Submitted by: Shrina Patel, PharmD.
Company/Organization: AstraZeneca Pharmaceuticals LP/Medical Affairs
Address: One MedImmune Way, Gaithersburg, MD 20878
Phone: 301-398-3905
E-mail: shrina.patel@astrazeneca.com
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NCCN Guidelines Panel: Non-Small 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 IMFINZI® (durvalumab). This request is based on the results of the Phase III MYSTIC trial, recently published in the *Journal of American Medical Association:* Oncology (JAMA) on April 9, 2020 and presented at the European Society for Medical Oncology Immuno-oncology (ESMO IO) congress in December 2018. In addition, data from the Blueprint Clinical Biomarker Harmonization Project and a large immunochemistry concordance study are included in this submission.

Specific change: We respectfully request the inclusion of IMFINZI (durvalumab) as first-line therapy for patients with PD-L1 expression positive ≥25% and EGFR, ALK, ROS1, BRAF, negative and no contraindications to PD-1 or PD-L1 inhibitors with either metastatic adenocarcinoma, large cell NSCLC or squamous cell carcinoma in the appropriate sections of the NCCN guidelines (page NSCL-28 and NSCL-29).

FDA Status:[1]

- **IMFINZI is not FDA approved for the treatment of Stage IV NSCLC.**
- IMFINZI is indicated for the treatment of adult 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
- IMFINZI is indicated for the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
- IMFINZI is indicated in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

Rationale:

The clinical evidence for durvalumab is based on the MYSTIC trial, a Phase III, randomized, open-label, multicenter, global study to determine the efficacy and safety of durvalumab monotherapy or durvalumab in combination with tremelimumab versus platinum-based standard of care (SoC) chemotherapy in the first-line treatment of adult patients with EGFR and ALK wild-type non-rearranged metastatic Stage IV NSCLC.[2] 1118 were randomized 1:1:1 to receive 20mg/kg of durvalumab every 4 weeks until disease progression, 20 mg/kg of durvalumab every

4 weeks until disease progression plus 1mg/kg of tremelimumab every 4 weeks up to 4 doses, or 4 to 6 cycles of platinum-based double chemotherapy of the investigator's choice. Patients were enrolled into the study irrespective of PD-L1 (intent to treat [ITT]) expression but were stratified by PD-L1 TC <25% or ≥25% histology. The primary endpoint, assessed in patients with ≥ 25% of tumor cells expressing PD-L1, were overall survival (OS) for durvalumab monotherapy vs. chemotherapy.[2] In support of this submission and the requested change, we are reporting the efficacy and safety results of the durvalumab monotherapy versus chemotherapy arm.

Efficacy Results:[2]

- As of October 4, 2018, at final analysis, median (range) follow-up for OS was 30.2 (0.3-37.2) months. Durvalumab monotherapy demonstrated clinical activity in patients whose tumors express PD-L1 on TCs ≥25%. The median OS was 16.3 months (95% CI,12.2-20.8) with durvalumab compared to 12.9 months (95% CI, 10.5-15.0) with chemotherapy (hazard ratio [HR], 0.76; 97.54% CI, 0.56-1.02; p=0.04);[2] this aligns to previously reported treatment- naïve PD-L1 biomarker- selected trials.[3]
- The 24-month OS rate was 38.3% (95%CI, 30.7-45.7) with durvalumab and 22.7% (95% CI, 16.5-29.5) with chemotherapy.
- For statistical significance at final analysis, *P*<0.0246 for durvalumab vs chemotherapy in PD-L1 TC ≥25% were required (Lan-DeMets spending function approximating O'Brien-Fleming boundary). As such, durvalumab monotherapy versus chemotherapy did not meet its primary endpoint of improved OS, in patients with PD-L1 expressing tumor cells ≥25%.
- At the time of study design, the primary end points were developed for all-comers (irrespective of tumor PD-L1 expression). The protocol was subsequently modified to restrict the primary analysis population to patients with PD-L1 TC ≥25% based on prior studies and the evolving treatment landscape. As a result, the primary study endpoints were evaluated in 44% of the overall randomized population with reduced power.

Safety Results:[2]

- All-grade adverse events (AEs) that were considered by the investigator to be treatment-related occurred in 54.2% and 83.0% of patients treated with durvalumab and chemotherapy, respectively.
- Grade 3 or 4 treatment related AEs occurred in 14.6% of patients treated in the durvalumab monotherapy arm versus 33.8% in the chemotherapy arm.
- Grade 5 treatment related AEs were reported in 2 patients (0.5%) in the durvalumab group and 3 patients (0.9%) in the chemotherapy group.
- Treatment related AEs leading to discontinuation occurred in 5.4% of patients in the durvalumab monotherapy arm versus 9.4% in the chemotherapy arm.
- Immune mediated adverse events occurred in 13.6% of patients in the durvalumab monotherapy arm and 3.4% of patients in the chemotherapy arm.

Blueprint Clinical Biomarker Harmonization Project

- Blueprint Phase 1 assessed the analytical and clinical comparability of 4 PD-L1 immunohistochemistry diagnostic assays used in clinical trials for NSCLC: Ventana SP263 for durvalumab, Ventana SP142 for atezolizumab, Dako 22C3 for pembrolizumab, and Dako 28-8 for nivolumab.[4]

- Overall, three of the assays (28-8, 22C3, and SP263) were similar in analytical staining performance assessed by percentage of tumor cells showing cell membrane staining. The SP142 assay generally stained fewer TCs across the 39 cases.[4]
- Blueprint Phase 2 assessed the results obtained in Phase 1 using real-world lung cancer samples. Phase 2 showed that 22C3, 28-8 and SP263 have comparable staining characteristics on tumor cells. SP142 was found to have less sensitivity.[5]

Additional Concordance Data[6]

- An additional analysis looked at the extent of concordance between Ventana SP263, Dako 22C3, and Dako 28-8 in a large NSCLC-specific study (493 individual cases). The three assays showed similar patterns of tumor membrane staining, with high correlation between percent PD-L1 staining. An overall percentage agreement of >90% was achieved between assays at multiple expression cutoffs, including 1%, 10%, 25%, and 50% tumor membrane staining.

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

- Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non–small cell lung cancer: the MYSTIC phase 3 randomized clinical trial [article and supplementary appendix published online ahead of print]. JAMA Oncol. 2020. http://dx.doi.org/ 10.1001/jamaoncol.2020.0237. Accessed April 9, 2020.
- Rizvi N, Chul Cho B, Reinmuth N, et al. Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. Presented at: European Society for Medical Oncology Immuno-oncology (ESMO IO) Meeting; December 13-16, 2018; Geneva, Switzerland.

Sincerely,

Asud Khaliq

Asud Khaliq, PhD
Franchise Head, Immuno-Oncology
OBU US Medical Affairs Oncology
AstraZeneca Pharmaceutical
One MedImmune Way
Gaithersburg, MD 20878
Asud.Khaliq@astrazeneca.com

Reference(s):

1. IMFINZI® (durvalumab) Prescribing Information.
2. Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non–small cell lung cancer: the MYSTIC phase 3 randomized clinical trial [article and supplementary appendix published online ahead of print]. *JAMA Oncol*. 2020. http://dx.doi.org/ 10.1001/jamaoncol.2020.0237. Accessed April 9, 2020
3. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer

(KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830.
4. Hirsch F, McElhinny A, Stanforth D, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. *J Thorac Oncol.* 2016.;12:208-222.
5. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of blueprint phase 2 project. *J Thorac Oncol.* 2018;13(9):1302-1311.
6. Ratcliffe MJ, Sharpe A, Midha A, et al. Agreement between programmed cell death ligand-1 diagnostic assays across multiple protein expression cutoffs in non-small cell lung cancer. *Clin Cancer Res*. 2017;23(14):3585-3591.