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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 on the FDA approved TAGRISSO® (osimertinib), and to formally request an update to the NSCLC guidelines.

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 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 to update the treatment recommendation language for osimertinib in patients with stage IB-IIIA EGFR mutation-positive NSCLC to be consistent with the osimertinib FDA approved label, inclusive of all R0 Resected stage IB-IIIA patients.

NCCN NSCLC v4.2021	**Current language in the guidelines**	**Proposed language**
NSCL-4	Stage IB (T2a, N0) and Stage IIA (T2b, N0) → Margins negative (R0)[v] → Observe or Chemotherapy[r] for high-risk patients[s] and osimertinib[w] [w]For patients with *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy	Stage IB (T2a, N0) and Stage IIA (T2b, N0) → Margins negative (R0)[v] → Observation or Osimertinib[w] or Chemotherapy[r] for high-risk patients[s] and osimertinb[w] [w]For patients with *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy

NSCL H (2 of 5)	Molecular testing for *EGFR* mutation to be performed on diagnostic biopsy or surgical resection sample to ensure the *EGFR* mutation results are available for adjuvant treatment decisions for patients with Stage IIB-IIIA or high risk stage IB-IIA NSCLC.	Molecular testing for *EGFR* mutation to be performed on diagnostic biopsy or surgical resection sample to ensure the *EGFR* mutation results are available for adjuvant treatment decisions for patients with NSCLC stage IB-IIIA
NSCL-E	Osimertinib for patients with completely resected stage IIB-IIIA or high risk stage IB-IIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to received platinum-based chemotherapy.	Osimertinib for patients with completely resected stage IB-IIIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to received platinum-based chemotherapy.

Rationale:

- The ADAURA trial is a global Phase III, randomized, double-blind, multicenter study assessing 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 were 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.
- The ADAURA trial enrolled all completely resected EGFRm stage IB-IIIA (per AJCC 7 staging) NSCLC patients, and all patients treated with Osimertinib derived clinical benefit regardless of stage, adjuvant chemo use, or other baseline clinical features.
- Limiting the use of osimertinib to patients with stage IIB-IIIA, and the subset of stage IB-IIA high risk patients, would be more restrictive than the FDA approved label, and inconsistent with the ADAURA trial reported efficacy and safety outcomes, showing clinical benefits for all patients studied, inclusive of stages IB-IIIA. This could prevent patients from being offered a treatment option with clinically meaningful disease free survival benefit in resected stage IB-IIIA *EGFR*m 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), $p<0.0001$.

- As of January 28, 2021, a clinically meaningful DFS benefit was observed with osimertinib as compared to placebo in patients with or without chemotherapy regardless of disease stage (Stage IB-IIIA) with a HR of 0.16 (95% CI 0.10, 0.26) and 0.23 (95% CI 0.13, 0.40), respectively.
    - Percentage of patients receiving adjuvant chemotherapy based on stage:
        - Stage IB – 57/216 patients (26%)
        - Stage II – 165/231 patients (71%)
        - Stage IIIA – 187/235 patients (80%)
- The DFS hazard ratios for the stage IB and stage II patient subgroups without chemotherapy treatment were 0.38 and 0.20, respectively.
- Health-Related Quality of Life (HRQoL), as measured by the SF-36 survey, was not impacted in patients treated with Osimertinib (at a median treatment duration of 22.5 months). Overall, HRQoL was maintained during adjuvant osimertinib treatment without quality of life differences vs placebo, despite prolonged treatment duration.

Safety Results:

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

Sincerely,
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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).
Wu YL, John T, Grohe G, et al. Postoperative chemotherapy use and outcomes from ADAURA: Osimertinib as adjuvant therapy for resected EGFR mutated NSCLC [presentation]. Presented at: 2020 World Conference on Lung Cancer (WCLC); January 28-31, 2021; Singapore.
Majem M, Goldman JW, John T, et al. Patient-reported outcomes from ADAURA: Osimertinib as adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC [presentation]. Presented at: 2020 World Conference on Lung Cancer (WCLC); January 28-31, 2021; Singapore.