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Date of Request: September 9, 2019
NCCN Guideline Panel: Small Cell Lung Cancer (SCLC)

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Small Cell Lung Cancer (SCLC) to review the enclosed data for inclusion of IMFINZI® (durvalumab), in combination with etoposide and platinum-based chemotherapy (EP), either cisplatin or carboplatin, as an option in first-line extensive-stage (ES)-SCLC. This request is based on the results of the Phase III CASPIAN trial presented at the World Conference on Lung Cancer (WCLC) on September 9, 2019.

Specific change:
We respectfully request the inclusion of durvalumab in combination with EP chemotherapy as a category 1 recommendation as a first-line treatment option for patients with ES-SCLC in the appropriate sections of the NCCN guidelines (pages SCL-E 1 of 3 and MS-6), based on the results of the CASPIAN trial meeting its primary endpoint of overall survival (OS), at a prespecified interim analysis, in patients treated with durvalumab in combination with EP versus chemotherapy alone.

We would like to submit the official presentation by Paz-Ares L et al, presented at the Presidential Symposium during WCLC, to support the addition of durvalumab in combination with EP as a first-line treatment option for patients with ES-SCLC. A full manuscript of these results is currently under review with a peer-reviewed medical journal—we will submit it for your review once published.

FDA status:[1]

- **IMFINZI® is not FDA approved for the treatment of ES-SCLC.**
- IMFINZI is FDA approved for unresectable, Stage III, non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- 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:

- SCLC is an aggressive form of lung cancer with a poor prognosis and limited treatment options. The overall 5-year survival rate is 6%, representing an ongoing significant unmet need.[2] The majority (75%) of patients are diagnosed in the late/metastatic stage

described as ES-SCLC and are considered incurable, with a median overall survival (OS) of 9-11 months with standard of care (SOC) chemotherapy.[4,5] For nearly 30 years, the SOC for first-line treatment of ES-SCLC has been systemic therapy with standard doublet chemotherapy with EP.[5] Although ES-SCLC is highly sensitive to EP in the first-line setting with response rates of 50-60%, majority of patients relapse after initial treatment.[6] Overall, responses to SOC are short-lived and there is a need for the development of more effective therapies to improve patient outcomes in ES-SCLC.

- The clinical evidence for durvalumab in first-line ES-SCLC is based on the CASPIAN trial, which is a Phase III randomized, multicenter, open-label, global study evaluating efficacy and safety of durvalumab ± tremelimumab in combination with chemotherapy as first-line treatment in patients with ES-SCLC. Patients were randomized 1:1:1 to receive durvalumab + EP, durvalumab + tremelimumab + EP or EP alone. Randomization was stratified according to the planned platinum-based therapy [carboplatin vs cisplatin]. Patients received up to 4 cycles of EP plus durvalumab every 3 weeks followed by maintenance durvalumab until disease progression in the durvalumab + EP arm, and up to 6 cycles of EP every 3 weeks in the EP arm; prophylactic cranial irradiation was allowed by investigator's discretion in the EP arm only. The primary endpoint was OS. The statistical boundary for superiority for the comparison of durvalumab + EP versus EP was met at the time of a pre-specified interim analysis.[7]

Efficacy results:[7]

- Durvalumab + EP resulted in a statistically significant improvement in OS compared to EP alone (HR=0.73; [95% CI, 0.591-0.909]; p=0.0047). Median OS for the durvalumab + EP arm was 13.0 months (95% CI, 11.5-14.8) versus 10.3 months (95% CI, 9.3-11.2) in the EP arm.
- OS at 12 months for the durvalumab + EP arm was 53.7% versus 39.8% in the EP arm.
- OS at 18 months for the durvalumab + EP arm was 33.9% versus 24.7% in the EP arm.
- Progression free survival (PFS) was improved with durvalumab + EP compared to EP (HR=0.78 [95% CI 0.645-0.936]). Median PFS in the durvalumab + EP arm was 5.1 months (95% CI, 4.7-6.2) compared to 5.4 months (95% CI, 4.8-6.2) in the EP arm.
- PFS at 12 months was 17.5% in the durvalumab + EP arm versus 4.7% in the EP arm.
- Confirmed objective response rate was 67.9 % in the durvalumab + EP arm compared to 57.6% in the EP arm; odds ratio [OR] 1.56 (95% CI 1.095-2.218).
- Duration of response at 12 months for durvalumab + EP arm was 22.7% versus 6.3% in the EP arm.
- Median duration of response in the durvalumab + EP arm was 5.1 months (95% CI, 4.9-5.3) versus 5.1 months (95% CI, 4.8-5.3) in the EP arm.

Safety results:[7]

- Grades 3 or 4 adverse events (AE), regardless of causality, occurred in 61.5% in patients treated with durvalumab + EP and 62.4% in patients receiving EP.
- Serious AEs, regardless of causality, occurred in 30.9% in the durvalumab + EP arm versus 36.1% in the EP arm.
- AEs leading to discontinued therapy, regardless of causality, occurred in 9.4% of patients in the durvalumab + EP arm versus 9.4% in the EP arm.
- Immune-mediated AEs occurred in 19.6% of patients in the durvalumab + EP arm versus 2.6% in the EP arm.
- Treatment-related AEs leading to death occurred in 1.9% of patients in the durvalumab + EP arm versus 0.8% in EP arm.

The following reference is submitted in support of this proposal and to assist in your review.

- Paz-Ares L, Chen Y et al. Overall survival with durvalumab plus platinum- etoposide in first-line extensive-stage SCLC: Results from the CASPIAN study [presentation]. Presented at: World Conference on Lung Cancer (WCLC). September 7-10 2019; Barcelona, Spain.
- IMFINZI® (durvalumab) Prescribing Information.

These materials include information that is not found in the currently approved prescribing information for IMFINZI. The enclosed information is intended to provide pertinent data and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for IMFINZI. This information is provided to NCCN evaluators for guideline review only.

Sincerely,

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References

1. IMFINZI® (durvalumab) Prescribing Information.
2. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
3. National Cancer Institute. NCI Dictionary of Cancer Terms – small cell lung cancer. Available at . Accessed October 16, 2018
4. Sabari JK, Lok BH, Laird JH, et al. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol. 2017;14(9):549–561.
5. Farago A.F., Keane F.K. Current standards for clinical management of small cell lung cancer. Transl. Lung Cancer Res. 2018;7:69–79.
6. Hurwitz JL, McCoy F, Scullin P, et al. New Advances in the Second-Line Treatment of Small Cell Lung Cancer. Oncologist. 2009;14(10):986-994.
7. Paz-Ares L, Chen Y et al. Overall survival with durvalumab plus platinum-etoposide in first-line extensive-stage SCLC: Results from the CASPIAN study [presentation]. Presented at: World Conference on Lung Cancer (WCLC). September 7-10 2019; Barcelona, Spain.