Labeling Supplement – Clinical Review
Division of Oncology 3

Application Type (NDA/BLA)	BLA
Application Number(s)/supplement number	BLA 761289 S-6
Received Date	1/26/2024
PDUFA Goal Date	7/24/2024
Review Completion Date	7/23/2024
Division/Office	DO3 / OOD
Medical Officer	Timil Patel, MD
Team Leader	Jamie Brewer, MD
Signatory	Steven Lemery. MD
Product: Established Name (Trade Name)	Imjudo (Tremelimumab)
Formulation	IV infusion
Applicant	AstraZeneca
Recommended Regulatory Action	Traditional approval

Executive Summary

AstraZeneca submitted a labeling supplement, for IMJUDO (tremlimumab-actl) (BLA 761289/S-6) to update the labeling to include the results of Study D419EC00001, "Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies"; this study was conducted to fulfill a post marketing requirement (PMR #4333-6).

FDA initially issued PMR #4333-1 at the time of the original approval of tremelimumab (BLA 761289) to conduct a pediatric study (D419EC00001). Due to recruitment challenges and a general lack of activity of tremelimumab in combination with durvalumab in pediatric patients, AstraZeneca submitted a PMR Release and Replace Request to modify PMR #4333-1 to investigate the effects of tremelimumab (in combination with durvalumab) in 21 patients instead of 45 patients in the dose expansion portion of the study.

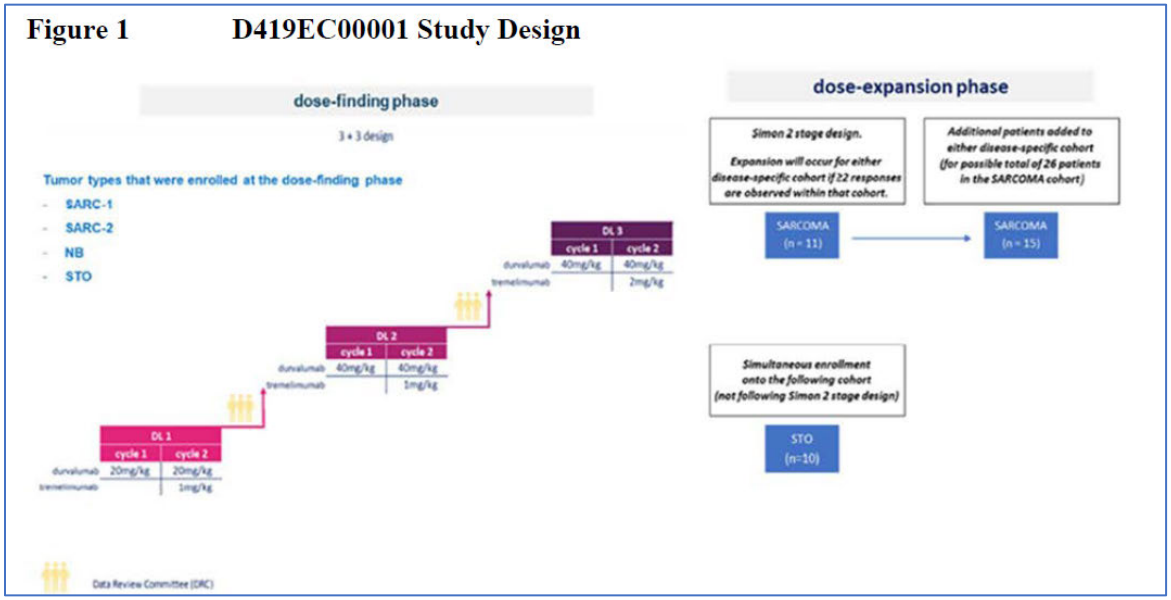
On September 5, 2023, FDA released PMR #4333-1 and replaced it with PMR #4333-6.

> PMR #4333-6: Conduct Study D419EC00001 (A Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of tremelimumab in combination with durvalumab in pediatric patients) to further characterize the safety, pharmacokinetics, and efficacy of tremelimumab in combination with durvalumab in patients from birth to <18 years of age with relapsed/refractory malignant solid tumors for whom no standard treatment is available. Include at least 12 patients in the dose escalation cohort and at least 21 patients in the dose expansion cohort.

No pediatric indication is being requested based on the results of this study due to limited efficacy. A description of the differences in the pharmacokinetics (PK) between pediatric patients and that observed in adult patients will be incorporated in Section 8.4 Pediatric Use of the USPI.

Background and Review of Clinical Data

Figure 1 D419EC00001 Study Design



Source: Astra Zeneca

Study D419EC00001
The study was an open-label, non-randomized, international, multicenter study of durvalumab in combination with tremelimumab administered every 4 weeks for 4 cycles followed by durvalumab monotherapy (every 4 weeks) in pediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumors (except primary central nervous system tumors). The study was conducted in 2 sequential phases: a dose-finding phase (Phase I), followed by a dose-expansion phase (Phase II). The primary objective was to identify a recommended Phase 2 dose (RP2D) of durvalumab in combination with tremelimumab followed by durvalumab monotherapy and to assess preliminary anti-tumor activity in pediatric solid tumors. Key secondary objectives were to determine PK and safety.

Patients from 1 to < 18 years of age with relapsed or refractory malignant solid tumors (except primary central nervous system tumors) were eligible to participate in this study. A total of 50 patients were enrolled in the study: 29 patients in the dose-finding phase and 21 patients in the dose-expansion phase. Patients were assigned to a treatment arm by body weight (BW, ≥ 35 kg and < 35 kg) and administered one of two dosing regimens (durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W or durvalumab 30 mg/kg + tremelimumab 1 mg/kg Q4W) during the dose-finding phase.

During the duration of the study, including dose-finding and dose-expansion phase, a total of 3 objective responses were reported among the 50 patients (45 younger than 17) (2 patients in the dose finding phase and 1 patient in the dose-expansion phase) including a partial response (PR) in a patient with osteosarcoma, a partial response (PR) in patient with renal cell carcinoma, and a partial response (PR) in a patient with chordoma. This overall response rate of less than 10% is consistent with the overall class of ICIs and not sufficient to establish use in pediatric patients (note that there are approvals of the class in certain specific tumor types (e.g., pembrolizumab for MSI-H/dMMR tumors).

In the dose finding phase of the study, 34% (10/29) of patients experienced a Grade 3 or 4 treatment emergent adverse event (TEAE), 10% (3/29) of patients experienced a severe adverse event (SAE), 5.3% (1/29) of patients experienced an TEAE leading to discontinuation of therapy (tremelimumab) and 11% of patients experienced an immune-mediated AE (imAE). The most commonly reported adverse events (AEs) (≥ 20%) in any dose group were

vomiting, anemia, headache, nausea, and alanine aminotransferase increased. In the dose expansion phase of the study, 48% (10/21) of patients experienced a Grade 3 or 4 TEAE, 43% (9/21) of patients experienced a SAE, 14% (3/29) patients experienced a TEAE leading to discontinuation of therapy (n=2 durvalumab and n=1 tremelimumab), and 19% (4/21) experienced an imAE. The most common TEAEs (≥ 20%) in the dose expansion phase of the study were pyrexia (52%), anemia (33%), and abdominal pain (24%). There were no Grade 5 adverse events in this study. The incidence of Grade 3 or 4 TEAEs, SAEs, AEs leading to treatment discontinuation were generally consistent in the dose finding and dose expansion phases with what has been observed in studies in adult patients (although there was a numerically lower incidence of SAEs and AEs leading to discontinuation observed in the dose finding phase of the pediatric study). The specific AEs most commonly observed in the pediatric study were different than those seen in studies in adult patients, however all AEs observed were generally consistent with GI and constitutional symptoms.

Labeling Changes

Section 8.4 of the USPI was updated to include the following language:

> The safety and effectiveness of IMJUDO have not been established in pediatric patients. Safety and efficacy were assessed but not established in a multi-center, open-label study (NCT03837899) in which 41 pediatric patients aged 1 to < 17 years with advanced solid tumors received IMJUDO in combination with durvalumab. No new safety signals were observed in pediatric patients in this study.
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> Tremelimumab-actl systemic exposure in pediatric patients ≥ 35 kg was within the range of the values previously observed in adults given the same weight-based dose, whereas the systemic exposure in pediatric patients < 35 kg was lower than that of adults.

Recommended Regulatory Action

The Clinical review team recommends approval of this sBLA. The clinical review team also recommends that the PREA PMR 4333-6 is considered fulfilled.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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