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Date of Request: January 17, 2019
NCCN Guidelines Panel: CNS Cancers

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Central Nervous System (CNS) Cancers to review the enclosed data provided as evidence in support of TAGRISSO® (osimertinib) in the CNS Cancers guideline for the treatment of patients with metastatic NSCLC having progressive leptomeningeal metastases (LM).

Specific change: We respectfully request the inclusion of the enclosed data as evidence for the use of osimertinib at clinical standard-dosage of 80 mg in metastatic NSCLC patients who have progressive LM disease.[1,2,3]

FDA Status: Osimertinib 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. Osimertinib 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. Osimertinib is not indicated for the treatment of NSCLC patients with LM disease.[4]

Rationale: This request is based on clinical evidence from the following studies: 1) a cohort of patients with LM having sensitizing mutations (exon 19 deletions and L858R mutations) receiving osimertinib at 80 mg in the first-line setting[1] 2) a retrospective analysis of T790M positive patients with LM across the AURA program (AURA, AURA2, AURA17 and AURA 3) who received osimertinib at 80 mg which was presented at the European Society for Medical Oncology (ESMO) Asia congress on November 25, 2018[2] 3) a prospective pilot study of T790M positive patients with LM receiving osimertinib at 80 mg[3].

FLAURA program[1]

In the FLAURA trial, patients with confirmed exon 19 deletions or L858R substitution mutations with measurable and/or nonmeasurable lesions on available baseline brain scans were included in this analysis of CNS response by neuroradiologic BICR. Patients with LM were not specifically excluded; however, LMs were assessed as nontarget lesions (NTLs) because of their mostly diffuse radiologic appearance. Patients received 80 mg osimertinib once daily. Five patients in the osimertinib arm had suspected LM. Of these 5 patients, 4 patients had complete radiological response (CR) and 1 patient had a radiographic non-CR and non-PD. Two patients in the standard EGFR TKI arm had suspected LM. Of these 2 patients, 1 had non-CR, non-PD and the other had no CNS follow-up.

AURA program[2]

The AURA program enrolled patients who were T790M positive and had asymptomatic, stable central nervous system (CNS) metastases which included those with LM. Patients received 80 mg osimertinib once daily. Baseline brain scans were required only in patients with known or treated CNS metastases at study entry. LM was retrospectively confirmed from the AURA program by way of neuroradiological blinded independent central review (BICR). The LM analysis cohort consisted of 22 patients. The endpoints of the analysis were LM objective response rate (ORR), LM duration of response (DoR), LM progression free survival (PFS), and LM overall survival (OS).

Efficacy Results:

Endpoint	Results
LM ORR	55% (95% CI 32, 76) Complete Response (CR): 27% Partial Response (PR): 27% Stable Disease (SD): 36%
LM DCR	91%
Median LM PFS	11.1 months (95% CI 4.6, non-calculable (NC))
Median LM DoR	NC months (95% CI 2.8, NC)
Median LM OS	18.8 months (95% CI 6.3, NC)

Pilot Study[3]

The prospective pilot study enrolled patients who were all T790M positive by tissue rebiopsy and had refractory LM after failure of standard EGFR-TKIs. Thirteen patients received clinical standard-dose osimertinib at 80 mg once daily. Of the 13 patients enrolled, 5 patients were confirmed and 8 patients were suspected for LM. The primary mutation of the patients were: 10 patients (77%) had exon 19 deletion and 3 patients (23%) had the L858R mutation. Two to 4 weeks after study initiation brain MRI and lumbar puncture were routinely performed. Extra central nervous system (CNS) responses were measured according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Since CNS radiographic changes are difficult to be measured by RECIST, they were evaluated as improved, stable, progressed and not evaluable (NE) based on neurological findings. The PFS was estimated based on a systemic (intra/extra CNS) evaluation.

Efficacy Results:

Endpoint	Results
CNS Radiographic Changes	Improved: 8 patients Stable: 3 patients Progressed: 1 patient NE: 1 patient
Cerebrospinal Fluid (CSF) penetration rate (25 samples of 13 patients)	2.5±0.3%
Median PFS	7.2 months (95% CI, 4.0-undeterminable)
Median OS	Not reached

Safety:

Rash was reported as grade ≤ 2 in 10 patients (77%) and paronychia grade ≤ 2 was reported in 6 patients (46%). No grade ≥ 3 adverse events (AEs), diarrhea or liver dysfunction were observed. Grade 2 interstitial lung disease (ILD) was confirmed in 1 patient. There were no dose interruptions and/or dose reductions due to ILD.

Sincerely,

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2. Ahn M-J, Chao HC, Cheng Y, et al. Osimertinib for patients with leptomeningeal metastases associated with EGFRm advanced NSCLC. Presented at ESMO Asia; November 23-25, 2018; Singapore. *Annals of Oncol.* 2018;29:suppl.9 Abstract 492O.
3. Nanjo S, Hata A, Okuda C, et al. Standard-dose osimertinib for refractory leptomeningeal metastases in T790M-positive *EGFR*-mutant non-small cell lung cancer [published online ahead of print November 30, 2017]. *Br J Cancer*. 2017. http://dx.doi.org/10.1038/bjc.2017.394. Accessed January 3, 2019.
4. TAGRISSO Prescribing Information.