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NCCN Guidelines Panel:	Non Small-Cell Lung Cancer

Dear Sir or Madam:

This letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for review of new data for osimertinib™ (TAGRISSO). The enclosed information may include information that is not found in the currently approved prescribing information for osimertinib. This information is provided to NCCN evaluators for guideline review purposes only.

1- Specific change: Request placement of T790M mutation testing in treatment algorithm (FDA approved indication).

Rationale: Physicians may not recognize the importance of identifying resistance mutations upon progression with 1st generation EGFR TKI. Current guidance (NSCL-17, version 4.2016) does not explicitly incorporate T790M mutation testing as part of treatment algorithm at progression and references it as a footnote.

- Per NCCN trend reporting, 26% of academic physicians and 30% of community physicians do not re-biopsy upon progression. Of those that do, only 10-14% are considering liquid biopsy as an option (NCCN Trends NSCLC, April 2016).
- Based on chart audits (AZ data on file), which measure actual rates at a patient level rather than stated practices via survey, the rates of testing are lower. Only 39% of patients experiencing progression on 1st line EGFR TKI undergo repeat testing for T790M mutation. Therefore 61% did not receive T790M mutation testing.

2- Specific change: Request addressing tissue and plasma testing for both driver mutations and T790M mutations in section regarding DNA mutational tests on MS-11. Additionally, based on the package insert of cobas® EGFR mutation test v.2, patients who are plasma negative for the mutation of interest should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.

Rationale: cobas® EGFR mutation test v.2 is approved to detect defined mutations in either tissue or plasma samples (cobas® website). Additionally, new data indicate that plasma tests for the T790M mutation are 60-65% sensitive compared to tissue (Jenkins, Oxnard et al.). Due to the false negative rate, patients with a negative plasma test should reflexively have tissue evaluated (Oxnard, et al). Patients that are T790M positive by plasma have similar ORR rates on osimertinib compared to those that are T790M positive by tissue. (Jenkins et al).

3- New data: Clinical activity of osimertinib in patients with metastatic NSCLC, EGFRm+, T790M mutation +, who have brain metastasis (not an FDA approved indication).

Rationale: Treatment response to osimertinib has been demonstrated in EGFR T790M mutation-positive NSCLC patients with brain metastasis, providing higher ORR compared to historical chemotherapy controls.(Barlesi et al, Dinglin et al, Ahn et al)

4. **New data: Clinical activity of osimertinib as a targeted therapy for metastatic NSCLC EGFRm patients who have leptomeningeal disease (not an FDA approved indication).**

   Rationale: Osimertinib shows activity among patients with leptomeningeal disease, a rare complication, which has low overall survival. (Yang et al).

5. **New data: Clinical activity of osimertinib as a targeted therapy for metastatic EGFRm NSCLC in treatment-naïve patients, including *de novo* T790M (not an FDA approved indication).**

   Rationale: Treatment response with osimertinib has been demonstrated in EGFRm TKI treatment-naïve NSCLC patients in AURA Study 1, Phase I (Ramalingam et al).

Sincerely,

Melissa Culp, PharmD

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.4.2016. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. http://www.NCCN.org. Accessed January 19, 2016.
2. NCCN Trend Report NSCLC, April 2016 (Complex C-N-1873-0616). Prepared through NCCN Trends™ for AstraZeneca for Internal Organizational Use.
3. cobas® EGFR mutation test v.2. Website http://www.cobasegfrtest.com/. Accessed 6/15/16.
4. Jenkins S, Yang J C-H, Ramalingam SS, et al. Plasma ctDNA analysis for detection of EGFR T790M mutation in patients with EGFR mutation-positive advanced non-small cell lung cancer [presentation]. Presented at 6th European Lung Cancer Conference; April 13-16, 2016; Geneva, Switzerland.
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6. Barlesi F, Gervais R, Lena H, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer with asymptomatic inoperable brain metastases: a multicentre phase Ii trial (GFPC 07-01). *Ann Oncol* (2011). 22(11):2466-70.
7. Dinglin XX, Huang Y, Liu H, et al. Pemetrexed and cisplatin combination with concurrent whole brain radiotherapy in patients with brain metastases of lung adenocarcinoma: a single-arm phase II clinical trial. *J Neurooncol* (2013). 112(3):461-6.
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9. Yang J C-H, Kim DW, Kim SW, et al. Osimertinib activity in patients with leptomeningeal disease from non-small cell lung cancer: updated results from the BLOOM study [presentation]. Presented at American Society of Clinical Oncology Conference; June 3-7, 2016; Chicago, IL.
10. Ramalingam SS, Yang J C-H, Lee CK, et al. Osimertinib (AZD9291) as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts [presentation]. Presented at 6th European Lung Cancer Conference; April 13-16, 2016; Geneva, Switzerland.