Submitted by: Betty Lu, PharmD
Company/Organization: AstraZeneca/Medical Affairs
Address: One MedImmune Way, Gaithersburg, MD 20878
Phone: 1-877-212-6597
E-mail: betty.lu@astrazeneca.com
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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 for TAGRISSO® (osimertinib). This request is based on the updated disease-free survival (DFS) results of the Phase III ADAURA trial presented at the 2020 American Society of Clinical Oncology (ASCO) annual meeting on May 31, 2020.

FDA Status:
TAGRISSO® is indicated for the first-line treatment of patients with metastatic 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 enclosed data will not result in changes to the current first-line FDA-approved indication. TAGRISSO® is also indicated for the treatment of 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.[1] The updated disease-free survival (DFS) results from the Phase III ADAURA trial are not currently reflected in the FDA label and have not yet been submitted.

Specific change #1 – Adjuvant Treatment Therapy:
Please consider osimertinib as an adjuvant treatment therapy option in patients with Stage IB-IIIA non-squamous epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC) with complete tumor resection. On NSCL-4 (NCCN NSCLC v4.2020), please consider adding osimertinib as an option for patients with EGFRm under adjuvant treatment for patients with Stage IB-IIIA. On NSCL-D (NCCN NSCLC v4.2020), please consider adding section for osimertinib as an adjuvant treatment option for patients with Stage IB-IIIA EGFRm NSCLC.

Data:
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 EGFRm 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) in Stage II-IIIA patients. Secondary endpoints: DFS in the overall Stage IB-IIIA population, DFS at 2, 3, 4, and 5 years, overall survival (OS), quality of life, and safety and tolerability as assessed by adverse event (AE) frequency.[2]

Baseline Characteristics and Disease-free Survival Results[2]:

TABLE I: Patient Demographics, DCO, January 17, 2020)

Characteristic	Osimertinib (n=339, %)	Placebo (n=343, %)
Race: Asian/Non-Asian	64/36	64/36
AJCC Staging at Diagnosis (7th Edition): IB/II/IIIA	31/35/34	31/34/35
Adjuvant Chemotherapy: did receive/did not receive	55/45	56/44
EGFR mutation at randomization*: Exon 19 deletion/L858R	55/45	56/44

DCO = Data Cut-off; AJCC = American Joint Committee on Cancer
*Central test

TABLE II: Median DFS, DCO, January 17, 2020

Disease Stage	Osimertinib	Placebo	HR
Stage II/IIIA (33% maturity)	NR (95% CI 38.8, NC)	20.4 (95% CI 16.6, 24.5)	0.17 (95% CI 0.12, 0.23) p<0.0001
Stage IB/II/IIIA (29% maturity)	NR (95% CI NC, NC)	28.1 (95% CI 22.1, 35.8)	0.21 (95% CI 0.16, 0.28) P<0.0001

DFS = disease free survival; DCO = Data Cut-off; HR = hazard ratio; NC = not calculated; NR = not reached.

TABLE III: Two-year DFS rate (%), DCO, January 17, 2020[†]

Disease Stage	Osimertinib	Placebo	Overall HR
Stage IB	87 (95% CI 77, 93)	73 (95% CI 62, 81)	0.50 (95% CI 0.25, 0.96)
Stage II	91 (95% CI 82, 95)	56 (95% CI 45, 65)	0.17 (95% CI 0.08, 0.31)
Stage IIIA	88 (95% CI 79, 94)	32 (95% CI 23, 42)	0.12 (95% CI 0.07, 0.20)

DFS = disease free survival; DCO = Data Cut-off; HR = hazard ratio
[†]Maturity (Overall population: Stage IB / II / IIIA) 29%: osimertinib 12%, placebo 46%

- Subgroup analysis demonstrated similar results for patients receiving adjuvant chemotherapy compared to those not receiving adjuvant chemotherapy.
  - Received adjuvant chemotherapy (n=378): HR 0.18 (95% CI 0.11, 0.29)
  - Did not receive adjuvant chemotherapy (n=304): HR 0.23 (95% CI 0.13, 0.38)
- Overall survival at 5% maturity was not reached for osimertinib or placebo.

Specific change #2 – Diagnostic Evaluation for Patient Identification:
Please consider adding molecular testing for EGFR mutation to be performed on diagnostic biopsy or post-surgical resection sample to ensure the EGFR mutation results are available for adjuvant treatment decisions to DIAG-A, Principles of Diagnostic Evaluation and NSCL-G, Principles of Molecular and Biomarker Analysis (NCCN NSCLC v4.2020). On NSCL-4, Findings at Surgery (NCCN NSCLC v4.2020), consider footnote addition for molecular testing recommendation for EGFR mutation on surgical resection sample to ensure EGFR mutation results are available for adjuvant treatment decisions in Stages IB-IIIA. On NSCL-6 and NSCL-7 (NCCN NSCLC v4.2020), consider footnote addition to 'Surgery' for molecular testing recommendation for EGFR mutation on surgical tissue or biopsy sample in Stages IB-IIIA.

Rationale:
The prevalence of EGFR mutations in early stage are estimated to be ~33% in a global NSCLC population and there are currently no approved targeted therapies in this setting and there are currently no approved targeted therapies for this population.[3] In clinical practice, the observed prevalence of these mutations and testing rates may be underreported and impacted by the differences between sequencing platforms, guideline algorithms, and clinical practice.[4]

In the ADAURA trial, the prevalence of EGFRm in screened patients was as follows: 2447 patients were screened between October 21, 2015 to January 30, 2019 in 244 centers. The results revealed 1087 patients (44%) were EGFRm (Asian, 63%/Non-Asian 37%). Eligible patients were screened by assessing the diagnostic biopsy or surgically resected tumor samples for EGFR mutations associated with EGFR-TKI sensitivity (exon 19 deletion, L858R), alone or in combination with exon 20 insertion, G719X, S768I, T790M or L861Q, using the cobas® EGFR Mutation Test v2 (Roche Molecular Systems).[5] The increased prevalence of patients with EGFRm observed is likely enriched due to the clinical trial setting in comparison to clinical practice.

The efficacy results of osimertinib from the ADAURA trial seen above provides a clinically meaningful rationale to recommend molecular testing for EGFR mutations in patients with Stage IB-IIIA resectable NSCLC.

Sincerely,
Nabil Chehab

Nabil Chehab, Ph.D.
Medical Head, EGFR Lung Cancer Franchise
US Medical Affairs
AstraZeneca Pharmaceuticals
One MedImmune Way
Gaithersburg, MD 20878
nabil.chehab@astrazeneca.com

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[1] TAGRISSO® (osimertinib) Prescribing Information.
[2] Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients with stage IB-IIIA EGFR mutation positive NSCLC after complete tumor resection: ADAURA [oral presentation]. Presented at: American Society of Clinical Oncology Virtual Scientific Program; May 29-May 31, 2020.
[3] Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7:78985-78993.
[4] Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small cell lung cancer biology and therapy. *Nat Rev Cancer*. 2019; 19(9):495-509.
[5] Tsuboi M, Herbst RS, John T, et al. Frequency of epidermal growth factor receptor (EGFR) mutations in stage IB-IIIA EGFR mutation positive non-small cell lung cancer (NSCLC) after complete tumour resection [poster presentation]. Presented at: European Society for Medical Oncology Congress; September 27-October 1, 2019; Barcelona, Spain.