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 IMFINZI® (durvalumab) as an option for the treatment of locally-advanced, unresectable NSCLC in patients whose disease has not progressed following platinum-based chemoradiation therapy. This request is based on the results of the Phase III PACIFIC trial published in the New England Journal of Medicine on September 8, 2017 and presented at the European Society for Medical Oncology (ESMO) Congress on September 9, 2017.

**Specific Change:** We respectfully request the addition of durvalumab as an option for patients with NSCLC who have been treated with platinum-based chemoradiation, wherever appropriate in the guidelines. We have noticed this population is mentioned on pages NSCL-2, NSCL-3, NSCL-5, NSCL-6, NSCL-8, NSCL-9, NSCL-11, and NSCL-12.

**FDA Status:**

1. IMFINZI is not FDA-approved for use in patients with locally-advanced, unresectable NSCLC.

2. IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
   - have disease progression during or following platinum-containing chemotherapy
   - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**Rationale:**

1. Concurrent chemoradiation is the standard of care in patients with locally-advanced, unresectable NSCLC and has been shown to improve outcomes compared to sequential radiation and chemotherapy. However, median progression-free survival (PFS) after concurrent chemoradiation is typically less than 12 months, demonstrating a significant unmet need in the management of locally advanced NSCLC. There have been no studies that demonstrate improved clinical benefit in this setting, including induction therapy prior to concurrent chemoradiation, consolidation therapy with chemotherapy (e.g., docetaxel, cisplatin) following chemoradiation, or the addition of epidermal growth factor receptor inhibitors (e.g., gefitinib, cetuximab, erlotinib).

2. The clinical evidence for durvalumab is based on a Phase III (PACIFIC), randomized, double-blind, placebo-controlled, multicenter study in patients with stage III locally-advanced, unresectable NSCLC who did not have disease progression after at least 2 cycles of platinum-based chemoradiotherapy within 1-42 days prior to randomization. Patients were randomized 2:1 to receive durvalumab 10 mg/kg IV every 2 weeks (n=473) or placebo.
(n=236). The primary efficacy endpoints were PFS (according to RECIST v 1.1) per blinded independent central review (BICR) and overall survival (OS). Secondary endpoints included objective response rate (ORR) and time to death or distant metastasis per BICR; and safety (per CTCAE v4.03).

**Primary Efficacy Results**

- Median PFS in the durvalumab arm was significantly longer (16.8 months; 95% CI: 13.0-18.1) compared to the placebo group (5.6 months; 95% CI:4.6-7.8, stratified hazard ratio 0.52; 95% CI:0.42-0.65; 2-sided p-value <0.001). The OS data collection is ongoing and AstraZeneca remains blinded to OS.
- In patients with measurable disease at baseline, ORR was 28.4% (95% CI: 24.28-32.89) in the durvalumab arm compared to 16% (95% CI:11.31-21.59) in the placebo group (relative risk 1.78 [95%CI, 1.27-2.51]; p-value <0.001). A total of 72.8% of patients treated with durvalumab had ongoing responses at 18 months compared to 46.8% in the placebo group.
- Median time to death or distant metastasis was longer with durvalumab when compared to the placebo group (23.2 versus 14.6 months; stratified hazard ratio 0.52 (95% CI: 0.39–0.69); 2-sided p-value <0.0001). A lower incidence of new metastases was observed in the durvalumab arm (20.4%) compared to placebo (32.1%), including lower incidences of new brain metastases (5.5% durvalumab arm; 11.0% placebo group).

**Safety Results:**

- Grade 3/4 adverse events (AE) occurred in 29.9% in patients treated with durvalumab and 26.1% in patients receiving placebo; the most common Grade 3/4 AE (pneumonia) in the durvalumab group occurred in 4.4% of patients versus 3.8% of patients in the placebo group. Treatment-related Grade 3/4 AEs were reported in 11.8% and 4.3% of patients in the durvalumab and placebo groups, respectively. A total of 15.4% of patients in the durvalumab-treated group and 9.8% in the placebo-treated group discontinued therapy due to any AE.

The following references are submitted in support of this proposal and to assist in your review.

- IMFINZI® (durvalumab) Prescribing Information.

Sincerely,

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Reference(s):

1. IMFINZI® (durvalumab) Prescribing Information.