.

6. Thyroid Cancer, Differentiated. Approve Zelboraf for 3 years if the patient meets ALL of the following conditions (A, B, and C):
- **A)** The patient has differentiated thyroid carcinoma (i.e., papillary, follicular, or Hürthle cell); AND
- **B)** The patient has disease that is refractory to radioactive iodine therapy; AND
- **C)** The patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zelboraf has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zelboraf® tablet, oral [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; November 2017.
2. Genetic Home Reference. BRAF gene. National Institutes of Health, US Department of Health & Human Service Web Site. Reviewed August 2018. Accessed on June 4, 2019. Available at: https://ghr.nlm.nih.gov/gene/BRAF.
3. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 2.2019 – March 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 4, 2019.
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4. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (Version 3.2019 – January 31, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019.
5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – April 29, 2019). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019.
6. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2019 – May 28, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019..
7. Brose MS, Cabanillas ME, Cohen EE, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(9):1272-1282.
8. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. *Blood.* 2014;124(4):483-492.
9. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 13, 2019.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	For melanoma, modify criteria for use as monotherapy to note that this applies to patients who has not previously experienced disease progression on prior BRAF inhibitor treatment. Previously, this was addressed as a Condition Not Recommended for Coverage but is now being moved to the criteria section of the policy. For hairy cell leukemia, add Rituxan, Intron® A as examples of previous therapies. Add Thyroid Cancer as an off-label indication; approve for 3 years, if the patient has differentiated disease refractory to radioactive iodine therapy, and if disease is BRAF-positive. Remove combination use with Mekinist (unless already started on therapy) from the Conditions Not Recommended for Approval (not needed as criteria do not approve for this use).	08/23/2017
Selected revision	Add criteria to approve for 3 years for Erdheim-Chester disease if the patient has the BRAF V600 mutation. Adjust melanoma criteria to remove "unresectable or metastatic" as a qualifier for melanoma and move to criteria section for initial therapy; add that "advanced" melanoma may be included in this criterion.	12/06/2017
Early annual revision	Align criteria for melanoma with Tafinlar PA criteria; remove criteria that does not allow coverage in patients who had disease progression while on a BRAF inhibitor. Remove continuation criteria in melanoma; now all approvals require that the patient has unresectable, advanced, or metastatic melanoma with a BRAF mutation.	05/23/2018
Annual revision	**Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy (including as adjuvant use), and if the agent will be used as part of a combination regimen for colon or rectal cancer. **Hairy Cell Leukemia:** To align with updated guidelines, change criteria to require at least one previous therapy (previously required two therapies prior to Zelboraf). **NSCLC:** The diagnosis was changed to remove the BRAF mutation from the approval condition. The requirement that the patient has BRAF V600E mutation was added to the criteria for patients with NSCLC.	06/18/2019

*For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx. TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; NCCN – National Comprehensive Cancer Network; NA – Not applicable; NSCLC – Non-small cell lung cancer.

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