May 6, 2020

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Capmatinib in Metastatic NSCLC With a Mutation That Leads to MET Exon 14 Skipping (METex14)

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NCCN Guidelines Panel:	Non-Small Cell Lung Cancer

To Whom It May Concern:

As the Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Non-Small Cell Lung Cancer v.3.2020 and the associated Drugs & Biologics Compendium™, we are enclosing data related to treatment with the recently FDA-approved Tabrecta™ (capmatinib) for your consideration[1]:

- Data to support the use of capmatinib in adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test

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Capmatinib for the treatment of METex14-mutated metastatic NSCLC
GEOMETRY mono-1 (NCT02414139) is a Phase II study that evaluated capmatinib 400 mg twice daily in patients with MET-amplified and METex14-mutated advanced NSCLC (N = 334) across multiple cohorts. Patient cohorts were based on MET dysregulation status and prior treatment. The efficacy of the METex14-mutated patients (regardless of MET amplification status/gene copy number) enrolled into Cohort 4 and Cohort 5b are presented below. The primary endpoint is overall response rate (ORR) per RECIST 1.1 by Blinded Independent Review Committee (BIRC) assessment. The key secondary endpoint is duration of response (DOR) as assessed by BIRC.[2,3]

The efficacy results summarized are for the METex14-mutated cohorts from a data cut-off date of April 15, 2019. There were 97 METex14-mutated patients enrolled in Cohorts 4 (n = 69, pretreated) and 5b (n = 28, treatment-naive). The ORR as assessed by the BIRC was 41% (95% CI, 29 – 53) in Cohort 4 and 68% (95% CI, 48 – 84) in Cohort 5b. The median DOR was 9.7 months (95% CI, 5.5 – 13.0) in Cohort 4 and 11.1 months (95% CI, 5.5 – not estimable) in Cohort 5b.[3,4] The DOR from a later data cut-off date (October 28, 2019) is presented in the prescribing information.[1]

A posthoc analysis was conducted for 13 patients in Cohort 4 and Cohort 5b with asymptomatic brain metastases at baseline. Of these 13 patients, 7 (54%) had an intracranial response, 4 (31%) had complete resolution of brain lesions, and 12 (92%) had intracranial disease control. These results are observational.[3,4]

The most common adverse reactions (≥20%) reported with capmatinib are peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite. Serious adverse reactions occurred in 51% of patients who received capmatinib. Serious adverse reactions in ≥ 2% of patients included dyspnea (7%), pneumonia (4.8%), pleural effusion (3.6%),

general physical health deterioration (3%), vomiting (2.4%), and nausea (2.1%). A fatal adverse reaction occurred in one patient (0.3%) due to pneumonitis. Permanent discontinuation of capmatinib due to an adverse reaction occurred in 16% of patients. The most frequent adverse reactions (≥1%) leading to permanent discontinuation of capmatinib were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%).[1]

Specific changes recommended for the Guidelines & Compendium

- Please consider including capmatinib as a preferred treatment for patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping (NSCL-I) and update related discussion sections (including the Predictive and Prognostic Biomarkers [starting on MS-11] and Molecular Testing for Biomarkers [starting on MS-13] sections).
- Please consider adding METex14 mutation testing as part of the workup for metastatic disease (NSCL-18) and creating a corresponding treatment algorithm page for METex14-mutated results (between NSCL-27 and NSCL-28).
- Please consider including METex14 mutation testing in the Principles of Molecular and Biomarker Analysis (NSCL-G).
- Please consider including METex14 as an oncogenic driver in the flowchart (along with EGFR, ALK, ROS1, and BRAF) which have targeted treatments (NSCL-28 and NSCL-29).

FDA status

Capmatinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.[1]

Rationale for recommended changes

- Based on the data from the GEOMETRY mono-1 study, capmatinib demonstrated efficacy and safety in METex14-mutated patients with advanced NSCLC.
- Testing for mutations leading to MET exon 14 skipping identifies patients who may benefit from capmatinib therapy.

Literature support

1. Tabrecta [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020.
2. Wolf J, Seto T, Han JY, et al. Capmatinib (INC280) in METex14-mutated advanced NSCLC: efficacy data from the phase II GEOMETRY mono-1 study. Journal of Clinical Oncology. 2019; 37:15(suppl): 9004. doi:10.1200/JCO.2019.37.15_suppl.9004
3. Heist R, Seto T, Han JY, et al. Capmatinib (INC280) in METex14-mutated advanced NSCLC: efficacy data from the phase 2 GEOMETRY mono-1 study. [SNO abstract CMET-22] Neuro-Oncology. 2019; 21:6(suppl): vi56. doi: 10.1093/neuonc/noz175.223
4. Heist R, Seto T, Han JY, et al. (2019, November) Capmatinib (INC280) in METex14-mutated advanced NSCLC: efficacy data from the phase 2 GEOMETRY mono-1 study. Symposium conducted at Society for NeuroOncology 24th Annual Meeting, Phoenix, AZ.

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

Thank you for your time and consideration.

Sincerely,

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