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Date of Request:	September 9, 2017
NCCN Guidelines Panel:	Non Small-Cell Lung Cancer (NSCLC)

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.

- 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.[2] 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.[3,4] There have been no studies that demonstrate improved clinical benefit in this setting, including induction therapy prior to concurrent chemoradiation[5], consolidation therapy with chemotherapy (e.g., docetaxel, cisplatin) following chemoradiation[6,7], or the addition of epidermal growth factor receptor inhibitors (e.g., gefitinib, cetuximab, erlotinib)[8,9,10].
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.[11,12] 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.

- Antonia S, Villegas A, Daniel Davey, et al. Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer [article and supplementary appendix published online ahead of print September 8, 2017]. *NEJM.* 2017. https://dx.doi.org/10.1056/NEJMoa1709937. Accessed September 8, 2017.
- Paz-Ares L, Villegas A, Daniel D, et al. PACIFIC: A double-blind, placebo-controlled Phase III study of durvalumab after chemoradiation therapy in patients with stage III, locally advanced, unresectable NSCLC [presentation]. Presented at: European Society of Medical Oncology (ESMO) Annual Meeting; September 8-12, 2017; Madrid, Spain.
- IMFINZI® (durvalumab) Prescribing Information.

Sincerely,

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Reference(s):

[1] IMFINZI® (durvalumab) Prescribing Information.

[2] Curran WJ, JR, Paulus R. Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage II non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103:1452-1460.

[3] Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-386.

[4] Bradley et al. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-199.

[5] Vokes EE, Herndon JE 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol.* 2007;25(13):1698-1704.

[6] Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 2008;26(35):5755-5760.

[7] Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol.* 2015;33(24):2660-2666.

[8] Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol*. 2008;26(15):2450-2456.

[9] Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-199.

[10] Lilenbaum R, Samuels M, Wang X, et al. A phase II study of induction chemotherapy followed by thoracic radiotherapy and erlotinib in poor-risk stage III non-small-cell lung cancer: results of CALGB 30605 (Alliance)/RTOG 0972 (NRG*). J Thorac Oncol*. 2015;10(1):143-147.

[11] Paz-Ares L, Villegas A, Daniel D, et al. PACIFIC: a double-blind, placebo-controlled phase III study of durvalumab after chemoradiation therapy (CRT) in patients with stage III, locally advanced, unresectable NSCLC [presentation]. Presented at: European Society of Medical Oncology (ESMO) Annual Meeting; September 8-12, 2016; Madrid, Spain. Abs LBA1_PR

[12] Antonia S, Villegas A, Daniel Davey, et al. Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer [article and supplementary appendix published online ahead of print September 8, 2017]. NEJM. 2017. https://dx.doi.org/10.1056/NEJMoa1709937. Accessed September 8, 2017.