HIGHLY CONFIDENTIAL

SUPPLEMENTAL MATERIALS

Methods Supplement

PK assessments

Serum concentrations of urelumab from patients participating in -001 (n = 115) and -006 (n = 154) were quantified using enzyme-linked immunosorbent assay (ELISA) with below limit of quantification (BLQ) ~ 250 μg/mL. A more sensitive electrochemiluminescent assay (ECLA) with BLQ ~25 μg/mL was used to determine urelumab concentrations in 64 patients participating in -011.

Pharmacodynamic assessments

Samples were collected predose on treatment days. For cytokine analysis in -011, serum samples were collected on days 1, 4, 22, and 29. A customized, multi-analyte immunoassay panel (Myriad RBM, Austin, TX) was used to measure proteins including IL-8, IP-10, MIG, MIP-1β, and other soluble factors not shown. For gene-expression analysis, whole blood was collected in PAXgene tubes on days 1, 8, 22, 29, and 43 for CA186-006 and on days 1, 4, 8, and 22 for CA186-011. Total RNA was isolated from samples (Qiagen) and reverse transcribed into cDNA using the Life Technologies ViLo cDNA Synthesis Kit. A customized TaqMan Low Density Array (TLDA) card (Applied Biosystem) was used to perform real-time PCR analysis of genes including *GBP1*, *MX1*, *RSAD2*, and *MIG* (measured in CA186-011 only), as well as other genes not shown. Expression of these genes was normalized to the housekeeping gene *GAPDH*.

Exposure-response analysis

The exposure-response (E-R) analysis of transaminitis AEs was characterized by logistic regression analysis of data from 333 patients participating in -001, -006, and -011. Dichotomous response variables to represent grade ≥2 and ≥3 hepatic AEs were defined using National Cancer Institute (NCI) Common Terminology Criteria for

Adverse Events (CTCAE) v4 and modeled separately. The E-R model assumes that the predictor variables, ie, average concentration at steady state (Cavgss) of urelumab exposure, have nonlinear effects on the logit of probability of hepatic adverse event (Pi,evt). During the time of this analysis, 4 patients from study 006 and 9 patients from study -011 were not included in E-R analysis due to unavailability of PK data. However, this is unlikely to change the outcome of the E-R analysis because the rate of grade 3 transaminitis AEs in the patients not included was comparable to that in the patients included (1 AE in 14 excluded patients versus 46 AEs in 333 included patients). Details of the patients from -006 and -011 not included in the analysis are shown (**Supplementary Table 2**)**.**

Supplementary Table 1. Patients Included in E-R Analysis [Online only]

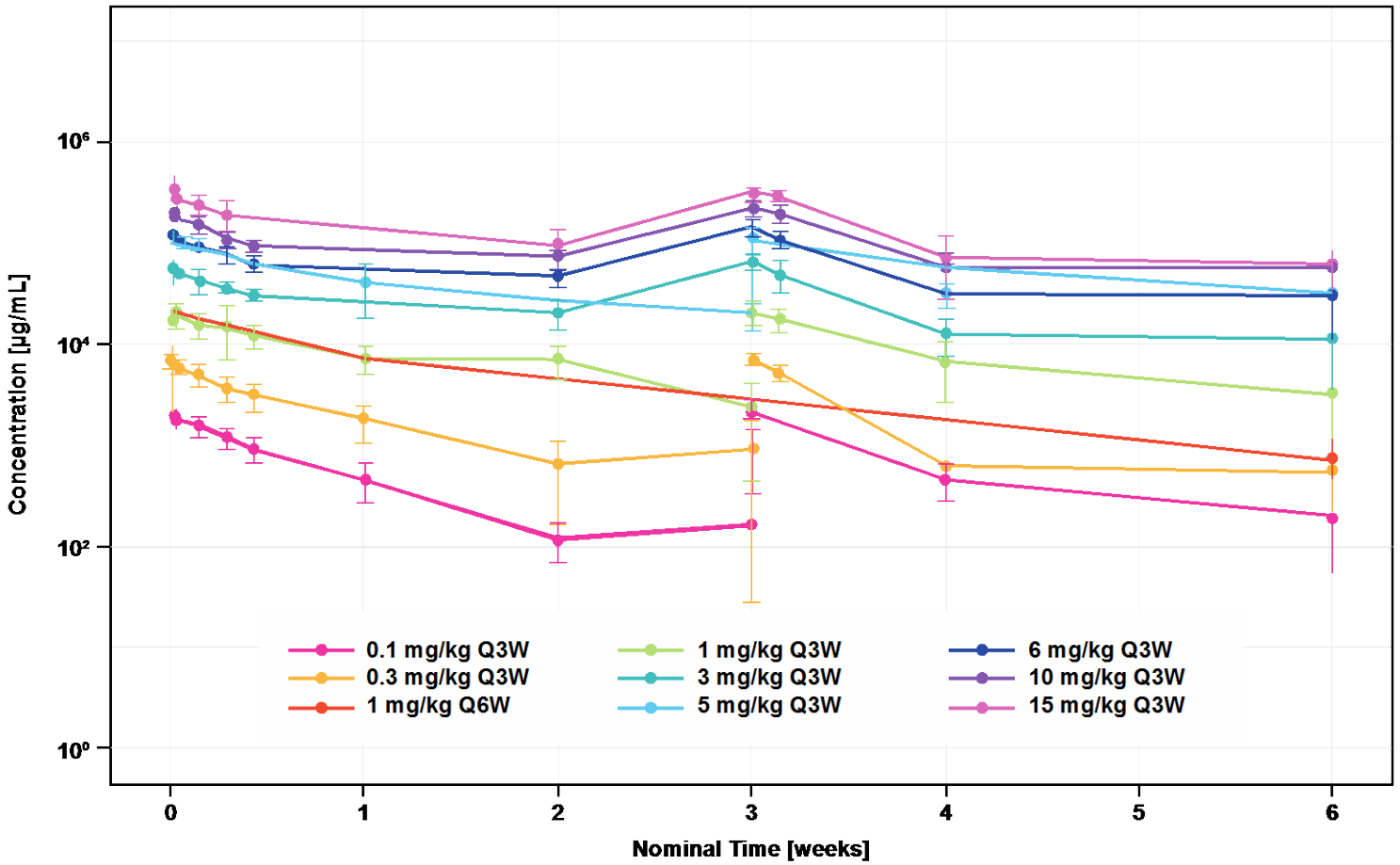
Clinical study	**Patients, N**
CA186-001	**115**
CA186-006	**154**
CA186-011	**64**

Supplementary Table 2. Patients From Studies -006 and -011 Not Included in E-R Analysis [Online only]

Patients not included in analysis	Dose group	LFT status*
CA186-006		
33-156	5 mg/kg	
39-57	5 mg/kg	
43-127	1 mg/kg	
46-144	5 mg/kg	
CA186-011		
3-26	0.3 mg/kg	-
5-5	0.1 mg/kg	Grade 1 (Bili)
5-16	0.3 mg/kg	Grade 1 (ALT)
5-18	0.3 mg/kg	-
5-19	0.3 mg/kg	Grade 1 (ALT/AST)
5-21	0.3 mg/kg	Grade 4
5-23	0.3 mg/kg	Grade 1 (ALT/AST)
7-17	0.3 mg/kg	-
8-5	0.3 mg/kg	-

*Maximum LFT grade attained in patient as per CTCAE v4 definition.

Supplementary Fig 1. Serum concentration:time profile of urelumab across the dose range evaluated (0.1 to 15 mg/kg)* [Online only]

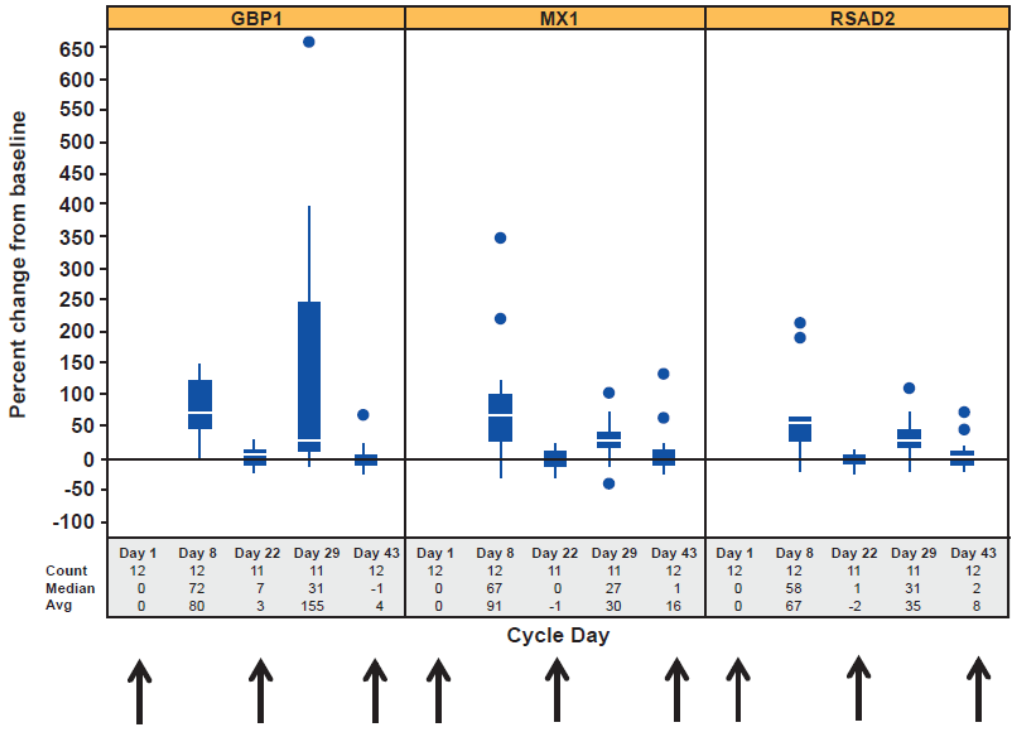


*n=333

Supplementary Fig 2. Induction of a range of IFN-response genes by urelumab 0.1 mg/kg

Induction of IFN-response genes in the whole blood of 31 patients treated with urelumab 0.1 mg/kg in studies -006 and -011. Patients were treated on days 1 and 22 as indicated. Guanylate-binding protein 1 (GBP1), GTP-binding protein MX1, and radical S-adenosyl methionine domain containing 2 (RSAD2) were measured in both studies. MIG was only measured in -011. Percentage change from baseline for each gene was plotted. Arrows indicate treatment days. Samples collected on treatment days were collected predose. Abbreviations: count, number of samples tested per time point; median, the quantity lying at the midpoint of a frequency distribution of observed values or quantities; Avg (abbreviation for average), the result obtained by adding together several quantities and then dividing this total by the number of quantities. [Online only]

CA186-006



CA186-011