

May 30, 2018



Submission Request

National Comprehensive Cancer Network[®] (NCCN[®])

RE: Clinical Evidence in Support of Tafinlar[®] (dabrafenib) and Mekinist[®] (trametinib) in Patients With Resected Stage III or Metastatic Stage IV *BRAF* V600-Mutant Melanoma

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Date of Request: May 30, 2018
NCCN Guidelines Panel: Melanoma

To Whom It May Concern:

As the NCCN Melanoma Panel reviews the NCCN Clinical Practice Guidelines in Oncology[®] (NCCN Guidelines[®]) for Melanoma v.2.2018 and the associated Drugs and Biologics Compendium[™], we have enclosed data relating to treatment with dabrafenib and trametinib for your consideration.

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Dabrafenib and trametinib in patients with resected stage III or metastatic stage IV *BRAF* V600-mutant melanoma

This request is for the Panel to consider modifying the current Melanoma Guidelines[®] and the associated NCCN Drugs and Biologics Compendium[™] based on the pivotal trials and FDA-approved labeling for dabrafenib and trametinib in *BRAF* V600-mutant melanoma.

Specific changes recommended for the Guidelines & Compendium

1. Please consider including a bullet for mutational testing to confirm *BRAF* status as part of the workup for stage III and IV melanoma: ME-4, ME-5, ME-6, ME-8, ME-9, ME-10, ME-11, ME-13 and ME-14.
2. Please consider modifying the treatment algorithms for adjuvant therapy (ME-5 and ME-13) to show locoregional options **or** systemic options rather than the current version that shows locoregional options first, followed by systemic options.

FDA status

Dabrafenib in combination with trametinib are indicated, for the adjuvant treatment of patients with melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. Dabrafenib in combination with trametinib are indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test. Dabrafenib in combination with trametinib are indicated for the treatment of patients with metastatic non-small cell lung cancer with *BRAF* V600E mutation as detected by an FDA-approved test. Dabrafenib in combination with trametinib are indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer with *BRAF* V600E mutation and with no satisfactory locoregional treatment options. Dabrafenib and trametinib are also approved as single agents for the treatment of unresectable or metastatic melanoma with *BRAF* V600E or V600E/K mutation, respectively.

Rationale for recommended change

1. Constitutive activation of the MAPK pathway via BRAF mutation occurs in approximately half of advanced melanomas; the mutated melanoma tends to exhibit a more aggressive biology. Targeted treatment with BRAF and MEK inhibitors has been associated with treatment benefits; molecular testing for BRAF mutations is needed to assess potential treatment options.¹ Mutational testing to confirm BRAF status is required by the FDA-approved label and supported by trial design in the pivotal studies for dabrafenib and trametinib in *BRAF V600*-mutant melanoma.²⁻⁷
2. The pivotal COMBI-ad trial evaluating dabrafenib plus trametinib in resected stage III *BRAF V600*-mutant melanoma included patients that had not received previous radiotherapy for melanoma.⁶

Literature support

1. Cheng L, Lopez-Beltran A, Massari F, et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. *Modern Pathol.* 2018; 31: 24-38.
2. Tafinlar [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
3. Mekinist [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
4. Long G, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *NEJM.* 2014; 371: 1877-88.
5. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *NEJM.* 2015; 372:30-39.
6. Flaherty K, Infante J, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *NEJM.* 2012; 376: 1694-1703.
7. Long G, Hauschild A, Santunami M, et al. Adjuvant dabrafenib plus trametinib in resected stage III BRAF-mutated melanoma. *NEJM.* 2017. September 10. [Epub ahead of print].

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Melanoma Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copies of Prescribing Information and referenced primary literature; author disclosures included within references