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Date of Request:	October 25, 2018
NCCN Guidelines Panel:	Malignant Pleural Mesothelioma (MPM)

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Malignant Pleural Mesothelioma (MPM) to review the enclosed data for inclusion of IMFINZI[®] (durvalumab), in combination with cisplatin and pemetrexed, as an option for the treatment of medically inoperable or unresectable MPM patients. This request is based on the results of the Phase II DREAM trial presented at the World Conference on Lung Cancer (WCLC) on September 24, 2018.

Specific Change: We respectfully request the addition of durvalumab in combination with cisplatin and pemetrexed as a first line treatment option for patients with medically inoperable or unresectable MPM, wherever appropriate in the guidelines. We have noticed this population is mentioned on pages MPM-2, MPM-3, MPM-A and MS-6.

FDA Status:¹

- IMFINZI is not FDA-approved for use in patients with medically inoperable or unresectable MPM.
- 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.

- IMFINZI is also indicated for the treatment of patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Rationale:

1. The clinical evidence for durvalumab is based on a Phase II (DREAM), multicenter, single-arm, open-label, non-randomized study with a safety run-in evaluating the clinical activity, safety, and tolerability of durvalumab in combination with cisplatin and pemetrexed as first line therapy in patients with MPM.^{2,3} The study uses a 2-stage Simon's design that includes 31 patients in stage 1 and 23 patients in stage 2 for a total of 54 patients.² An initial safety run-in using a 3+3 design was conducted in 6 patients for 2 cycles of induction dose before additional patients were recruited. No dose limiting toxicities were observed.² Patients were treated with durvalumab 1125 mg, cisplatin 75 mg/m², and pemetrexed 500 mg/m² every 3 weeks for 6 cycles (induction dose), followed by durvalumab alone (1125 mg every 3 weeks) for up to 12 months (maintenance dose) or until disease progression or toxicity.⁴
2. The primary efficacy endpoint was progression-free survival at 6 months (PFS6) using modified Response Evaluation Criteria Solid Tumors (mRECIST) for MPM. Secondary endpoints included objective response rate (ORR) (complete response or partial response as per mRECIST for MPM and immune RECIST (iRECIST)), frequency and severity of AEs (as per Common Terminology Criteria

for Adverse Events version 4.03), PFS (as per mRECIST for MPM and iRECIST), and overall survival (OS).^{3,4}

Efficacy Results⁴

- PFS6 occurred in 31 of 54 patients (57%) and median PFS was 6.2 months (95% CI: 5.5-9.0), based on mRECIST.
- ORR by mRECIST was 46% and ORR by iRECIST was 48%.
- The 12-month OS estimate was 65% (95% CI: 53- 79%); median survival has not been reached.
- As of final data analysis, median follow-up was 14.4 months.
 - Two patients have yet to reach 12-month follow-up window.

Safety Results:⁴

- Grade 3-5 adverse events (AEs) occurred in 36 patients (66%).
 - Neutropenia and nausea were the most common grade ≥ 3 AEs, occurring in 13% and 11% of patients respectively.
- Grade 3-4 immune-related AEs occurred in 8 patients (15%).
 - The most common grade ≥ 3 immune-related AEs were increased amylase/lipase, adrenal insufficiency and renal impairment, occurring in 1 patient (2%) each.
 - Immune-related AEs of any grade requiring high dose steroids or other immunosuppression therapy occurred in 7 patients (13%).

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

- Nowak AK, Kok PS, Lesterhuis WJ, et al. DREAM: Final results of a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma [presentation]. Presented at IASLC 19th World Conference on Lung Cancer (WCLC); September 23-26, 2018; Toronto, Canada.
- IMFINZI[®] (durvalumab) Prescribing Information.

Sincerely,

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Reference(s):

- ¹ IMFINZI[®] (durvalumab) Prescribing Information.
- ² Nowak AK, Lesterhuis WJ, Hughes BGM, et al. DREAM: A Phase 2 trial of DuRvalumab with first line chemotherapy in Mesothelioma with a safety run in [presentation]. Presented at American Society of Clinical Oncology (ASCO); June 1-5, 2018; Chicago, IL
- ³ AstraZeneca Pharmaceuticals LP; University of Sydney. A phase 2 trial of durvalumab with first line chemotherapy in mesothelioma with a safety run in. anzctr.org.au website. <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370989>. Accessed August 30, 2018.
- ⁴ Nowak AK, Kok PS, Lesterhuis WJ, et al. DREAM: Final results of a phase 2 trial of DuRvalumab with first line chemotherapy in Mesothelioma [presentation]. Presented at IASLC 19th World Conference on Lung Cancer (WCLC); September 23-26, 2018; Toronto, Canada.