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Date of Request: December 21, 2020
NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Non-Small Cell Lung Cancer (NSCLC) to review the enclosed data from the FDA approval of TAGRISSO® (osimertinib).

FDA Status:
TAGRISSO® has received FDA approval as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. The updated disease-free survival (DFS) results from the Phase III ADAURA trial are currently reflected in the FDA label.

TAGRISSO® is also indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test and for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Specific change- Adjuvant Treatment Therapy:
We respectfully request the recommendation for osimertinib as a treatment option in the adjuvant setting be changed to category 1 recommendation after tumor resection in patients with Stage IB-IIIA non-squamous epidermal growth factor receptor mutation (Exon 19 del or exon 21 L858R mutation) positive non-small cell lung cancer (NSCLC). We respectfully request the following changes:

- NSCL-4 (NCCN NSCLC v2.2021), update recommendation by deleting the word "consider". Change from "consider osimertinib" to "osimertinib (category 1)".
- NSCL-E (NCCN NSCLC v2.2021), update recommendation by deleting the word "consider". Change from "Consider osimertinib for patients with completely resected Stage IB-IIIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy" to "osimertinib for patients with completely resected Stage IB-IIIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (category 1)".

Specific change- *EGFR* mutation testing:

- NSCL-3, NSCL-6, NSCL-7 footnote q (NCCN NSCLC v2.2021), updating the language from "Consider testing for *EGFR* mutation on surgical tissue or biopsy in stages IB-IIIA" to "Test for *EGFR* mutation on surgical tissue or biopsy in stages IB-IIIA".
- NSCL-H 2 of 5, EGFR: Diamond 2 (NCCN NSCLC V2.2021), the removal of the wording "Consider adding" and "post-" before surgical.
    - Specifically, please change "Consider adding molecular testing for *EGFR* mutation to be performed on diagnostic biopsy or post-surgical resection to ensure the *EGFR* mutation

results are available for adjuvant treatment decisions for patients with stage IB to IIIA NSCLC" to "Molecular testing for *EGFR* mutation to be performed on diagnostics biopsy or surgical resection to ensure *EGFR* mutation results are available for adjuvant treatment decisions for patients with stage IB to IIIA NSCLC".

Rationale:

- The ADAURA trial is a Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of adjuvant osimertinib 80 mg once daily vs placebo in patients with Stage IB-IIIA non-squamous *EGFR*m NSCLC with complete tumor resection, +/- adjuvant chemotherapy. Patients were randomized 1:1 to treatment with once daily oral osimertinib 80 mg or placebo for a treatment duration of 3 years. The primary endpoint was disease-free survival (DFS) by investigator assessment in Stage II-IIIA patients. Secondary endpoints: DFS in the overall Stage IB-IIIA population, overall survival (OS), health-related quality of life, and safety. Sites of recurrence, including CNS, was a pre-specified exploratory endpoint.
- Conducting *EGFR* mutation testing is required for appropriate patient identification and informing treatment decisions for osimertinib eligible patients.

Efficacy Results:

- As of January 17, 2020, the Median DFS for patients with Stage II/IIIA (33% maturity) were Not Reached (NR) (95% CI 38.8, Not Calculable (NC)) for osimertinib and 19.6 months (95% CI 16.6, 24.5) for placebo; HR 0.17 (95% CI 0.12, 0.23), $p<0.0001$.
- The Median DFS for patients with Stage IB/II/IIIA (29% maturity) were NR (95% CI NC, NC) for osimertinib and 27.5 months (95% CI 22.0, 35.0) for placebo; HR 0.20 (95% CI 0.15, 0.27), $p<0.0001$.

Safety Results:

- Safety and tolerability information was reported and submitted to the NCCN on May 31, 2020 and September 19, 2020.

The following references are submitted in support of this proposal and to assist in your review.

- TAGRISSO® (osimertinib) Prescribing Information
- Wu Y-L, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. *N Engl J Med*. 2020;383:18 (1711-1723).

Sincerely,

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