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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 inclusion of TAGRISSO® (osimertinib) into the NSCLC guideline as a category 1 recommendation for the first-line treatment of metastatic epidermal growth factor receptor (EGFR) mutation-positive NSCLC.

Specific change: We respectfully request the inclusion of osimertinib as a category 1 recommendation for the first-line treatment of metastatic EGFR mutation-positive NSCLC based on the attached FLAURA phase III trial results presented at the European Society of Medical Oncology (ESMO) Annual Meeting on September 9, 2017 in Madrid, Spain.¹

FDA Status: Osimertinib is not currently FDA-approved for the first-line treatment of metastatic EGFR mutation-positive NSCLC.

Rationale: This request is based on clinical evidence from the phase III FLAURA trial evaluating the efficacy and safety of osimertinib versus a standard of care (SoC) EGFR-TKI in treatment-naïve patients with locally advanced or metastatic EGFR mutation-positive NSCLC which was presented at the European Society for Medical Oncology congress on September 9, 2017.

The study randomized 556 patients (279 to osimertinib, 277 to SoC EGFR-TKI). Patients received osimertinib (80 mg orally, once daily) or SoC, EGFR-TKI (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]). At the time of the data cut-off (June 12, 2017), 342 progression events (62% PFS maturity) had occurred in the Full Analysis Set (FAS).

Efficacy Results:

- Progression-free survival (PFS) based on investigator assessment (according to RECIST 1.1) was significantly longer with osimertinib compared to SoC (18.9 months vs 10.2 months; hazard ratio (HR) 0.46; 95% CI: 0.37-0.57; P<0.0001)
- Improvements in PFS based on investigator assessment were consistent across predefined subgroups of interest with all PFS HRs at less than 0.60
 - PFS was significantly longer with osimertinib vs SoC in patients with and without CNS metastases at baseline (With: 15.2 vs 9.6 months, respectively; HR 0.47, 95% CI: 0.30-0.74; p=0.0009. Without: 19.1 vs 10.9 months, respectively; HR 0.46, 95% CI: 0.36-0.59; p<0.0001)
- Overall Survival (OS) interim analysis: median overall survival has not been reached for either arm (data are currently immature). HR 0.63 (95% CI 0.45-0.88), p=0.0068 (a p-value of <0.0015 was required for statistical significance at current maturity)
- Objective Response Rate (ORR): ORR was 80% for osimertinib compared to 76% for SoC (odds ratio [OR] 1.28; 95% CI: 0.85-1.93; P=0.2335)
- Duration of Response (DoR): The median DoR based on investigator assessment was 17.2 months (95% CI: 13.8-22.0) for osimertinib and 8.5 months (95% CI: 7.3-9.8) for SoC

Safety Results:

- Any Grade ≥ 3 adverse events (AEs) occurred in 34% of osimertinib patients and in 45% of SoC patients
- In patients treated with osimertinib, the most common all-causality AEs were diarrhea (58%, any grade [2% Grade ≥ 3]) and dry skin (32%, any grade [$<1\%$ Grade ≥ 3]). In the comparator arm group the most common all-causality AEs were diarrhea (57%, any grade [3% Grade ≥ 3]) and dermatitis acneiform (48%, any grade [5% Grade ≥ 3])
- Discontinuation of treatment due to any AE occurred in 13% of osimertinib patients and in 18% of SoC patients

We would like to provide additional supportive evidence for the efficacy and safety of osimertinib in first-line EGFR mutation-positive NSCLC from the first-line cohort of the AURA phase I/II study which was recently published in the *Journal of Clinical Oncology*.² AURA a Phase I/II, open-label, multicenter study evaluated the clinical activity and safety of osimertinib as first-line treatment of an expansion cohort of 60 treatment naïve patients with advanced EGFR mutation-positive NSCLC. Patients were treated with either osimertinib 80 mg orally once daily (n=30) or 160 mg orally once daily (n=30).

Efficacy results for the AURA first-line 80 mg cohort:

- PFS: Median PFS based on investigator assessment was 22.1 months (95% CI: 13.7-30.2)
- ORR: Confirmed ORR was 67% (95% CI: 47-83)
- DoR: Median DoR based on investigator assessment was 19.3 months (95% CI: 12.3-24.7)
- Disease Control Rate (DCR): The DCR was 93% (95% CI: 78-99)

Safety results for the AURA first-line 80 mg cohort:

- The safety and tolerability profile of osimertinib 80 mg as first-line therapy in the AURA Phase I study was consistent with pre-treated patients in the other expansion cohorts

The following references are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications/presentations.

Reference(s):

1. Ramalingam SS, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib vs standard-of-care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA [presentation]. Presented at: European Society of Medical Oncology (ESMO) Annual Meeting; September 9-12, 2017; Madrid, Spain.
2. Ramalingam SS, Yang JCH, Lee CK, et al. Osimertinib as first-line treatment for EGFR mutation positive advanced non-small cell lung cancer [published online ahead of print]. *J Clin Oncol*. 2017. <http://dx.doi.org/10.1200/JCO.2017.74.7576>. Accessed September 8, 2017.

Sincerely,

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