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ARTICLE

Model Informed Dosing Regimen and Phase I Results of the Anti-PD-1 Antibody Budigalimab (ABBV-181)

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Budigalimab is a humanized, recombinant, Fc mutated IgG1 monoclonal antibody targeting programmed cell death 1 (PD-1) receptor, currently in phase I clinical trials. The safety, efficacy, pharmacokinetics (PKs), pharmacodynamics (PDs), and budigalimab dose selection from monotherapy dose escalation and multihistology expansion cohorts were evaluated in patients with previously treated advanced solid tumors who received budigalimab at 1, 3, or 10 mg/kg intravenously every 2 weeks (Q2W) in dose escalation, including Japanese patients that received 3 and 10 mg/kg Q2W. PK modeling and PK/PD assessments informed the dosing regimen in expansion phase using data from body-weight-based dosing in the escalation phase, based on which patients in the multihistology expansion cohort received flat doses of 250 mg Q2W or 500 mg every four weeks (Q4W). Immune-related adverse events (AEs) were reported in 11 of 59 patients (18.6%), of which 1 of 59 (1.7%) was considered grade ≥ 3 and the safety profile of budigalimab was consistent with other PD-1 targeting agents. No treatment-related grade 5 AEs were reported. Four responses per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were reported in the dose escalation cohort and none in the multihistology expansion cohort. PK of budigalimab was approximately dose proportional and sustained > 99% peripheral PD-1 receptor saturation was observed by 2 hours postdosing, across doses. PK/PD and safety profiles were comparable between Japanese and Western patients, and exposure-safety analyses did not indicate any trends. Observed PK and PD-1 receptor saturation were consistent with model predictions for flat doses and less frequent regimens, validating the early application of PK modeling and PK/PD assessments to inform the recommended dose and regimen, following dose escalation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Programmed cell death 1 (PD-1) receptor inhibition has shown improved tumor response and survival in several oncology indications. Budigalimab is a humanized, recombinant, Fc mutated IgG1 monoclonal antibody targeting PD-1 with preclinical PD-1 blocking activity and is being evaluated in a phase I trial in solid tumors.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This is the first report summarizing the activity and safety of budigalimab and rationale for flat dosing of budigalimab based on pharmacokinetic/pharmacodynamic (PK/PD) analyses and modeling and simulations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Clinical data of budigalimab suggests active doses with acceptable safety profile, tolerability and PK/PD characteristics as approved anti-PD-1 agents, with a flat exposure-safety relationship at the clinical doses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Reverse translation of PK/PD characteristics for same-class approved agents, and quantitative clinical pharmacology tools can be utilized and leveraged in early phase I dose escalation trials to select and justify a dosing regimen and scheme for further evaluation in oncology expansion and combination trials.

Trial Registration: NCT03000257

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Programmed cell death 1 (PD-1) is a cell-surface receptor that is upregulated on activated lymphocytes. PD-1 interacts with programmed cell death ligand 1 (PD-L1) or PD-L2, resulting in a dominantly negative checkpoint signal that limits subsequent antigen receptor-driven cellular activation. The ligands for PD-1 are differentially expressed in various tissues, but importantly, are expressed on antigen-presenting cells of the immune system and are upregulated on many types of tumor cells. Upregulation of PD-L1 within the tumor microenvironment is a proposed mechanism of tumors to subvert protective antitumor immune responses by the host. Antibodies directed against PD-1 that block the interaction of the receptor with its ligand result in inhibition of negative signaling and efficacy.[1,2]

PD-1 targeting monoclonal antibodies (mAbs) have been approved as monotherapy or in combination with other anticancer agents in multiple indications by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA).[3–5] Body-weight-based dosing is often used for therapeutic mAbs with the perception that this dosing approach reduces the intersubject variability in drug exposure.[6] The mAbs have unique pharmacokinetic (PK)/pharmacodynamic (PD) characteristics, such as a selective target and a large therapeutic window,[6] that make them well-suited for flat dosing. Flat dosing has many advantages over body-weight-based dosing, including increased convenience for the prescriber, reduced preparation time, easier administration, improved patient compliance, and reduced manufacturing wastage; which is especially important because manufacturing mAbs is time-consuming and expensive.[7,8] Recently, population PK modeling, simulations, and exposure-response results from patients have established that flat dosing regimens of approved anti-PD-1 agents (e.g., nivolumab and pembrolizumab) provides comparable exposure-response relationships for efficacy and safety, and benefit-risk profile as body-weight-based dosing regimens.[8,9]

Budigalimab, also known as ABBV-181, is a humanized, recombinant, IgG1 mAb targeting PD-1 receptor. It contains a human IgG1 heavy chain isotype that was modified by two point mutations (L234A and L235A) shown to reduce Fc receptor interactions and limit effector function. Budigalimab is being evaluated in a phase I, first-in-human clinical trial (NCT03000257) in patients with solid tumors.[10–12] The objectives of study NCT03000257 were to establish safety, tolerability, the PK/PD profile of budigalimab, and select the recommended dose(s) for further evaluation. The study included a dose escalation phase during which budigalimab was administered at 1, 3, and 10 mg/kg i.v. every 2 weeks (Q2W) in patients with previously treated advanced solid tumors (**Figure S1**). Prior to initiating the expansion part of study NCT03000257, flat dosing regimens were adopted based on PK modeling and simulations. This paper summarizes the following data from study NCT03000257: (i) the safety, efficacy, and PD properties from the dose escalation and expansion cohorts, (ii) PK across dose groups using body weight and flat dosing, (iii) the comparability of exposure and target activity of body-weight-based and flat dose regimens, (iv) the exposure-safety analysis and clinical data from the dose escalation phase and multihistology expansion cohort, and (v) the comparison of the safety, efficacy, and PK/PD profiles for Western and Japanese patients.

METHODS

Study design and eligibility

This was a multicenter, open-label, multi-arm, first-in-human phase I clinical trial. **Figure S1** describes the overall study schema. Patients enrolled in the dose escalation and multihistology expansion cohort from 12 sites in 5 countries (United States, Australia, Finland, France, and Japan). After completion of the dose escalation phase of the study in Western patients, dose escalation was performed in Japanese patients who were enrolled in the 3 and 10 mg/kg Q2W dose escalation cohorts.

For the dose escalation phase, eligible patients had advanced solid tumors and had failed standard treatments; previous treatment with a PD-1 targeting agent was permitted. For the multihistology expansion cohort, eligible patients had advanced or metastatic solid tumors that had never been treated with a PD-1 or PD-L1 targeting agent and for which no anti-PD-1/PD-L1 targeting agent was approved. Additional eligibility requirements are described in the **Supplemental Methods**.

The study protocol and informed consent form were approved by the institutional review board at each participating site prior to the initiation of any screening or study-specific procedures. Written informed consent was obtained from each individual participating in the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonization.

Study procedures

Patients were enrolled in the dose escalation part of the study following a 3 + 3 escalation scheme with a 28-day dose-limiting toxicity observation period. Subsequent dose escalation cohorts were enrolled following review of the safety data from the previous cohort. Additional Western patients were enrolled at each dose escalation level to better characterize the PK/PD properties of budigalimab. After the completion of dose escalation, the expansion cohorts were enrolled concurrently (**Figure S1**). All patients received budigalimab until progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or unacceptable toxicity. Patients experiencing progression per RECIST version 1.1[13] could continue budigalimab provided they met the following criteria: absence of symptoms and signs indicating disease progression, no decline performance status, and absence of rapid progression of disease or progression at critical anatomic sites; these patients were followed per iRECIST criteria.[14] Additional study procedures are described in the **Supplemental Methods**.

Study objectives

The primary objective of this study was to evaluate the safety, tolerability, and PK of budigalimab monotherapy, to determine the maximum tolerated dose and/or maximally administered dose and the recommended phase II dose (RP2D) for budigalimab. The secondary objective

of this study was to evaluate the preliminary activity of budigalimab monotherapy. Exploratory objectives included evaluation of the PD and exploratory biomarkers for association with PK, safety, and clinical responses, and assessing the baseline PD-L1 expression and relationship with outcome.

Statistical analysis

Patients who received any amount of budigalimab were included in the analyses. The safety of budigalimab monotherapy was assessed by evaluating the study drug exposure, adverse events (AEs), serious adverse events, deaths, as well as changes in laboratory determinations and vital sign parameters. Analyses of AEs included only treatment-emergent AEs, defined as an event that occurs or worsens on or after the first dose of study drug through 90 days after the last dose or to the start of another anticancer therapy, whichever occurs earlier. All AEs were coded to a preferred term based on the Medical Dictionary for Regulatory Activities. Descriptive statistics were used to summarize AE information by treatment cohort. Efficacy data was listed for each patient individually that showed a response by RECIST version 1.1 or iRECIST.

Biomarker sampling and assessments

PD-L1 in archival tumor. Archival formalin-fixed paraffin-embedded tumor was requested at enrollment and tested for tumor PD-L1 expression using the DAKO 28-8 pharmDx immunohistochemistry assay.

PD-1 receptor levels and lymphocyte numbers. Whole blood EDTA samples for measurements of PD-1 receptor levels on CD4 T central memory (CD4 T_{CM}) cells ($CD3^+4^+28^+95^+$) were collected in cycle 1 and cycle 3 on day 1 before infusion (0 hour, predose) and 2 hours postinfusion. Samples were also collected at 24, 48, 168, and 336 hours (i.e., on days 2, 3, 8, and 15) in cycles 1 and 3. Whole blood EDTA samples for measurements of absolute numbers of circulating $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells were collected on C1D1 prior to infusion, at C1D2, C1D8, and prior to infusion on C2D1. Heparinized blood was used to measure Ki67 on $CD8^+CD3^+$ T cells in a subset of patients at C1D1 prior to infusion, C1D15, and C2D1. Samples were shipped for real-time testing within 72 hours. PD-1 levels, lymphocyte numbers, and Ki67 staining were determined using a qualified or validated flow cytometry assay on a FACSCantoII at Covance worldwide laboratory locations. PD-1 receptor saturation was analyzed as the percent of total free receptor vs. baseline using GraphPad Prism.

Cytokine assessments. Serum samples for measurements of soluble biomarkers were collected on C1D1 prior to infusion and 4 hours postinfusion, as well as at 24 hours (C1D2), 168 hours (C1D8), and prior to infusion on C2D1 and C4D1. Frozen aliquots were batch tested for CXCL9, CXCL10, and soluble IL-2Ralpha as part of a Luminex panel run at Myriad RBM (Austin, TX). Data were analyzed using GraphPad Prism.

Pharmacokinetic sampling and assessments

Serial blood samples for measurements of budigalimab concentrations in serum were collected in cycles 1 and 3, prior to infusion, within 15 minutes after the end of infusion (postdose), and at 2, 4, and 24 hours following the end of the infusion. PK samples were also collected at 48, 168, and 336 hours (i.e., days 3, 8, and 15) after the end of infusion and predose in each cycle. In addition, PK samples were collected at 504 hours (i.e., day 22) as applicable for the less frequent dosing regimens. The lower limit of quantitation was 50 ng/mL for budigalimab.

Budigalimab serum concentrations were quantified using a validated bioanalytical assay and analyzed using noncompartmental analysis in Phoenix WinNonlin (version 6.2, Pharsight, Mountain View, CA). Peak serum concentrations (C_{max}), time to peak concentration (T_{max}), area under the curve to infinity (AUC_{inf}), and terminal half-life were determined for budigalimab. PK profiles and parameters were compared across Japanese and Western patients.

PK modeling, simulations, and PK/PD analysis

A fit-for-purpose, simple two-compartment population PK model assuming linear PK was developed to describe the early budigalimab PK data in $N = 16$ subjects from dose escalation (*Supplemental Methods: NONMEM Control Stream for Budigalimab Population PK Model*). Nonlinear mixed effects modeling was used, with first-order conditional estimation with interaction method, in NONMEM software (version 7.4.2) compiled with a GNU Fortran compiler. Model development was guided by goodness-of-fit plots, likelihood ratio tests, and plausibility of parameter estimates. An effect of body weight on clearance (CL) and volume was included as an exponential function in the model. Various other covariates, such as age, sex, race, albumin, bilirubin, alanine amino transferase, aspartate amino transferase, and body surface area were tested for effects on CL and volume but were not found to have statistical significance in this fit-for-purpose model, based on the limited dataset ($N = 16$ subjects) from dose escalation. Additionally, any longitudinal, time-varying effects on CL owing to improvements in disease status, as has been reported to occur for other PD-1 targeting agents, could not be conducted, owing to the early stage data from dose escalation.[15,16]

The population PK model was utilized to conduct PK simulations in order to predict the PK profiles and exposures at varying dosing regimens, including flat dosing regimens of 250 mg Q2W, 375 mg Q3W, and 500 mg Q4W. The PK profiles were predicted based on a total of 100,000 simulations (500 simulations × 200 replicates) conducted for patients with a wide distribution of body weights (47–128 kg). Geometric means of PK parameters (with 95% prediction intervals) were evaluated for comparison of the body-weight-based and flat dosing regimens.

Additionally, PK/PD assessments were conducted utilizing the population PK model-predicted exposures and evaluating these with respect to *in vitro* data on the saturation of PD-1-positive CD4 T_{CM} cells (effective concentration 99% (EC_{99}) value of 0.1 μg/mL) and PD-L1 blockade (half-maximal effective concentration (EC_{50}) value of 0.012 μg/mL).[17] The

Table 1 Summary of patient demographics, baseline disease characteristics and study drug exposure

	Dose escalation phase			Multi-histology expansion cohort
Budigalimab dose	**1 mg/kg i.v. Q2W**	**3 mg/kg i.v. Q2W**	**10 mg/kg i.v. Q2W**	**250 mg i.v. Q2W or 500 mg i.v. Q4W**
Number of patients	12	10	11	26
Geographic region				
Western countries	12	6	7	20
Japan		4	4	6
Median age (range), years	56 (47–84)	66.5 (52–84)	53 (37–72)	60 (42–77)
Male sex, *n* (%)	6 (50)	5 (50.0)	4 (36.4)	6 (23.1)
Median bodyweight (range), kg	75 (53–126)	77 (42–113)	62 (56–107)	67 (37–116)
ECOG-PS				
0	4 (33.3)	4 (40.0)	5 (45.5)	8 (30.8)
1	8 (66.7)	6 (60.0)	6 (54.5)	17 (65.4)
2	0	0	0	1 (3.8)
Number of prior systemic therapies				
1	1 (8.3)	1 (10)	0	4 (15.4)
2	0	3 (30)	6 (54.5)	7 (26.9)
≥ 3	11 (91.6)	6 (60)	5 (45.5)	15 (57.7)
PD-L1 status, *n*/*n* assessed (%)				
Positive	4/11 (33.3)	5/9 (50)	5/11 (45.5)	10/20 (38.5)
Negative	7/11 (58.3)	4/9 (40)	6/11 (54.5)	10/20 (38.5)
Disease histology, *n* (%)				
Anal cancer	0	1 (10.0)	0	0
Anterior skull base neuroblastoma	0	0	1 (9.1)	0
Bile duct cancer/cholangiocarcinoma	0	1 (10.0)	0	3 (11.5)
Bladder cancer	0	0	0	1 (3.8)
Breast cancer	1 (8.3)	0	1 (9.1)	3 (11.5)
Carcinoma with neuroendocrine Characteristics	0	0	0	0
Cervical cancer	1 (8.3)	0	1 (9.1)	3 (11.5)
Cholangiocarcinoma	1 (8.3)	1 (10.0)	0	1 (3.8)
Colon/rectum cancer	3 (25.0)	0	0	0
Duodenal carcinoma	0	0	1 (9.1)	0
Endometrial cancer	0	1 (10.0)	0	1 (3.8)
Esophageal cancer	0	2 (20.0)	1 (9.1)	1 (3.8)
Eye cancer	0	0	1 (9.1)	0
Kidney cancer	1 (8.3)	0	0	0
Leiomyosarcoma	0	0	1 (9.1)	0
Lung cancer - small -cell	0	0	1 (9.1)	0
Nasopharyngeal	0	0	0	1 (3.8)
Ovarian cancer	1 (8.3)	0	2 (18.2)	7 (26.9)
Pancreatic cancer	1 (8.3)	0	0	2 (7.7)
Penile cancer	0	1 (10.0)	0	0
Peritoneal cancer	1 (8.3)	1 (10.0)	0	0
Peritoneal mesothelioma	0	1 (10.0)	0	0
Prostate cancer	0	1 (10.0)	0	2 (7.7)
Sarcoma - soft tissue cancer	1 (8.3)	0	0	0
Stomach cancer	0	0	1 (9.1)	1 (3.8)
Q2W/Q4W dosing frequency, *n* (%)	12 (100)/0	10 (100)/0	11 (100)/0	21 (80.8)/5 (19.2)
Median doses of budigalimab (range)	9.5 (4–47)	5.5 (1–10)	4 (1–17)	3 (1–29)
Median days on budigalimab (range)	120 (43–653)	64 (1–134)	64 (1–232)	29.5 (1–395)
Budigalimab dose interruption, *n* patients (%)	3 (25)	2 (20)	4 (36)	1 (4)

(Continues)

Table 1 (Continued)

Budigalimab dose	Dose escalation phase			Multi-histology expansion cohort
	1 mg/kg i.v. Q2W	3 mg/kg i.v. Q2W	10 mg/kg i.v. Q2W	250 mg i.v. Q2W or 500 mg i.v. Q4W
Reason for budigalimab discontinuation				
AE	3 (25)	1 (10)	1 (9.1)	1 (3.8)
Death	0	0	0	1 (3.8)
Lost to FU	0	0	0	0
Lack of clinical benefit	0	0	1 (9.1)	0
Disease progression	8 (66.7)	9 (90)	8 (72.7)	24 (92.3)
Withdrawal of consent	1 (8.3)	0	1 (9.1)	0

AE, adverse event; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; FU, follow-up; PD-L1, programmed cell death 1.

PD-1 receptor saturation was thus predicted at the respective trough concentrations across the varying clinical regimens.

Exposure-safety analysis

Budigalimab average concentrations following cycle 1, which would provide the most relevant measure of the budigalimab PK, as is known for this class of agents,[18,19] were utilized for the exposure-safety analysis for patients from dose escalation and the multihistology expansion cohorts. All reported AEs, including immune-related events, with maximum grade, were evaluated for trends with respect to budigalimab exposures.

RESULTS

Demographics

Patients from the nondisease-specific cohorts were included in the clinical, biomarker, and PK assessment. As of July 5, 2019, there were 59 total patients were enrolled in the multihistology dose escalation (33 patients) and multihistology expansion (26 patients) cohorts. **Table 1** summarizes the baseline characteristics, study drug exposure, and disposition of all 59 patients.

Safety

During treatment, 57 of 59 patients (97%) had at least one AE of any grade; 38 of 59 patients (64%) had at least 1 grade ≥ 3 AE. No dose-limiting toxicities were observed in Western or Japanese patients.

Immune-related AEs were reported in 11 of 59 patients (18.6%); 3 patients (25%), 2 patients (20%), 3 patients (27.3), and 3 patients (11.5%) in the 1, 3, 10 mg/kg dose escalation cohorts and the multihistology expansion cohort, respectively, and 1 of 59 patients (1.7%) was considered grade ≥ 3 (**Table S1**). AEs resulting in discontinuation of budigalimab were reported in 16 of 59 patients (27.1%); 2 of 16 patients experienced AEs considered related to budigalimab (**Table S2**). The most common immune-related AEs were related to thyroid dysfunction, including three patients with hypothyroidism (1 patient each in the dose escalation phase) and one patient each with hyperthyroidism and autoimmune thyroiditis in the multihistology expansion cohort. One patient in the 1 mg/kg dose escalation cohort experienced new onset type 1 diabetes presenting as grade 3 diabetic ketoacidosis. Grade 5 AEs were reported in 15 of 59 patients (25.4%), all reported as or in the context of disease progression; none were considered related to budigalimab.

Efficacy

Four responses (all partial responses (PRs) per RECIST version 1.1 and observed in patients naïve to PD-1 or PD-L1 targeting agents) were reported in the dose escalation part of the study. In the 1 mg/kg cohort, there were two responders: one confirmed PR in a patient with renal cell carcinoma with 15% PD-L1 tumor cell staining (2 + maximum staining intensity) and one unconfirmed PR in a patient with squamous non-small cell lung cancer with 70% PD-L1 tumor cell staining (3 + maximum staining intensity). In the 3 mg/kg cohort, there was one unconfirmed PR in a patient with cholangiocarcinoma with unknown PD-L1 status (tissue not submitted). In the 10 mg/kg cohort, there was one confirmed PR in a patient with leiomyosarcoma with 0% PD-L1 tumor cell staining. None of the responders experienced progression per RECIST version 1.1 criteria and discontinued the study for

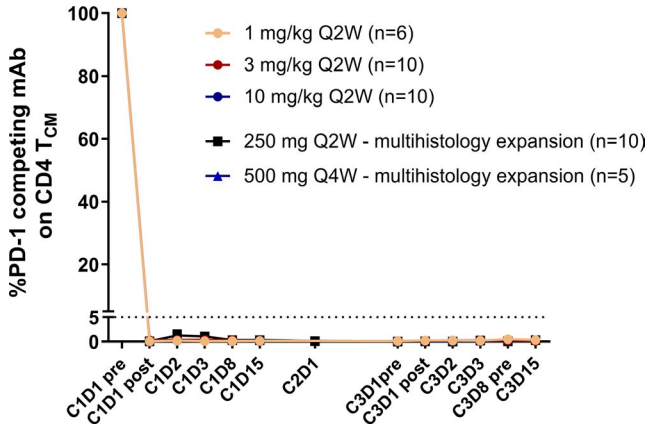

Figure 1 Percentage programmed cell death 1 (%PD-1) receptor saturation on CD4 T central memory (CD4 T_{CM}) by cycle (C) and day (D). Mean ± SEM values are shown for each cohort. All patients included in the analysis had baseline and at least one post-baseline assessment, with the baseline normalized to 100%. The number of patients included in each cohort is given in parentheses. mAb, monoclonal antibody.

reasons other than radiographic progression. No responses were reported in the multihistology expansion cohort.

Pharmacodynamics

CD4 T_{CM} cells were evaluated for PD-1 receptor saturation due to their relatively high baseline expression of PD-1 and abundance in peripheral blood. All clinically tested doses of budigalimab led to complete (> 95%) PD-1 receptor saturation within 2 hours postdosing and sustained saturation throughout the dosing interval, and over 3 months of evaluation (**Figure 1**).

Reported PD biomarker changes with PD-1 blockade include transient drops in peripheral T cell numbers, increased T cell proliferation, and increased serum chemokine levels.[1,20,21] Transient drops in $CD4^+$and $CD8^+$T cell numbers were observed, with all doses of budigalimab tested in both Western and Japanese patients (**Figure S2**). Increased CD8 T cell proliferation as measured by a > 2-fold change in Ki67 was detected in 10 of 20 tested patients (**Figure S2**). Increases in the interferon-gamma-induced chemokines CXCL9 (MIG) and CXCL10 (IP-10), as well as soluble IL-2Ralpha were observed with all doses of budigalimab in both Western and Japanese patients within 24 hours, with peak expression at 4–8 weeks (**Figure S3**). These budigalimab biomarker changes are consistent with results reported for other PD-1 inhibitors.[20,21]

Pharmacokinetics

As of July 5, 2019, a total of 140 patients received budigalimab throughout the dose escalation and expansion cohorts of the study and were considered for the PK analysis; preliminary PK data were available for *N* = 124 patients, of which 59 patients were from the escalation and multihistology expansion cohorts. Mean budigalimab serum concentration vs. time profiles from cycle 1 (after the first dose) following administration of body-weight-based doses of 1, 3, and 10 mg/kg Q2W, and flat doses of 250 mg Q2W and 500 mg Q4W are shown in **Figure 2a**. Budigalimab exhibits approximately dose-proportional PKs across the dose-range evaluated with approximately two-fold accumulation with Q2W dosing and negligible accumulation with Q4W dosing in cycle 3 compared with cycle 1. The preliminary mean PK parameters for body-weight-based and

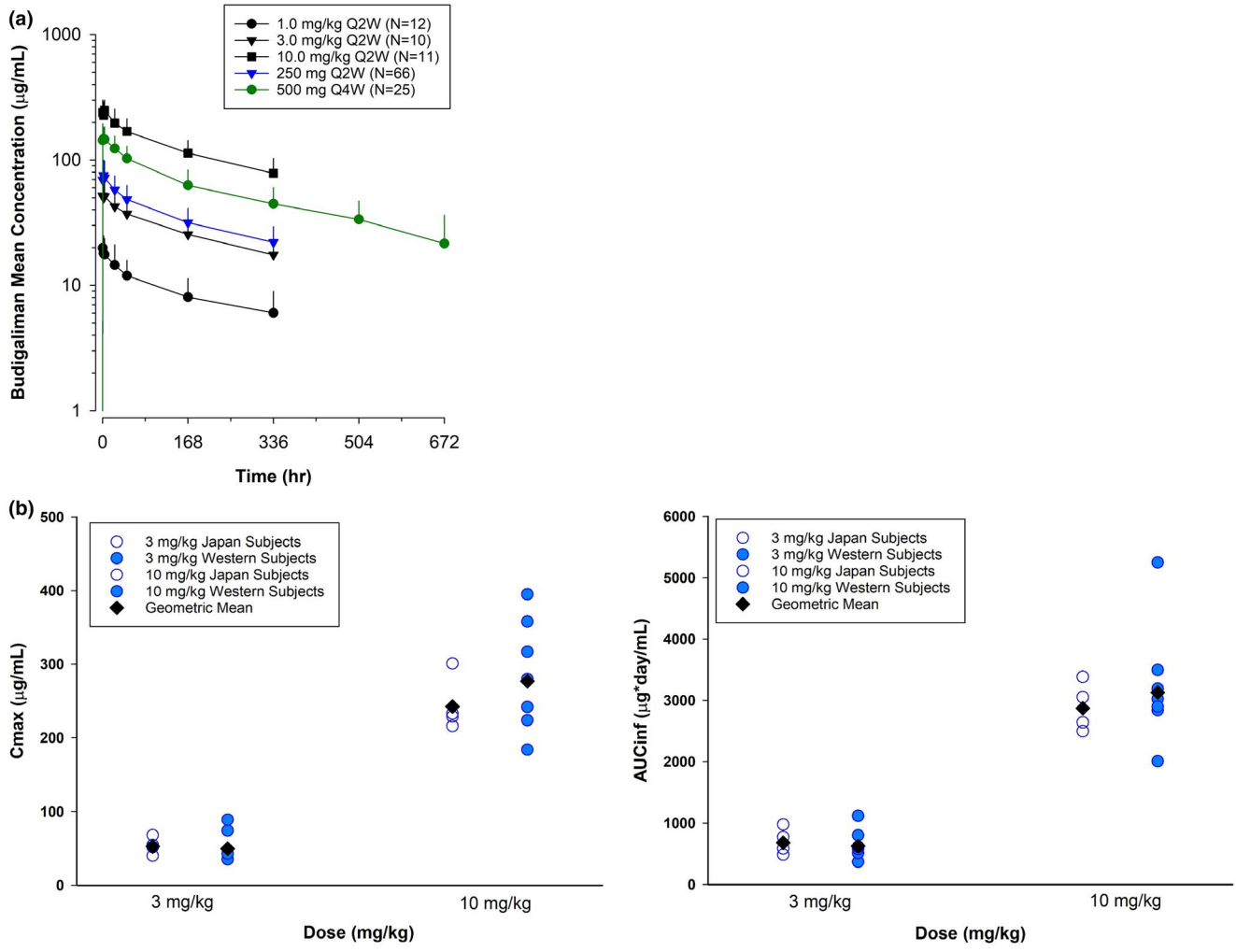

Figure 2 Preliminary pharmacokinetic profiles for flat and body-weight-based dosing of budigalimab. (**a**) Mean serum concentration-time profiles of budigalimab in cycle 1 following first intravenous administration of 1 mg/kg, 3 mg/kg, 10 mg/kg (Q2W), 250 mg (Q2W) and 500 mg (Q4W) budigalimab. Plots are shown on log-linear scale. (**b**) Comparison of budigalimab cycle 1 maximum plasma concentration (C_{max}) and area under the curve (AUC) for Japanese and Western patients.

Table 2 Preliminary pharmacokinetic parameters of budigalimab in Cycle 1 following flat and body-weight-based dosing

	Dose escalation cohorts			Expansion cohorts	
PK parameter, unit	**1.0 mg/kg (*N* = 12)**	**3.0 mg/kg (*N* = 10)**	**10.0 mg/kg (*N* = 11)**	**250 mg Q2W (*N* = 66)**	**500 mg Q4W (*N* = 25)**
T_{max}, hour[a]	1.75 (1.75–3.5)	3.5 (1.75–5.5)	3.5 (1.75–5.5)	3.5 (1.75–25.5)	3.5 (1.75–5.5)
C_{max}, µg/mL	19.2 (34%)	50.7 (34%)	264 (24%)	78.4 (33%)	160 (27%)
AUC_{inf}, day*µg/mL	215 (56%)	646 (34%)	3033 (26%)	789 (38%)[c]	1906 (42%)
$t_{1/2}$, days[b]	10.7 (36%)	10.8 (25%)	10.1 (30%)	8.9 (37%)[c]	11.9 (46%)

AUC_{inf}, area under the curve to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration.
[a]T_{max} presented as median and range.
[b]$t_{1/2}$ presented as the harmonic mean. Based on pharmacokinetic sampling following first dose, this provides an apparent estimate for the half-life due to inadequate sampling in the terminal elimination phase.
[c]*N* = 63.

flat doses of budigalimab are shown in **Table 2**. Exposures with 250 mg Q2W and 500 mg Q4W appear higher owing to the demographics (body weight) of the patients enrolled to these cohorts; nevertheless, dose normalized PK profiles and parameters with flat doses of 250 and 500 mg are comparable with the body-weight-based dosing regimens (**Table 1**). Although the data set is limited, the PK parameters do not exhibit trends by tumor type or PD-L1 expression status (data not shown). **Figure 2b** shows a comparison of budigalimab C_{max} and AUC values for Japanese patients receiving 3 and 10 mg/kg Q2W dose of budigalimab with Western patients. The data indicate comparable exposure (C_{max} and AUC) to Western patients (geometric mean ratios close to 1), suggesting no difference in PK between the two populations (**Table S3**).

Population pharmacokinetic modeling and simulations

Population PK modeling and simulation analyses were conducted following completion of dose escalation, to evaluate flat and less frequent dosing regimens that would provide dosing flexibility in the expansion phase (**Table S4**), based on the RP2D of 3 mg/kg Q2W (see Discussion section). The analyses indicated that flat dosing of budigalimab of either 250 mg Q2W or 500 mg Q4W (and 375 mg Q3W) would result in similar overall exposures and trough concentrations (minimum plasma concentration (C_{min})) achieved with body-weight-based dosing of 3 mg/kg Q2W. **Figure 3** represents the model-predicted budigalimab C_{min} (**Figure 3a**) and C_{max} (**Figure 3b**) values following multiple dosing with the alternate dosing regimens. Based on the model predictions, the flat and less frequent dosing regimens were administered to patients in the expansion phase. The observed PK data for the flat and alternate doses of budigalimab from the expansion phase are consistent with predictions from population PK modeling and simulations that were conducted prior to the start of the expansion phase (**Figure 4**).

Pharmacokinetic/pharmacodynamic assessments

Budigalimab geometric mean C_{min} value (17.5 µg/mL) following the first dose of 3 mg/kg Q2W is 175-fold the EC_{99} value for *in vitro* saturation of the PD-1-positive CD4 T_{CM} cells (0.1 µg/mL) and 1,460-fold the EC_{50} value of the *in vitro* PD-L1 blockade (0.012 µg/mL). This was reflected in the clinical data that showed complete and sustained saturation of peripheral PD-1-positive CD4 T_{CM} cells throughout the dosing interval. Population PK modeling and simulations, as well as PK/PD analyses indicated

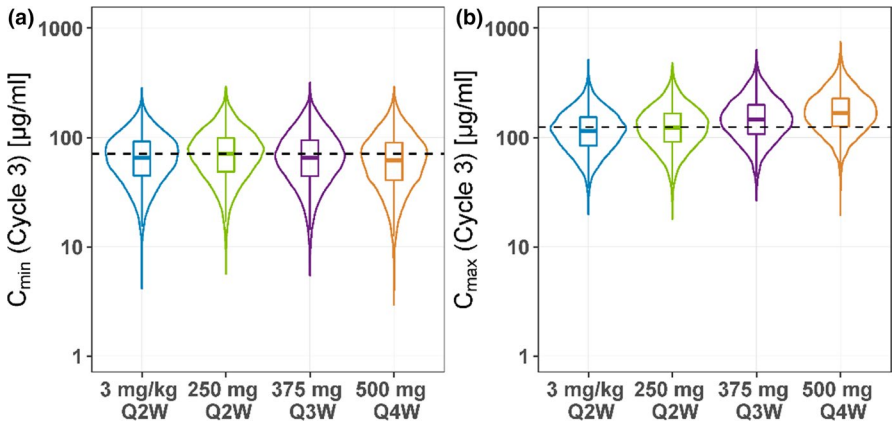

Figure 3 Violin-plots of model-predicted (**a**) minimum plasma concentration (C_{min}) and (**b**) maximum plasma concentration (C_{max}) for budigalimab following multiple dosing (week 12) of 3 mg/kg and 250 mg Q2W, 375 mg Q3W, and 500 mg Q4W regimens. Dashed lines represent 3 mg/kg Q2W median values.

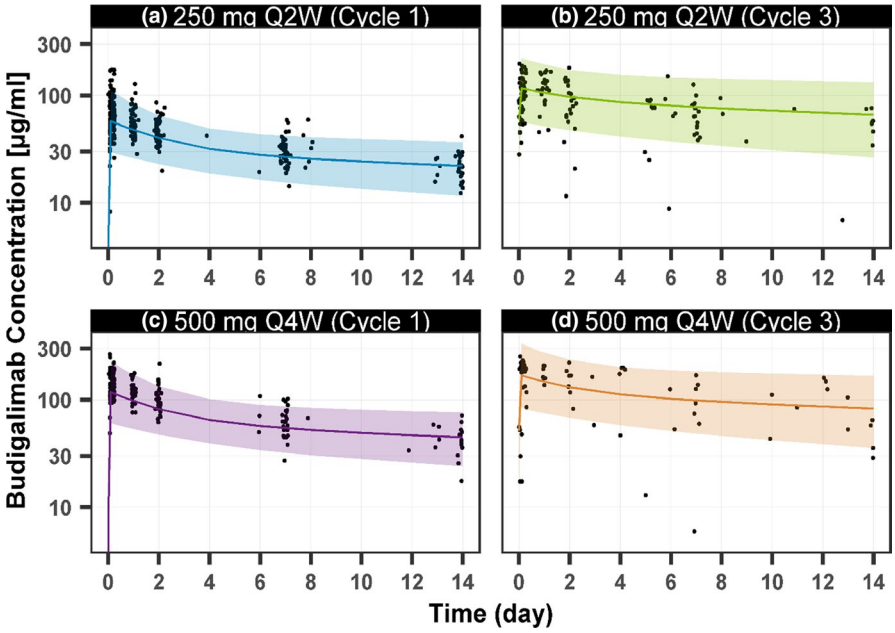

Figure 4 Model-predicted pharmacokinetic (PK) profiles overlaid with observed data. The solid lines represent population median PK predictions and dashed lines with shaded region represent the 95% prediction intervals. The observed serum concentration data points for budigalimab are shown as scatter (filled symbols) for the (**a**) 250 mg Q2W dose during cycle 1, (**b**) 250 mg Q2W dose during cycle 3, (**c**) 500 mg Q4W dose during cycle 1, and (**d**) 500 mg Q4W dose during cycle 3.

the exposures and trough levels achieved with alternate dosing regimens corresponding to a body-weight-based regimen of 3 mg/kg Q2W (i.e., 250 mg Q2W), and at the same weekly dose (i.e., 375 mg Q3W or 500 mg Q4W; **Figure 3**) will result in saturation of PD-1 positive CD4 T_{CM} cells (by over ~ 600-fold)[17] and significant PD-L1 pathway blockade (over ~ 1,300-fold). In addition to the predicted PD activity, the flat doses and less frequent regimen were predicted to result in exposures lower than the highest dose evaluated in the phase I study (10 mg/kg Q2W), that was safe and tolerated. Thus, these regimens were predicted to result in the necessary PD activity with no impact on safety, based on the available safety data from the phase I study.

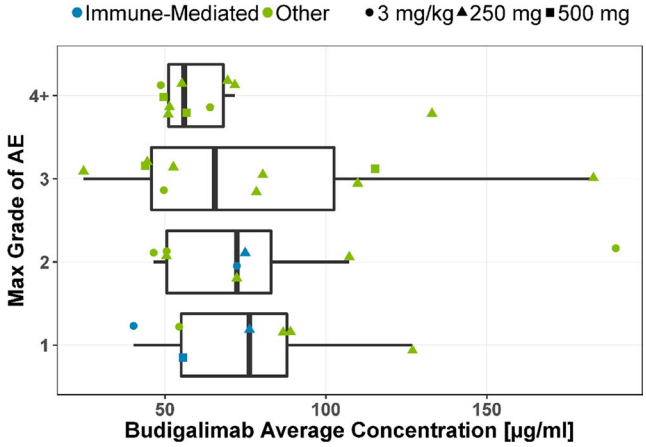

Figure 5 Exposure-safety analysis. Incidence of the maximum grade of adverse events (AEs) recorded (immune related and other, shown in blue and green filled symbols, respectively) with respect to budigalimab average concentrations in cycle 1. AEs across the 3 mg/kq Q2W, 250 mg Q2W, and 500 mg Q4W dose groups are represented with different symbols, respectively.

Exposure-safety analysis

Preliminary safety results during dose escalation suggested that doses of 1–10 mg/kg budigalimab administered Q2W were well-tolerated with no major safety concerns. Exposure-safety analysis from expansion cohort indicated no apparent trends in exposure-response based on the preliminary clinical data (**Figure 5**).

DISCUSSION

This first-in-human trial demonstrated that budigalimab can be administered safely at doses of 1-10 mg/kg Q2W, 250 mg Q2W, and 500 mg Q4W. There were no differences in the safety events between Western and Japanese patients and tolerability of budigalimab remained the same between the two populations. Most treatment-related AEs associated with budigalimab were low grade (**Table S1**). Only two patients (3.3%) discontinued budigalimab because of treatment-related AEs (1 patient with diabetic ketoacidosis in the 1 mg/kg Q2W dose escalation cohort and 1 patient with back pain in the 10 mg/kg Q2W dose escalation cohort). Although these data represent a small sample size, treatment with budigalimab was not associated with novel safety signals.[3–5]

Budigalimab demonstrated evidence of antitumor activity in tumor types (renal cell carcinoma, non-small cell lung cancer, and squamous cell carcinoma of the head and neck) where other PD-1 targeting agents have also demonstrated monotherapy activity.[22–27] The early efficacy data indicate that budigalimab has activity and may have a broader

application as a monotherapy or in combination with other agents.

PD data from this first-in-human study indicates complete peripheral PD-1 receptor saturation on CD4 T_{CM} in all tested doses and schedules that was durable for the entire dosing interval. Additionally, expected downstream biologic effects on T cells (as reported for other PD-1 blocking agents) were observed at all doses evaluated, including transient modulation of peripheral $CD4^+$ and $CD8^+$ T cell numbers, enhancement of T cell proliferation, and upregulation of IFN gamma-induced chemokines. No differences in PD effects were detected between Japanese and Western patients.

Budigalimab PK data indicates dose proportionality at the evaluated clinical doses and a twofold accumulation with Q2W dosing. There was minimal incidence of antidrug antibody formation with repeated dosing, which also did not show any adverse effect on budigalimab exposure or safety. Budigalimab exposures were similar between Japanese and Western patients and target saturation at all doses during the entire dosing interval supports the viability of Q2W or less frequent dosing.

Budigalimab is an anti-PD-1 monoclonal antibody belonging to the same class as the two approved agents, nivolumab and pembrolizumab. Phase I data from nivolumab and pembrolizumab trials were utilized for reverse translation approaches to further identify the budigalimab RP2D selection. Complete saturation of peripheral PD-1 receptors on CD4 T_{CM} cells, the mainstay PD marker for dose selection across this class of therapeutics, was observed with all doses and exposures evaluated in dose escalation (i.e., 1, 3, and 10 mg/kg). Although the target saturation in the tumor is unknown, the extent of PD-1 receptor saturation provided by the 3 mg/kg dose increases the likelihood for subjects to achieve saturable levels in the tumor throughout the dosing interval compared to the 1 mg/kg dose. Although saturable levels may be expected to be maintained at the highest dose of 10 mg/kg as well, the continued high exposure of budigalimab in patients at the highest human dose evaluated in the study was not deemed necessary based on data from the approved PD-1 inhibitors. Furthermore, the lower dose of 1 mg/kg has been shown to be less effective[28–31] for other approved anti-PD-1 agents, nivolumab and pembrolizumab.

Budigalimab exposures at the 3 mg/kg Q2W dose are comparable to nivolumab 3 mg/kg Q2W and pembrolizumab 2 mg/kg Q3W doses, which were the body-weight-based doses initially approved (see **Table S5** for PK parameter comparisons). The concentrations (EC_{50} values) resulting in the *in vitro* PD-L1 blockade for budigalimab and the two approved PD-1 agents are comparable (data on file at AbbVie). In addition to *in vitro* data, the initial approved doses of nivolumab and pembrolizumab (based on body weight) demonstrated to maintain target saturation at the approved doses, consistent with that observed for budigalimab at the 3 mg/kg dose.

Simulations[32,33] using physiologically-based PK modeling and mechanistic modeling approaches illustrate that the target receptor occupancy in the tumor is maintained at > 90% for both nivolumab and pembrolizumab at their approved body-weight-based doses, whereas lower dose levels may not achieve > 90% saturation throughout the dosing interval, and higher concentrations do not provide a significant benefit in terms of saturation within the tumor environment.

Thus, the RP2D selection for budigalimab was based on external data in addition to the early phase I results: (i) similarities in preclinical activity, (ii) overall mechanism of action, (iii) clinical PKs (at the 3 mg/kg Q2W budigalimab dose), (iv) consistent early clinical safety data in dose escalation, and (v) PK/PD data indicating complete and sustained saturation of PD-1 receptors on CD4 T_{CM} cells at the exposures achieved throughout the dosing interval.

Budigalimab PK simulations and PK/PD assessments were used to make early predictions for the effect of less frequent and flat dosing on PK parameters and consequently PD-1 saturation. The quantitative assessment and RP2D selection were based on a benefit-risk analysis using available data from the 33 subjects in the escalation arm of the phase I trial. This included the predictions and safety data from the highest dose of 10 mg/kg Q2W cohort, and consequently for the expansion phase of the trial, flat doses of 250 mg Q2W, 375 mg Q3W, and 500 mg Q4W were chosen to support less frequent dosing and subsequently reduce the burden on patients.

The flat doses of 250 mg Q2W and 500 mg Q4W (and 375 mg Q3W) were evaluated in the dose expansion phase and observed PK/PD results were consistent with the model predictions. As expected, the Q3W and Q4W regimen resulted in comparable C_{min} with the 250 mg Q2W regimen (observed data not shown for 375 mg Q3W regimen). As anticipated, based on the dose escalation data (from 10 mg/kg cohort), a higher C_{max} with the Q4W regimen compared with 3 mg/kg or 250 mg Q2W regimen did not result in higher safety-related events. No impact on achieving complete PD-1 saturation was observed across the doses of 1-10 mg/kg Q2W or the flat doses of 250 mg Q2W, 375 mg Q3W, or 500 mg Q4W.

Exposure-safety assessments confirmed that there was no relationship between the exposure of 3 mg/kg Q2W, 250 mg Q2W, or 500 mg Q4W and AEs, including immune-related AEs across multiple tumor types. These findings further support the interchangeability and flexibility of less frequent dosing of budigalimab.

In conclusion, this study demonstrates that budigalimab is an active anti-PD-1 agent with an acceptable safety and tolerability profile. The dosing recommendation made early in dose escalation, enabling a switch in the expansion phase, is based on the robust translational and quantitative clinical pharmacology evaluation, and provides an example of the applicability of such analyses to inform the RP2D very early in a phase I trial. The exposure, safety, PD activity, and efficacy of budigalimab flat dosing were similar to those observed with the initially evaluated body-weight-based dosing (data initially reported at European Society for Medical Oncology (ESMO) 2018 and Japanese Society of Medical Oncology (JSMO) 2019).[34,35] Recommended doses of budigalimab at 250 mg Q2W or 500 mg Q4W flat dose simplifies dosing and administration, and further development of budigalimab as

monotherapy and in combination with other approved and novel anticancer agents is ongoing.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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Data Availability Statement. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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