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Date of Request:	December 14, 2016
NCCN Guidelines Panel:	Non Small-Cell Lung Cancer, Dr. David Ettinger and Dr. Douglas Wood

Dear NSCLC Panel Chairs and Members:

On behalf of AstraZeneca, I respectfully request the NSCLC Panel to consider recommending osimertinib as a Category 1 agent in the NCCN Guidelines for the treatment of metastatic NSCLC patients who are EGFR T790M mutation-positive and who have progressed on or after an EGFR TKI therapy based on the following publication:

Mok, TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M positive lung cancer [published online ahead of print on December 6, 2016]. *N Engl J Med*. 2016. http://www.nejm.org/doi/full/10.1056/NEJMoa1612674.

FDA clearance: Osimertinib was approved by the FDA on November 13, 2015 for metastatic EGFR T790M mutation-positive NSCLC patients who have progressed on or after EGFR TKI therapy. This indication was approved under accelerated approval. The AURA3 data have been submitted to the FDA to verify clinical benefit and support full approval.

1. Specific change: We request changing osimertinib to a Category 1 level evidence for metastatic EGFR T790M mutation-positive NSCLC patients who have progressed on or after EGFR TKI therapy (page NSCL-19) with consideration to simplify the algorithm to clearly delineate osimertinib as an option in all T790M positive patients regardless of disease presentation.

Rationale: The clinical evidence from a registration Phase III trial of osimertinib compared to platinum-based doublet chemotherapy in patients with centrally-confirmed locally advanced or metastatic EGFRm T790M-positive NSCLC patients who have progressed on first-line EGFR TKI, was presented at the World Congress on Lung Cancer, December 6, 2016 and published in NEJM.

- In brief, 419 patients were randomized 2:1 to osimertinib:chemotherapy; the primary endpoint of PFS based on RECIST 1.1 is listed below.
    - Investigator assessed median PFS:
        - Osimertinib- 10.1 months (95% CI: 8.3, 12.3)
        - Chemotherapy- 4.4 months (95% CI: 4.2, 5.6)
        - HR 0.30 (95% CI: 0.23, 0.41); p-value: <0.001
    - The improvement in PFS was seen consistently across predefined subgroups of interest, including patients with baseline CNS metastases
        - Median PFS in patients with CNS metastases at baseline (n=144)
            - Osimertinib- 8.5 months (95% CI: 6.8, 12.3)

        - Chemotherapy- 4.2 months (95% CI: 4.1, 5.4)
        - HR 0.32 (95% CI: 0.21, 0.49)
    - The safety profile of osimertinib was consistent with previous data and was associated with lower rates of grade ≥3 adverse events than chemotherapy (23% vs. 47%)
    - AURA3 allowed for crossover to the osimertinib investigational arm: 60% (n=82) of patients receiving chemotherapy had crossed over to the osimertinib arm at the time of this data analysis

2. Specific change: We request altering or adding the following footnote based on the listed references.

- Please add to footnote nn: Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation[3-5]

The following additional data was presented at the World Conference on Lung Cancer and is being provided for your review.

Updated clinical evidence from Phase II trials supports improvements in CNS overall response rates.[6]

- In 50 patients with measurable brain scans at baseline and follow-up:
    - CNS ORR: 54% (95% CI: 39, 68)
        - CNS responses were observed regardless of prior brain radiation status
    - Estimated percentage remaining in response at 9 months: 75% (95% CI: 53, 88)
    - Median CNS PFS (months): not calculable (95% CI: 7, not calculable)
        - Median follow-up for CNS PFS (months): 11.2 months

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. Mok, TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M positive lung cancer [published online ahead of print on December 6, 2016]. *N Engl J Med*. 2016. http://www.nejm.org/doi/full/10.1056/NEJMoa1612674. Accessed on December 14, 2016.

2. Papadimitrakopoulou VA, Wu Y-L, Ahn M-J, et al. Randomised phase III study of osimertinib vs platinum-pemetrexed for EGFR T790M-positive advanced NSCLC (AURA3) [presentation]. Presented at 17th World Conference on Lung Cancer; December 4-7, 2016; Vienna, Austria.

3. TAGRISSO® (osimertinib) Prescribing Information.

4. cobas® EGFR Mutation Test v2 Package Insert.

5. Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small cell lung cancer [published online ahead of print, June 27, 2016] *J Clin Onc*. 2016. http://jco.ascopubs.org/content/early/2016/06/22/JCO.2016.66.7162. Accessed on December 14, 2016.

6. Goss G, Tsai CM, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two Phase II trials [oral presentation]. Presented

at: World Conference on Lung Cancer Conference; December 4-7, 2016; Vienna, Austria. Abstract MA16.11.

Sincerely,

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