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Date of Request: November 20, 2020
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 additional recommended dosage of 1500 mg every 4 weeks for patients weighing ≥30 kg for IMFINZI, approved by the FDA.

Specific change: We respectfully request inclusion of the newly approved Q4W dosing option for IMFINZI (durvalumab) in NSCLC in the appropriate section of the NCCN guidelines (page NSCL-E):

Patients with a body weight of ≥30 kg	Durvalumab 10 mg/kg every 2 weeks or 1500 mg every 4 weeks for up to 12 months
Patients with a body weight of <30 kg	Durvalumab 10 mg/kg every 2 weeks for up to 12 months

FDA Status:[1]

- IMFINZI is now approved by the FDA with two dosing options, in patients with a body weight of ≥30 kg: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks, for the treatment of unresectable Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Rationale:

- Approval for the additional recommended dosage of 1500 mg every 4 weeks in patients weighing ≥30 kg is based on pharmacokinetic (PK) data, the relationship of exposure to safety, and efficacy.[1]
  - Based on the modeling of PK data and exposure relationships for safety, there are no anticipated clinically meaningful differences in efficacy and safety for the doses of 1500 mg every 4 weeks compared to 10 mg/kg every 2 weeks in patients weighing >30 kg with NSCLC.
- The steady state AUC, Ctrough, and Cmax in patients administered with 1500 mg every 4 weeks are 6% higher, 19% lower, and 55% higher than those administered with 10 mg/kg every 2 weeks, respectively.
- The PK data and impact of baseline and time-varying patient/disease characteristics on PK as well as comparison of PK exposures following weight-based and flat-dosing regimens are summarized below.[2]

Summary of Pharmacokinetic Information

Baverel et al. *Clin Pharmacol Ther*. 2018;103:63-642.[2]

- Pooled data from two Phase 1/2 studies that evaluated durvalumab safety and antitumor activity in the treatment of advanced solid tumors (Study 1108, Phase 1/2, N=977) and

locally advanced or metastatic non-small cell lung cancer (ATLANTIC, Phase 2, N=432) was used in this analysis.[2]
    - A total of 1409 patients provided data following durvalumab administration. Dose levels in Study 1108 ranged from 0.1–10 mg/kg IV Q2W and from 15 mg/kg IV every 3 weeks (Q3W) to 20 mg/kg IV Q4W; ATLANTIC used a dose of 10 mg/kg IV Q2W.
    - Durvalumab PK was evaluated using a 2-compartment model with both linear and non-linear clearances. The mean (between-patient variability) linear clearance (CL) and central volume of distribution (V1) were 0.232 L/day (27.0% coefficient of variation [CV]) and 3.51 L (20.9% CV), respectively, where linear clearance was reached for doses above 3mg/kg Q2W.
    - Although population PK analysis identified statistically significant covariates (body weight, sex, creatinine clearance, post-baseline anti-drug-antibody, Eastern Cooperative Oncology Group performance status, soluble PD-L1 levels at baseline, tumor size, and albumin), none were found to be clinically relevant (effect on PK parameters <30%), indicating no need for dose adjustment.
    - Age, race, tumor type, lactate dehydrogenase, neutrophil-to-lymphocyte ratio, renal function (mild to moderate), and hepatic function (mild) had no impact on PK.
- The effect of weight-based and flat-dosing regimens were evaluated using simulations based on the final PK model (semimechanistic time-varying CL). Two IV flat-dosing regimens were evaluated against 10 mg/kg IV: 750 mg Q2W and 1500 mg Q4W.
    - Simulation results indicated similar median steady-state exposure and associated variability, with no increased incidence of extreme concentration values for a flat-dosing regimen (1500 mg Q4W or 750 mg Q2W) compared to an equivalent weight-based dosing regimen (10 mg/kg Q2W) as illustrated in the figure below.

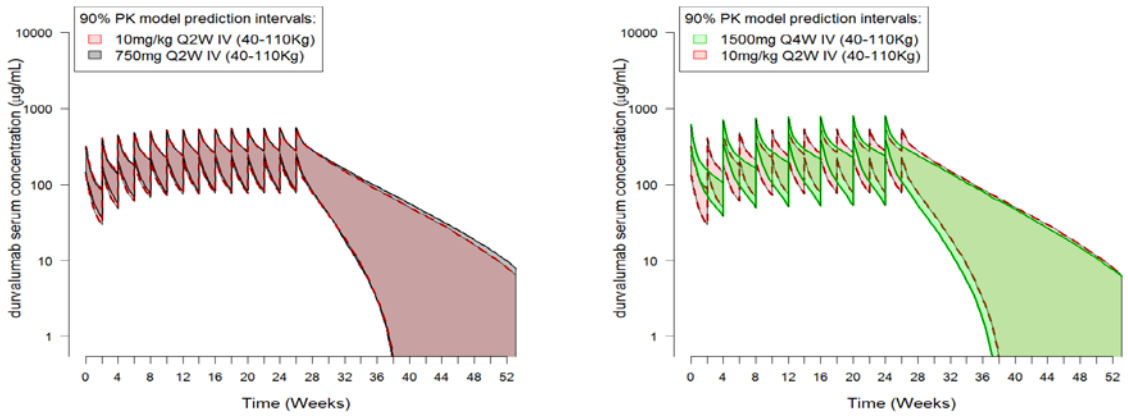

Figure. Simulated PK profiles of durvalumab following weight-based dosing regimens (10 mg/kg Q2W IV) compared with flat dosing. left. 750 mg Q2W IV; right. 1,500 mg Q4W IV. The area (pink and green) represents the 90% prediction interval from the semi-mechanistic time-varying CL model according to two different dosing schemes; they are delimited by the 5th and 95th percentiles of the simulated PK data obtained from a pool of n=1,000 virtual patients. Only the body weight covariate effect was investigated (no time-varying covariate were used for simulations).

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

- IMFINZI® (durvalumab) Prescribing Information.
- Durvalumab-Summary of Data in AstraZeneca Phase 3 Clinical Trials with Q4W Dosing in Lung Cancer Standard Response Letter

- Baverel PG, Dubois VFS, Jin CY, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status [article and supplementary appendix]. *Clin Pharmacol Ther*. 2018;103:631-642.

Sincerely,

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Reference(s):

1. IMFINZI® (durvalumab) Prescribing Information.
2. Baverel PG, Dubois VFS, Jin CY, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status [article and supplementary appendix]. *Clin Pharmacol Ther*. 2018;103:631-642.