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Date of Request:	May 13, 2016
NCCN Guidelines Panel:	Non Small-Cell Lung Cancer

Dear Sir or Madam:

This letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for review of data for TAGRISSO™ (osimertinib). TAGRISSO is a tyrosine kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. Currently, this is the only medication FDA approved in this patient population.

NCCN guidelines recommend patients receiving an EGFR TKI be monitored for progression. When patients with EGFRm status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance. Identifying the mechanism of acquired resistance would help in identifying the appropriate subsequent treatment at progression (NCCN 2016).

The enclosed information is intended to provide supporting data and may include information that is not found in the currently approved prescribing information for TAGRISSO. The information should not be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information (PI) for TAGRISSO.

The rationale for the recommended change is to provide health care professionals with information regarding the efficacy and safety of TAGRISSO that have been evaluated in clinical trials.

1. **Consideration of TAGRISSO as an acceptable targeted therapy for metastatic EGFRm NSCLC in treatment-naïve patients (not an FDA approved indication).**

   Rationale: Treatment response to osimertinib has been demonstrated in EGFRm TKI treatment-naïve NSCLC patients in AURA Study 1, Phase I (Janne et al).

   - In 30 treatment-naïve EGFRm advanced NSCLC patients, with a median length of RECIST follow-up of 13.7 months, immature data with osimertinib 80 mg demonstrated overall response rate (ORR) of 67% (95% CI: 47, 83) and disease control rate (DCR) of 93% (95% CI: 78, 99). In those with response, the median duration of response was 13.6 months. Of all patients

treated, 75% were alive and progression-free at 12 months (Ramalingam et al.).

2. **Consideration of TAGRISSO as an acceptable targeted therapy for metastatic EGFRm NSCLC in patients who are T790M negative who have progressed on a prior EGFR TKI (not an FDA approved indication).**

   Rationale: Evaluation of a cohort of patients in AURA Phase I, who were T790M mutation negative by central testing and treated with osimertinib, demonstrated limited efficacy. (Janne et al, ELCC presentation April 2015 and AACR presentation November 2015)

   - In 69 patients who tested T790M negative via central testing, the ORR at various doses of osimertinib was 23% (95% CI: 14, 35). DCR was 64% (95% CI: 51, 75).
   - Evaluation of the tissue biopsy by local tissue test indicated that of those negative by central testing:
     - 16% tested positive and had an ORR of 55%
     - 51% tested negative and had an ORR of 11%
     - 33% tested unknown and had an ORR of 30%
   - Evaluation by ctDNA/plasma testing indicated that of those negative by central testing:
     - 38% tested positive and had an ORR of 23%
     - 30% tested negative and had an ORR of 14%
     - 32% were uninformative and had an ORR of 36%

3. **Consideration of TAGRISSO as an acceptable targeted therapy for metastatic EGFRm NSCLC in patients who are T790M unknown who have progressed on a prior EGFR TKI (not an FDA approved indication).**

   Rationale: Evaluation of a small cohort of patients in AURA Phase I, who were T790M mutation unknown based on central testing and treated with osimertinib suggest moderate rates of response in this population (In house data).

   - In patients (n=20) with unknown status by central testing, but confirmed results by local testing, T790M status and ORR were:
     - T790M positive local test (n=15): ORR was 60%.
     - T790M negative local test (n=3): ORR was 66.7%
     - T790M unknown local test (n=2): ORR was 100%.
   - Median PFS was 11.3 months. The estimated percentage of patients alive and progression-free was 88.2% at 3 months, 75.1% at 6 months, and 67.6% at 9 months.
   - In patients with a confirmed response (n=13), median duration of response (DoR) was 11.1 months. All of these patients were estimated to have a DoR >3 months, 74.1% of patients were estimated to have DoR >6 months, and 64.8% of patients were estimated to have DoR >9 months.

4. **Consideration of TAGRISSO as an acceptable targeted therapy for metastatic EGFRm NSCLC in patients who have brain metastasis or leptomeningeal disease (not an FDA approved indication).**

Rationale: Treatment response to osimertinib has been demonstrated in EGFR T790M mutation-positive NSCLC patients with brain metastasis or leptomeningeal disease in AURA Phase II extension and AURA 2.

- In 158 EGFRm T790M NSCLC patients with baseline brain metastasis, immature data with osimertinib 80 mg demonstrates ORR of 62% and a median PFS of 8.0 months (Ahn MJ et al.).
- In the 161 EGFRm T790M NSCLC patients with baseline brain metastasis treated with osimertinib and measured for progression events by BICR,
    - 42.2% qualified for RECIST progression
    - 14.3% demonstrated RECIST progression in the brain/CNS
    - 8.1% demonstrated progression due to non-target lesions in the brain/CNS
    - 8.7% demonstrated new lesions in the brain/CNS
    - 6.8% died (Ahn MJ et al).
- In the 250 EGFRm T790M NSCLC patients without baseline brain metastasis treated with osimertinib and measured for progression events by BICR,
    - 29.6% qualified for RECIST progression
    - 1.2% demonstrated RECIST progression in the brain/CNS
    - 0% demonstrated progression due to non-target lesions in the brain/CNS
    - 1.2% demonstrated new lesions in the brain/CNS, and
    - 2.4% died (Ahn MJ et al).

- A cohort of patients in the BLOOM study with metastatic EGFRm NSCLC and leptomeningeal disease included 13 patients treated with osimertinib. Efficacy assessments were conducted in 12 patients with positive baseline CSF cytology; 11 of the 12 patients had sufficient follow-up for analysis.
    - 3/12 patients withdrew; no assessments were available
    - 3/8 patients had improved neurological exam per investigator; of 5 patients with normal neurological exam at baseline, 4 had no change
    - 1/8 patients had CSF cytology clearance; 5/9 patients had negative CSF cytology at their latest visit
    - 6/7 patients had LM imaging improvement per investigator
    - 8 patients have received >4 months of treatment and all 8 remain on osimertinib (Kim DW et al.)

The following articles and presentations of data are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.4.2016. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. http://www.NCCN.org. Accessed January 19, 2016.

2. Janne PA, Yang JC-H, Kim D-W, et al. AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer. N Engl J Med 2015;372:1689-1699.

3. Ramalingam SS, Yang JCH, Lee CK, et al. AZD9291 in treatment-naïve EGFRm advanced NSCLC: AURA first-line cohort [presentation]. Presented at 16th World Conference on Lung Cancer; September 6-9, 2015; Denver, CO.

4. Janne PA, Ahn MJ, Kim DW, et al. A phase I study of AZD9291 in patients with EGFR-TKI-resistant advanced NSCLC- updated progression-free survival and duration of response data [presentation]. Presented at 5th European Lung Cancer Conference; April 15-18, 2015; Geneva, Switzerland.

5. Janne PA, Felip E, Kim DW, et al. Characterization of the activity of AZD9291 in patients with 'T790M negative' advanced non-small cell lung disease (aNSCLC) [poster]. Presented at American Association for Cancer Research; November 5-9, 2015; Boston, MA.

6. AstraZeneca In-house Data.

7. Ahn MJ, Tsai CM, Yang JCH, et al. AZD9291 activity in patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) and brain metastasis: data from Phase II studies [poster]. Presented at The European Cancer Congress; September 25-29, 2015; Vienna, Austria.

8. Kim DW, Ahn MJ, Lee DH, et al. AZD9291 activity in patients with leptomeningeal disease from non-small cell lung cancer: a Phase I study [presentation]. Presented at American Association for Cancer Research; November 5-9, 2015; Boston, MA.

9. TAGRISSO Prescribing Information.

Sincerely

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