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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): CNS disease recurrence results of the Phase III ADAURA trial presented at the 2020 European Society for Medical Oncology (ESMO) annual meeting on September 19, 2020 and the full peer-reviewed publication: Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected *EGFR*-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med.* September 19, 2020. DOI:10.1056/NEJMoa2027071. Initial results were previously 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 EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test and 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 enclosed data will not result in changes to the current FDA-approved indications.

The disease-free survival (DFS) results from the Phase III ADAURA trial are not currently reflected in the FDA label. However, Tagrisso was granted Breakthrough Therapy Designation (BTD) for the adjuvant treatment of patients with Stage IB-IIIA *EGFR*-mutated non-small cell lung cancer on July 30, 2020.

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 v8.2020), please consider adding osimertinib as an option for patients with EGFRm under adjuvant treatment for patients with Stage IB-IIIA with negative margins after resection. On NSCL-D (NCCN NSCLC v8.2020), please consider adding section for osimertinib as an adjuvant treatment option for patients with completely resected 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. Baseline patient demographics can be found on Table 1 of the attached publication. 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, health-related quality of life, and safety. Sites of recurrence, including CNS, was a pre-specified exploratory endpoint.[2,6,7] Key data are reported below; additional details can be found in the attached references.

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

Disease Stage	Osimertinib	Placebo	Overall HR
Stage II/IIIA	90 (95% CI 84, 93)	44 (95% CI 37, 51)	0.17 (99.06% CI 0.11, 0.26) p<0.001
Stage IB/II/IIIA	89 (95% CI 85, 92)	52 (95% CI 46, 58)	0.20 (99.12% CI 0.14, 0.30) p<0.001
CNS DFS	98 (95% CI 95, 99)	85 (95% CI 80, 89)	0.18 (95% CI 0.10, 0.33)
Received adjuvant chemotherapy	89 (95% CI 83, 93)	49 (95% CI 41, 56)	0.16 (95% CI 0.10, 0.26)
Did not receive adjuvant chemotherapy	89 (95% CI 81, 94)	58 (95% CI 49, 67)	0.23 (95% CI 0.13, 0.40)

CI = confidence interval; DFS = disease free survival; DCO = Data Cut-off; HR = hazard ratio; CNS = central nervous system
[†]Maturity (Stage II/IIIA) 33%: osimertinib 11%, placebo 55%

- 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 (99.06% CI 0.11, 0.26), p<0.001.
- 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 (99.12% CI 0.14, 0.30), p<0.001.
- Subgroup analysis demonstrated consistent DFS benefit for patients receiving adjuvant chemotherapy compared to those not receiving adjuvant chemotherapy.
  - Received adjuvant chemotherapy (n=410, 60%): HR 0.16 (95% CI 0.10, 0.26)
  - Did not receive adjuvant chemotherapy (n=272, 40%): HR 0.23 (95% CI 0.13, 0.40)
- In the overall population (Stage IB, II, IIIA), total DFS events were observed in 37 (11%) patients receiving osimertinib and 159 (46%) patients receiving placebo.
  - Local/regional disease recurrence was observed in 23 (7%) patients receiving osimertinib and 61 (18%) patients receiving placebo.
  - Distant disease recurrence (either distant only or with local/regional recurrence) was observed in 14 (4%) patients receiving osimertinib and 96 (28%) patients receiving placebo.
- CNS recurrence occurred in 4 patients (1%) treated with Osimertinib versus 33 patients (10%) treated with placebo.
- At data cut-off, 29 patients in the overall population had died (9 in the Osimertinib group and 20 in the placebo group).

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 v8.2020). On NSCL-4, Findings at Surgery (NCCN NSCLC v8.2020), 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 v8.2020), 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, 64%/Non-Asian 36%). 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,
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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.
[6] Tsuboi M, Wu YL, He J, et al. Osimertinib adjuvant therapy in patients with resected EGFR mutated NSCLC (ADAURA): CNS disease recurrence [oral presentation]. Presented at: European Society for Medical Oncology; September 19-September 21, 2020.
[7] Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected *EGFR*-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med*, September 19, 2020. DOI:10.1056/NEJMoa2027071.