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Date of Request:	April 19, 2018
NCCN Guidelines Panel:	Central Nervous System Cancers

Dear Sir or Madam:

On behalf of AstraZeneca, the purpose of this letter is to inform the National Comprehensive Cancer Network (NCCN) Panel for Central Nervous System Cancers of recent data regarding the efficacy of osimertinib in patients with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) and brain metastases in both previously untreated patients and in patients whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

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. TAGRISSO is also indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by and FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.[1]

Specific Change: We respectfully request that inclusion of osimertinib be considered as an option under Brain Metastases, Newly Diagnosed for EGFR mutation-positive NSCLC based on data from FLAURA, a randomized, double-blinded, Phase 3 trial evaluating the efficacy of osimertinib compared to standard of care (SoC) EGFR TKIs gefitinib and erlotinib in previously untreated EGFR mutation-positive NSCLC patients.

FLAURA enrolled 556 patients to assess the efficacy and safety of osimertinib 80 mg once-daily treatment (n=279) versus current first-line SoC EGFR TKIs erlotinib (150 mg orally, once daily) or gefitinib (250 mg orally, once daily) (n=277) in previously untreated patients with locally advanced or metastatic EGFR mutation-positive NSCLC. Patients with neurologically asymptomatic or stable central nervous system (CNS) metastases were eligible for enrollment. In the CNS subset analysis of the FLAURA trial, the CNS efficacy of osimertinib was compared to SoC EGFR-TKI. Patients with symptomatic and unstable metastases were not permitted, unless after definitive therapy for CNS metastases and then stable for ≥ 2 weeks after completion of definitive therapy and steroids.[2,3]

- The overall PFS in patients with baseline CNS metastases was 15.2 months (95% CI: 12.1, 21.4) in the osimertinib group (n=53) and 9.6 months (95% CI: 7.0, 12.4) in the SoC group (n=63). Hazard ratio (HR) was 0.47 (95% CI: 0.30, 0.74), $p<0.001$.[2]
- The CNS objective response rate (ORR) in the CNS full analysis set was 66% (95% CI: 52, 77) in the osimertinib group (n=61) and 43% (95% CI: 31, 56) in the SoC group (n=67).[3]
- The probability of experiencing a CNS progression event, in the absence of experiencing non-CNS progression or death, was consistently lower with osimertinib treatment than with SoC.[3]
- Of 556 patients, 200 patients (36%) had baseline brain scans reviewed by blinded independent central review (BICR); this included 106 patients in the osimertinib arm and 94 patients in the investigator choice of EGFR TKI arm. Of these 200 patients, 41 had measurable CNS lesions per RECIST v1.1. Results of pre-specified exploratory analyses of CNS ORR and duration of response by BICR in the subset of patients with measurable CNS lesions at baseline are summarized below:[1]

	Osimertinib (n=22)	EGFR TKI (n=19)
CNS Tumor Response Assessment[a,b]		
CNS ORR, % (95% CI)	77% (55, 92)	63% (38, 84)
Complete Response	18%	0%
Duration of CNS Response[c]		
Number of responders	17	12
Response Duration ≥6 months	88%	50%
Response Duration ≥12 months	47%	33%

[a]According to RECIST v1.1
[b]Based on confirmed response
[c]Based on patients with response only; duration of response defined as the time from the date of first documented response (complete response or partial response) until progression or death event

Specific Change: We respectfully request that the reference cited to support the use of osimertinib in Recurrent Disease, EGFR T790M mutation-positive NSCLC be updated to the full publication as listed below.

> Goss G, Tsai C-M, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two Phase II trials. *Ann Oncol.* 2018;29(3):687-93.

Specific Change: We respectfully request that osimertinib be considered as an option for patients with leptomeningeal metastases (LM) and EGFR mutation-positive NSCLC.

In an updated analysis of the osimertinib cohort of the ongoing, Phase I, open-label BLOOM study, 41 patients (21 T790M unselected and 20 T790M positive) with EGFR mutation positive NSCLC who progressed on standard treatment and had LM were treated with osimertinib 160 mg once daily.[4]

- Twenty-one patients enrolled in the T790M unselected patient population were evaluable at the data cut-off of February 3, 2017.
- In these patients, the overall LM response was 43% (95% CI: 22, 66), and median duration of response was 18.9 months (range: 5.6-19.3 months; 95% CI: 11.1, not calculable).
- Of ten patients with 'abnormal' baseline neurological assessment, seven patients had improvement from baseline.
- Six out of 20 patients who met the criteria for the CSF response analysis set had a confirmed CSF response.
- Osimertinib mean concentration in CSF was 7.5 nM (range 2.2-26.4 nM), and the mean decrease in EGFR-mutant DNA copy was 39% in 15/21 patients from screening to Cycle 2 Day 1.

Sincerely,

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Reference(s):

[1] TAGRISSO Prescribing Information.

[2] Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018; 378:113–25.

[3] Vansteenkiste J, Reungwetwattana T, Nakagawa K, et al. CNS response to osimertinib versus standard of care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA. [Oral presentation]. Presented at: European Society for Medical Oncology Asia Congress, November 17-19, 2017; Singapore.

[4] Yang J CH, Cho BC, Kim DW, et al. Osimertinib for patients with leptomeningeal metastases from EGFR-mutant non-small cell lung cancer [poster]. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL.