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 reflex 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