# **Supplementary Material**

At the discretion of the investigator, eligible patients who had completed the initial course of tremelimumab monotherapy (750 mg via intravenous [IV] infusion every 4 weeks for seven cycles, then every 12 weeks for two additional cycles) or who were in the tremelimumab monotherapy follow-up period, with confirmed disease progression were given the option of being retreated with tremelimumab monotherapy or being sequenced to either

* durvalumab monotherapy (1.5 g via IV infusion every 4 weeks for up to 12 months) or
* durvalumab + tremelimumab combination therapy (durvalumab 1.5 g via IV infusion every 4 weeks + tremelimumab 75 mg via IV infusion every 4 weeks for up to four cycles each, followed by durvalumab via IV infusion every 4 weeks for up to 8 months (up to 12 months total) or until progressive disease (PD; whichever occurred first).

Secondary objectives were to assess the safety and efficacy of durvalumab monotherapy and durvalumab + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy using the criteria as set for tremelimumab monotherapy; these outcomes are reported here in the supplementary material.

## **Durvalumab analysis set, *n* = 4**

The median total treatment duration of patients sequenced to durvalumab monotherapy was 3.7 months. Confirmed ORR was 25% (*n* = 1) (95% CI, 0.6–80.6); the patient had partial response (PR). The other durvalumab patients (*n* = 3) had PD and there were none with stable disease. The duration of response (DoR) for the one responder was 7.3 months and the disease control rate (DCR) at 4 months was 25.0% (*n* = 1). Due to the small sample size, overall survival (OS) was not estimable; the estimated survival rate at 12 months was 50.0%. The 25%, 50%, and 75% progression-free survival (PFS) was 1.81 months, 2.86 months, and 6.62 months, respectively.

No deaths in this subgroup were considered related to treatment by the investigator. The most common reason for death was disease under study (*n* = 2, 50%). Adverse events (AEs) were reported in all four patients (100%); AEs were causally related to durvalumab in one instance. No immune-mediated AEs (imAEs) were reported during treatment with durvalumab monotherapy. The most common reason for treatment discontinuation was worsening of the condition under investigation (*n* = 3, 75%). Immunogenicity data are not available for the durvalumab group.

## **Durvalumab + tremelimumab combination therapy analysis set, *n* = 7**

The median duration of exposure to durvalumab and tremelimumab during combination therapy was 2.8 months. There were no confirmed responses in this subset of patients. One patient had stable disease (14.3%). The DCR at 4 months was 28.6% (*n* = 2). Median OS was 11.86 months. The estimated survival rate at 12 months was 34.0%. The 25%, 50%, and 75% PFS was 1.81 months, 2.83 months, and 3.65 months, respectively.

AEs were reported in all seven patients (100%), with Common Terminology Criteria for Adverse Event (CTCAE) grade ≥3 AEs reported in two patients (28.6%). In two patients, AEs were determined to be causally related to either durvalumab or tremelimumab. While undergoing combination therapy, one patient (14.3%) had an imAE (not classed as grade ≥3). One patient died as a result of their disease from an unrelated AE (as considered by the investigator) of hypovolemic shock leading to death. The most common reason for treatment discontinuation was worsening of the condition under investigation (*n* = 6, 85.7%), followed by withdrawal by patient (*n* = 1, 14.3%).

For the combination therapy analysis set, immunogenicity data were available for six anti-drug antibody (ADA)-evaluable patients with urothelial carcinoma (UC) (Supplementary Table 1). The treatment-emergent ADA-positive patient in the tremelimumab monotherapy arm was resequenced to the combination therapy arm. This patient was also classified as treatment-emergent ADA-positive (ADA incidence was 16.7%) and was the only patient in the combination therapy arm who tested positive for the presence of neutralizing antibody (nAb) at any visit (nAb prevalence was 16.7%).

## **Pharmacokinetics (PK)**

To compare the exposure of tremelimumab in UC with other solid tumors, a population PK model (built in NONMEM, version 7.3; ICON, Gaithersburg, MD) was utilized. The final population PK model was developed from a dataset of 746 subjects treated with tremelimumab (1 mg/kg: 637 subjects with 1600 measurable concentrations; 3 mg/kg: 40 subjects with 275 measurable concentrations; and 10 mg/kg: 69 subjects with 168 measurable concentrations) enrolled in three legacy clinical studies (D4193C00003 [CONDOR], D4190C00006 [Study 006], and D4190C0010 [Study 10]) of head and neck squamous cell carcinoma, non-small cell lung cancer, and advanced solid tumors (including a cohort of UC patients), respectively. The data contained serum concentrations of tremelimumab both from monotherapy and in combination with durvalumab.

The PK of tremelimumab in the dose range tested was best described by a two-compartment model with first order elimination from the central compartment, and redistribution into the peripheral compartment. No time-varying clearance as identified following tremelimumab treatment. The impact of baseline demographic covariates (age, sex, race, and body weight), hepatic- and renal function-related covariates (creatinine clearance, serum creatinine, total bilirubin, alanine aminotransferase, and aspartate aminotransferase), disease-related covariates (Tumor type, Eastern Cooperative Oncology Group, lactate dehydrogenase, albumin, and smoking status (current versus former versus non-smoker), and molecule-related covariates (ADA and durvalumab + tremelimumab combination therapy) on the PK of tremelimumab were investigated. Covariates were selected using a forward addition and backward elimination method (based on the significance levels of *P* < 0.01 and *P* < 0.001, respectively).

Observed PK data from this study following administration of tremelimumab monotherapy in combination with durvalumab at a dose of 1500 mg every 4 weeks by IV infusion was compared with simulated PK data at the same dose regimen based on the final population PK model of tremelimumab and a virtual population of *n* = 100 solid tumor patients. The observed exposure levels of tremelimumab and durvalumab were within the expected ranges based on prior knowledge. Moreover, there was no indication of PK interaction between these two agents.

## **Supplementary Table 1.** Immunogenicity ADA, FAS, and COMBO

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| --- | --- | --- |
| **ADA Category** | **FAS, *n* (%)** | **COMBO, *n* (%)** |
| ADA evaluable populationa | 26 (81.3) | 6 (100.0) |
| ADA prevalenceb,c | 4 (15.4) | 1 (16.7) |
| ADA incidenceb,d  | 1 (3.8) | 1 (16.7) |
| ADA positive postbaseline and positive at baselineb | 0 | 0 |
| ADA positive postbaseline onlyb | 1 (3.8) | 1 (16.7) |
| ADA positive at baseline onlyb | 3 (11.5) | 0 |
| Treatment-boosted ADAb,e | 0 | 0 |
| Persistent positiveb,f | 0 | 0 |
| Transient positiveb,g | 1 (3.8) | 1 (16.7) |
| nAb postive at any visitb | 1 (3.8) | 1 (16.7) |

Data are reported as of September 2018. FAS, full analysis set.

aADA-evaluable set is defined as the number of patients in the safety analysis set who had non‑missing baseline ADA and at least one non-missing postbaseline results. The denominator is the number of patients in the safety analysis set in the treatment group.

bThe denominator is the number of ADA-evaluable patients in the treatment group.

cADA prevalence is the proportion of patients with positive ADA result at any time, baseline or postbaseline.

dTreatment-emergent ADA positive is the sum of treatment-induced ADA and treatment-boosted ADA. The proportion of treatment-emergent ADA positive patients is ADA incidence. The single patient in the ADA incidence row was the same patient in the tremelimumab monotherapy group and then moved to durvalumab +tremelimumab combination therapy.

eTreatment-boosted ADA is defined as baseline ADA titer that was boosted by ≥4-fold during the study period.

fPersistently positive is defined as having at least 2 postbaseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA-positive result at the last available assessment.

gTransiently positive is defined as having at least 1 postbaseline ADA-positive measurement and not fulfilling the conditions for persistently positive.