September 27, 2017

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Adjuvant Use of Tafinlar® (dabrafenib) and Mekinist® (trametinib) in Patients With Resected Stage III *BRAF V600*-Mutant Melanoma

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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.1.2017 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with dabrafenib and trametinib for your consideration:

- Data to support the use of adjuvant dabrafenib and trametinib in patients with resected Stage III *BRAF V600*-mutant melanoma

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Adjuvant dabrafenib and trametinib in patients with Resected stage III *BRAF V600*-mutant melanoma

This request is for the Panel to consider the addition of dabrafenib and trametinib as an adjuvant treatment option in patients with resected Stage III *BRAF V600*-mutant melanoma in the Melanoma Guidelines® and the associated NCCN Drugs and Biologics Compendium™.

In the double-blind, placebo-controlled, Phase III COMBI-AD study (N = 870), patients with resected stage III *BRAF V600E*- or *V600K*-mutant melanoma were randomized to receive dabrafenib 150 mg twice daily plus trametinib 2 mg daily (n = 438) or placebo (n = 432) for 12 months. At a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.47; 95% confidence interval [CI], 0.39 to 0.58; P<0.001).[1]

In total, 435 patients in the dabrafenib plus trametinib and 432 patients in the placebo arm were included in the safety analysis. Of the adverse events (AEs) that occurred in ≥ 20% in the dabrafenib plus trametinib arm, the most common any-grade included: pyrexia (63%), fatigue (47%), nausea (40%), headache (39%), Chills (37%), Diarrhea (33%), vomiting (28%), arthralgia (28%), and rash (24%). Serious AEs (SAEs) were reported in 36% of the patients receiving dabrafenib plus trametinib versus 10% in the placebo arm. One fatal SAE of pneumonia occurred in a patient receiving dabrafenib plus trametinib.[1]

Specific changes recommended for the Guidelines & Compendium

Please include dabrafenib and trametinib as an adjuvant treatment option for patients with resected Stage III *BRAF V600*-mutant melanoma.

FDA status
Dabrafenib and trametinib are not approved for the adjuvant treatment of patients with resected Stage III *BRAF V600*-mutant melanoma. Dabrafenib and trametinib are approved in combination for the treatment of patients with unresectable or metastatic melanoma with *BRAF V600E* or *V600E/K* mutations as detected by an FDA-approved test. 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
The results of the COMBI-ad study have demonstrated safety and efficacy of adjuvant dabrafenib and trametinib in patients with resected Stage III *BRAF V600*-mutant melanoma.

Literature support
1. 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: Copy of Prescribing Information and referenced primary literature; author disclosures included within references