October 8, 2020

Submission Request
National Comprehensive Cancer Network® (NCCN)®

RE: Clinical Evidence in Support of Use of Tafinlar® (dabrafenib) and Mekinist® (trametinib) in Patients With Unresectable, Metastatic, or Recurrent *BRAF V600E*-Mutated Biliary Tract Cancer

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NCCN Guidelines Panel:	Hepatobiliary Cancers

To Whom It May Concern:

As the NCCN Hepatobiliary Cancers Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Hepatobiliary Cancers v.5.2020 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 dabrafenib and trametinib in patients with unresectable, metastatic, or recurrent *BRAF V600E*-mutated biliary tract cancer

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Dabrafenib and Trametinib in Patients with Unresectable, Metastatic, or Recurrent *BRAF V600E*-mutated Biliary Tract Cancer

This request is for the Panel to consider the addition of dabrafenib and trametinib as a treatment option in patients with unresectable, metastatic, or recurrent *BRAF V600E*-mutated biliary tract cancer in the Hepatobiliary Cancers Guidelines® and the associated NCCN Drugs and Biologics Compendium®.

A prospective analysis was conducted for a cohort of 43 patients with *BRAF V600E*-mutated, unresectable, metastatic, locally advanced, or recurrent biliary tract cancer enrolled in the Phase II, open-label, single-arm, multicenter, Rare Oncology Agnostic Research (ROAR) basket trial (NCT02034110). Patients were eligible if they progressed or were intolerant to a prior gemcitabine-based chemotherapy regimen. Patients were treated with dabrafenib 150 mg twice daily plus trametinib 2 mg once daily on study. At this interim analysis (data cutoff date of March 29, 2019), patients had a median follow-up of 10 months (interquartile range: 6-15). The primary endpoint was overall response rate (ORR) assessed by both the investigator and by an independent central review. The investigator-assessed ORR was 51% (95%CI: 36-67) and ORR by central review was 47% (95%CI: 31-62).[1]

The safety analysis included the 43 patients in the biliary tract cancer cohort. The most common adverse events (AEs) that occurred in ≥ 30% of any grade included: pyrexia (67%), nausea (42%), vomiting (35%), fatigue (33%) and diarrhea (30%). The most common Grade 3/4 adverse event was increased γ-glutamyltransferase, reported in five (12%) patients. Serious AEs occurred in 17 (40%) patients with pyrexia being the most frequent, reported in eight (19%) patients. There were two deaths due to sepsis and they were not treatment-related. [1]

In addition, the subprotocol H (EAY131-H) of the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH, NCT02465060) trial studied the treatment of *BRAF V600*-mutated tumor types with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The study included four patients with *BRAF V600E*-mutated cholangiocarcinoma and partial responses were observed in three patients. A breakdown of adverse events was not available for the cholangiocarcinoma patients. In the overall study, adverse events were reported as comparable to the previously reported safety profiles of dabrafenib and trametinib.[2]

Specific changes recommended for the Guidelines and Compendium

- Consider including dabrafenib and trametinib as a treatment option under Useful in Certain Circumstances for *BRAF V600E*-mutated, unresectable, metastatic, or recurrent biliary tract cancers on page BIL-C 2 of 3.
- Consider updating the corresponding Treatment for Advanced Biliary Tract Cancers Discussion section regarding Targeted Therapy.
- Consider adding testing for the *BRAF V600E* mutation in patients with unresectable, metastatic, or recurrent biliary tract cancer.

FDA status

Dabrafenib and trametinib are not approved for the treatment of patients with unresectable, metastatic, or recurrent *BRAF V600E*-mutated biliary tract cancers.

Dabrafenib and trametinib are approved in combination for:

- the treatment of patients with unresectable or metastatic melanoma with *BRAF V600E* or *V600K* mutations as detected by an FDA-approved test.
- 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.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with *BRAF V600E* mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) 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 as detected by an FDA-approved test, respectively.

Rationale for recommended change

Data from the ROAR and NCI-MATCH studies have demonstrated the activity of dabrafenib and trametinib in patients with unresectable, metastatic, or recurrent *BRAF V600E*-mutated biliary tract cancers.

Literature support

1. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial [electronic publication]. Lancet Oncol. 2020. doi: 10.1016/S1470-2045(20)30321-1.

2. Salama A, Li S, Macrae E, et al. Dabrafenib and trametinib in patients with tumors with BRAF V600E mutations: results of the NCI-MATCH trial subprotocol H [electronic publication]. J Clin Oncol. 2020. doi: 10.1200/JCO.20.00762.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Hepatobiliary Cancers 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,

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