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REVIEW ARTICLE

Clinical Pharmacology Profile of the Claudin 18.2 Antibody Zolbetuximab

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Abstract

Zolbetuximab is a first-in-class chimeric (mouse/human) monoclonal antibody targeted to the tight junction protein claudin 18.2 (CLDN18.2), an emerging biomarker in gastric/gastroesophageal junction (G/GEJ) cancer. This review summarizes the clinical pharmacology of zolbetuximab on the basis of available clinical trial data. Population pharmacokinetics (PK) were evaluated using data from eight clinical studies ($n = 714$). Zolbetuximab PK following intravenous administration was described by a two-compartment model with linear and time-dependent clearance components. On the basis of simulations using the 800/600 mg/m^2 every 3 weeks (Q3W) dosing regimen from phase 3 trials, gastrectomy (versus no gastrectomy) was predicted to increase zolbetuximab C_{trough} by $\geq 50\%$, but without apparent effects on the benefit–risk profile of zolbetuximab. No dose adjustments are necessary for individuals with mild/moderate renal impairment or mild hepatic impairment. Zolbetuximab PK was not different among the ethnicities evaluated (White, Asian, Chinese, Japanese, Korean). There were no apparent safety or PK ramifications of zolbetuximab coadministration with oxaliplatin or 5-fluorouracil. The incidence of antidrug antibodies to zolbetuximab was low, with no apparent clinical consequence. Exposure-response analysis suggested that higher zolbetuximab exposures may prolong survival outcomes but may also increase the probability of experiencing gastrointestinal events and infusion-related reactions. A proposed alternative 800/400 mg/m^2 every 2 weeks (Q2W) regimen for use in combination with Q2W chemotherapy was shown to have comparable safety and efficacy to the 800/600 mg/m^2 Q3W regimen. Zolbetuximab, the first and only approved therapy targeted to CLDN18.2, is a valuable new treatment option for patients with CLDN18.2-positive, locally advanced unresectable or metastatic G/GEJ cancer.

Key Points

Zolbetuximab is the first and only approved monoclonal antibody directed against the tight junction protein claudin 18.2 (CLDN18.2) for the treatment of locally advanced unresectable or metastatic CLDN18.2-positive G/GEJ cancer.

On the basis of currently available pharmacokinetic data, patient factors such as mild/moderate renal impairment, mild hepatic impairment, ethnicity, or treatment in combination with chemotherapy do not appear to have any clinically relevant impact on zolbetuximab exposure.

Exposure-response analyses support the efficacy and safety of the 800/600 mg/m^2 every 3 weeks regimen used in clinical trials.

An alternative 800/400 mg/m^2 regimen given every 2 weeks is expected to have comparable clinical outcomes and is a convenient dosing strategy for use in combination with similarly scheduled chemotherapy regimens.

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Tomasz Wojtkowski: Employee of Astellas at the time the study was conducted.

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1 Introduction

Gastric/gastroesophageal junction (G/GEJ) adenocarcinoma is a type of cancer with high global prevalence and mortality burden. According to 2022 GLOBOCAN data, stomach cancer was ranked as the fifth most commonly diagnosed cancer (4.9% of all cancers) and the fifth leading cause of cancer-related death (6.8% of all cancer-related deaths) worldwide [1]. The highest population incidence rates for stomach cancer (per 100,000 people, male/female) are in Eastern Asia (23.0/9.7), Eastern Europe (16.2/7.7), South America (12.8/6.1), and Western Asia (11.0/5.8) [1]. Unfortunately, because of the ambiguity of gastric cancer symptoms, the great majority of cases are diagnosed at an advanced stage [2, 3]. There remains an urgent need for new, effective therapies to address locally advanced unresectable or metastatic disease. Standard first-line therapy with fluoropyrimidine- and platinum-based chemotherapy, such as mFOLFOX6 (modified 5-fluorouracil [5-FU], leucovorin [or folinic acid], and oxaliplatin), is associated with a median survival of approximately 1 year [4–7]. Targeted treatments are a promising option for the future of advanced gastric cancer management, particularly as research efforts continue to uncover new clinically relevant biomarkers and genomic data. To date, clinically promising approaches have included monoclonal antibodies directed against molecular targets such as human epidermal growth factor receptor 2 (HER2), programmed cell death protein 1, and epidermal growth factor receptor [8].

The tight junction protein claudin 18.2 (CLDN18.2) has emerged as a promising new biomarker in G/GEJ cancer [9]. CLDN18.2 is expressed almost exclusively in the gastric mucosa and no other healthy tissues [8, 10]. Expression is often retained following malignant transformation of cells, which makes it a useful therapeutic target [8]. A recent analysis found the prevalence of CLDN18.2 positivity among individuals with G/GEJ adenocarcinoma to be 44% on the basis of a cutoff of moderate (2+) and/or strong (3+) staining intensity in ≥ 75% of tumor cells [11]. Other studies, some using different positivity criteria, have reported CLDN18.2 prevalence rates in gastric tumors of 46.5% (≥ 75% cutoff for 2+ or 3+ staining intensity) [12], 87% (at least 1+ intensity in any portion of tumor cells) [13], 52% (cutoff of ≥ 40%, 2+ or 3+ staining intensity) [13], and 72% (cutoff of ≥ 70%, 2+ or 3+ staining intensity) [14].

Zolbetuximab is a first-in-class chimeric (mouse/human) monoclonal antibody targeted to CLDN18.2 [15]. Zolbetuximab has been developed as a first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy for patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumors are CLDN18.2-positive and HER2-negative. In March 2024, zolbetuximab (Vyloy®; Astellas Pharma, Inc.) received approval from Japan's Ministry of Health, Labour and Welfare, making it the first and only approved therapy targeted to CLDN18.2. Approvals followed in August by the Medicines and Healthcare products Regulatory Agency in the United Kingdom, in September by the European Medicines Agency in the European Union and the Ministry of Food and Drug Safety in Korea, in October by the US Food and Drug Administration, and in January 2025 by the National Medical Products Administration in China. These regulatory actions were supported by data from the phase 3 SPOTLIGHT [15] and GLOW [16] studies, which demonstrated similar and statistically significant reductions in disease progression or death (−25% for SPOTLIGHT and −31% for GLOW) and risk of death (−25% and −23%, respectively) in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma who received zolbetuximab plus chemotherapy compared with placebo plus chemotherapy.

A total of nine clinical studies (Supplementary Table 1 in the Online Resource) have investigated the use of zolbetuximab in adult patients with advanced adenocarcinoma of the stomach, esophagus, or GEJ with CLDN18.2 expression. This review summarizes the clinical pharmacology of zolbetuximab on the basis of available data, including population pharmacokinetics (PK) and the impact of various covariates, PK effects on concomitant chemotherapy, effects of organ impairment and ethnicity on zolbetuximab PK, exposure-response analyses for efficacy and safety, effect of zolbetuximab on the QTcF interval, and incidence and ramifications of antidrug antibodies (ADAs).

2 Population PK

Population PK (PopPK) modeling of zolbetuximab was performed using data from 714 individuals with advanced adenocarcinoma of the stomach, esophagus, or GEJ (CLDN18.2-positive tumors) across eight clinical studies (three phase 1 studies; the phase 2 studies MONO [17], FAST [14], and ILUSTRO [18]; and the phase 3 studies SPOTLIGHT [15] and GLOW [16]; Supplementary Table 1 in the Online Resource). An initial PopPK model was developed on the basis of a two-compartment model with first-order elimination. Subsequently, a revised model with empirically decaying zolbetuximab clearance (CL) was developed to assess the time dependency of zolbetuximab CL. In this revised model, zolbetuximab PK following intravenous (IV) infusion administration was described by a two-compartment model with linear and time-dependent CL components. Despite using a different model structure with associated changes in covariates, the revised model had

similar estimations of key PK parameters such as the average concentration throughout treatment (C_{ave}) and the maximum concentration (C_{max}) after the first dose ($C_{max,1st}$). However, this revised model better characterized the zolbetuximab PK profile, especially for time-dependent changes, and was thus selected as the final model [19].

Model-estimated metrics of zolbetuximab exposure based on the dosing regimen used in zolbetuximab phase 3 studies (800 mg/m^2 loading dose followed by 600 mg/m^2 every 3 weeks; 800/600 mg/m^2 Q3W) are presented in Table 1. The loading dose of 800 mg/m^2 was used to achieve higher median trough concentration (C_{trough}) and C_{ave} during the initial cycles when compared with 600 mg/m^2 as the initial dose. Steady state was achieved by 24 weeks, with a mean (standard deviation [SD]) C_{max} and area under the concentration-time curve (AUC) from the time of dosing to the start of the next dosing interval (AUC_{τ}) of 453 (82) µg/mL and 4125 (1169) day × µg/mL, respectively. Zolbetuximab CL decreased over time, with a maximal reduction from baseline of 57.6%, resulting in a population mean steady-state clearance (CL_{ss}) of 0.0117 L/h. The estimated volume of distribution was 5.53 L and estimated elimination half-life ranged from 7.6 to 15.2 days. Taking the loading dose into account, simulations showed a mean (SD) accumulation ratio of 1.96 (0.53) for zolbetuximab AUC from the time of dosing to 21 days after dosing (AUC_{21d}). There was no suggested accumulation in C_{max} of zolbetuximab (mean [SD] accumulation ratio, 1.01 [0.12]).

On the basis of simulations conducted for the 800/600 mg/m^2 Q3W dosing regimen, prior patient gastrectomy (versus no prior gastrectomy) was predicted to increase zolbetuximab C_{trough} (after the first dose and at steady state) by ≥ 50% (50–114%). Patients with prior gastrectomy also demonstrated higher AUC (34% and 26% for AUC_{21d} after the first dose and at steady state, respectively) and higher C_{ave} (30%) compared with those without prior gastrectomy, while C_{max} was comparable for prior gastrectomy versus no prior gastrectomy (−9% and 2% difference for $C_{max,1st}$ and $C_{max,ss}$, respectively). Despite these differences, on the basis of clinical findings, the observed variations in drug exposure are not anticipated to adversely affect the benefit–risk profile of zolbetuximab. Gastrectomy status did not notably affect adverse event (AE) incidence or study drug discontinuation in clinical trials. With regard to efficacy, a slight trend toward greater benefit was observed for study participants with prior gastrectomy compared with those without prior gastrectomy. Consequently, no dose adjustment is deemed necessary for patients with prior gastrectomy who are treated with zolbetuximab.

For all other covariates assessed (body surface area [5th and 95th percentiles], serum albumin [5th and 95th percentiles], hemoglobin [5th and 95th percentiles], total bilirubin [5th and 95th percentiles], and female sex), geometric mean ratios (GMRs) of exposure metrics were predicted to be within or near 0.80- to 1.25-fold relative to a reference population.

Table 1 Model-estimated exposure metrics of zolbetuximab (800/600 mg/m^2 Q3W)

Mean (SD)	First dose (800 mg/m^2)	Steady state (600 mg/m^2 Q3W)
C_{max} (µg/mL)	454 (87)	453 (82)
AUC_{21d} (day × µg/mL)	2176 (606)	4125 (1169)
C_{trough} (µg/mL)	36.8 (23.2)	114 (50)
C_{ave} (µg/mL)	158 (48)	

First dose simulation was for a 3-week interval after the first dose. For steady state, simulation was for a 3-week interval from weeks 28 to 31.

AUC_{21d} area under the concentration-time curve from the time of dosing to 21 days after dosing, *C_{ave}* average concentration, *C_{max}* maximum concentration, *C_{trough}* trough concentration immediately prior to dosing with multiple dosings, *Q3W* every 3 weeks, *SD* standard deviation

3 PK Effects of Concomitant Therapy

Zolbetuximab is not a cytokine modulator, there are no known effects of its mechanism of action on cytochrome P450 or drug transporters, and the risk of drug–drug interactions is considered low. Yet, given that zolbetuximab is evaluated in combination with fluoropyrimidine- and platinum-containing chemotherapy, potential PK interactions were assessed in cohort 2 of ILUSTRO [18], in which participants with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma received zolbetuximab in combination with mFOLFOX6. Blood samples to determine plasma oxaliplatin (measured as total platinum and free platinum) and 5-FU concentrations were collected after dosing mFOLFOX6 on cycle 1 day 1 (without zolbetuximab, which was started on cycle 1 day 3) and cycle 2 day 1 (with zolbetuximab) and analyzed using validated assays.

Coadministration of zolbetuximab with oxaliplatin appeared to slightly increase the $AUC_{24h,D}$ (dose-normalized AUC from the time of dosing to 24 h postdosing) of total platinum and free platinum by about 10–16%. The geometric least squares mean (GLSM) ratios of total platinum and free platinum were 110.64% (90% confidence interval [CI] 103.08%, 118.76%) and 116.08% (90% CI 103.53%, 130.15%), respectively. Coadministration of zolbetuximab with oxaliplatin appeared to increase $C_{max,D}$ (dose-normalized C_{max}) of free platinum (by about 30%) but not total platinum. The GLSM ratios of total platinum and free platinum were 107.41% (90% CI 99.56%, 115.88%) and 130.43% (90% CI 111.56%, 152.49%), respectively [18]. The mean plasma concentration-time profiles of total platinum and free platinum after administration of oxaliplatin alone (as part of mFOLFOX6) and in

the presence of zolbetuximab are shown in Supplementary Fig. 1 (see Online Resource).

The apparent increase in platinum exposure may be attributed to the nonrandomized, one-sequence crossover study design, as the "without zolbetuximab" samples were drawn on day 1 of the first cycle and the "with zolbetuximab" samples were drawn on day 1 of the second cycle. In phase 3 trials of zolbetuximab combined with chemotherapy, there was no evidence for clinical safety implications related to increased platinum exposure. Rates of permanent discontinuation or dose interruption of oxaliplatin therapy were not significantly different between zolbetuximab plus chemotherapy and placebo plus chemotherapy groups. Although these rates were numerically higher in the zolbetuximab plus chemotherapy group compared with the placebo plus chemotherapy group (up to 2.9%), this difference was predominantly owing to gastrointestinal AEs, which are known toxicities of zolbetuximab and chemotherapy. There were no differences between groups for other AE categories, including chemotherapy-specific AEs (e.g., peripheral sensory neuropathy for oxaliplatin). On the basis of these considerations, the apparent increase in total platinum and free platinum exposure after coadministration of oxaliplatin and zolbetuximab did not appear to change the safety profile of mFOLFOX6 or CAPOX (capecitabine and oxaliplatin) and is not considered clinically significant.

Concomitant administration of zolbetuximab plus mFOLFOX6 in cohort 2 of ILUSTRO [18] did not affect the systemic exposure of 5-FU (Supplementary Fig. 2 in the Online Resource).

Data from cohort 2 (zolbetuximab plus mFOLFOX6) and cohort 3A (zolbetuximab plus pembrolizumab) of ILUSTRO [18] also indicated that combination therapy with mFOLFOX6 or pembrolizumab did not affect zolbetuximab exposure.

4 Exposure-Response Analysis

The exposure-response analysis for efficacy and safety was conducted using data from the phase 2 study FAST [14] ($n = 135$) and the phase 3 studies SPOTLIGHT [15] ($n = 553$) and GLOW [16] ($n = 497$). All three studies were randomized controlled studies of zolbetuximab in combination with chemotherapy in first-line patients with G/GEJ adenocarcinoma. Multivariable Cox proportional hazard models were used to assess the relationship between time-to-event efficacy endpoints and zolbetuximab exposure metrics; multivariable logistic regression models were used to analyze all other efficacy and safety endpoints. The potential effects of the following covariates on the efficacy and safety endpoints were evaluated: demographics, baseline disease state, CLDN18.2 positivity, chemotherapy backbone, and steroid usage (for efficacy only) [19].

In FAST [14], SPOTLIGHT [15], and GLOW [16], the primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS), and a key secondary endpoint was overall survival (OS). Statistically significant relationships were observed for IRC-assessed PFS and OS with all tested zolbetuximab exposure metrics. In all relationships, participants with higher exposures tended to have longer PFS and OS than those with lower exposures. Most of the exposure metrics evaluated for efficacy endpoints were highly correlated (data not shown). C_{ave}, the calculation of which took all dosing interval information (including dosing interruptions) into consideration, was selected for further analysis.

The results of multivariable Cox proportional hazard modeling analysis of PFS and OS using C_{ave} as a predictor suggest that worse baseline Eastern Cooperative Oncology Group performance status and a chemotherapy backbone of epirubicin, oxaliplatin, and capecitabine (EOX) or CAPOX (compared with mFOLFOX6) will likely result in shorter PFS/OS, and individuals with nonmeasurable lesions will likely have longer PFS/OS. In addition, participants with larger tumor diameters at baseline or lower CLDN18.2 positivity will likely have shorter PFS. The apparent difference from EOX and CAPOX compared with the mFOLFOX6 chemotherapy backbone used in the model was likely owing to the difference in study or chemotherapy effect, as shorter PFS and OS were also observed for EOX and CAPOX in patients who received chemotherapy without zolbetuximab. Notably, the mFOLFOX6 group had a larger proportion of individuals from Japan or South Korea compared with the EOX group, which enrolled in the European Union, or the CAPOX group, which had a larger proportion of individuals from mainland China.

With regard to safety, statistically significant relationships were observed between zolbetuximab $C_{max,1st}$ and combined gastrointestinal toxicity (GITX; nausea, vomiting, and abdominal pain) of grade ≥ 3, GITX of grade ≥ 2, nausea and vomiting of grade ≥ 3, nausea and vomiting of grade ≥ 2, and infusion-related reactions (IRRs) (all $P < 0.0001$). In all relationships, participants with higher exposures tended to have a higher probability of experiencing these safety events than those with lower exposures. IRRs were also significantly associated with EOX and CAPOX chemotherapy (compared with mFOLFOX6).

5 Organ Impairment

Zolbetuximab concentration-time profiles were simulated using the 800/600 mg/m^2 Q3W dosing regimen for subgroups on the basis of severity of renal or hepatic

impairment. Renal impairment categories were based on estimated creatinine clearance (CL_{CR}) at baseline using the Cockcroft–Gault formula: mild ($CL_{CR} \geq 60$ to < 90 mL/min), moderate ($CL_{CR} \geq 30$ to < 60 mL/min), or severe ($CL_{CR} \geq 15$ to < 30 mL/min). Hepatic impairment category determinations were made on the basis of the National Cancer Institute Organ Dysfunction Working Group criteria [20]. Simulated zolbetuximab concentration-time profiles for each renal and hepatic impairment subgroup are shown in Fig. 1. The GMRs of zolbetuximab exposure metrics to reference populations ($n = 306$ [normal renal function]; $n = 602$ [normal hepatic function]) for mild renal impairment ($n = 298$), moderate renal impairment ($n = 109$), and mild hepatic impairment ($n = 108$) were within 0.878–1.123 and considered not clinically meaningful. The GMR for severe renal impairment to normal renal function was not calculated because only one participant had severe renal impairment. The number of participants with moderate hepatic impairment was limited ($n = 4$), but no significant differences were observed. The effect of severe hepatic impairment was not evaluated because there were no participants with severe hepatic impairment enrolled in clinical studies [19].

6 Ethnicity

To assess potential differences among ethnic subpopulations, GMRs and 90% CIs compared with the reference population were calculated for all the estimated parameters from the PopPK model using the 800/600 mg/m^2 Q3W regimen used in phase 3 studies. Ethnic subgroups with sufficient numbers for meaningful analysis included White ($n = 358$), Asian ($n = 301$), Chinese ($n = 105$), Japanese ($n = 73$), and Korean ($n = 64$). Across all ethnic subgroups, GMRs of zolbetuximab exposures to the reference population were within 0.893–1.104 and were considered not clinically meaningful. Exposure metrics for Asian versus non-Asian and White versus non-White subgroups are shown in Fig. 2.

7 Effect on QT Interval

Zolbetuximab monotherapy data from a Japanese phase 1 study (8951-CL-0104) and cohort 1A of the global phase 2 ILUSTRO study [18] were included in the analysis of zolbetuximab's effect on QT interval (total $n = 44$). In each study, triplicate electrocardiograms were collected along with time-matched PK samples at multiple timepoints and were centrally read. The relationship between zolbetuximab serum concentration and baseline-adjusted QT interval corrected for heart rate according to Fridericia's formula (dQTcF) was assessed using the linear mixed-effects model. Concentration, sex, and study were each taken as a fixed effect, with intercept specified as a random effect with a patient effect. This model provided a positive slope estimate (95% CI) of 0.0160 (0.00257, 0.0294) msec × mL/μg. Although the slope was statistically significant ($P = 0.0199$), the upper one-sided 95% CIs of the model-predicted dQTcF values were < 20 msec at the estimated geometric mean of C_{max} for both dose regimens evaluated (800/600 mg/m^2 Q3W and 1000 mg/m^2 Q3W; geometric means presented in Supplementary Table 2 in the Online Resource).

Of the 44 participants included in the analysis, 7 observations in 5 participants had a QTcF interval > 450 msec and 7 observations in 7 participants had a QTcF change from baseline > 30 msec. No participant had a QTcF interval > 480 msec or a change from baseline > 60 msec. Generally, no trend of clinically meaningful changes from baseline in QTcF interval were observed. No treatment-emergent AEs (TEAEs) were reported in association with these electrocardiogram findings. A scatter plot of zolbetuximab serum concentrations against dQTcF did not show a clear trend of nonlinear concentration-QTcF relationship on the basis of visual inspection (Supplementary Fig. 3 in the Online Resource).

Overall, these results indicate that zolbetuximab serum concentration is not associated with a clinically meaningful effect on QTcF.

8 Q3W Versus Q2W Dosing

The two phase 3 clinical studies of zolbetuximab (SPOTLIGHT [15] and GLOW [16]) were carried out using a Q3W dosing regimen (800 mg/m^2 loading dose followed by 600 mg/m^2 Q3W), which is asynchronous with the scheduling of mFOLFOX6. This dose and schedule were chosen on the basis of the observed data from the FAST study [14], in which the addition of zolbetuximab 800/600 mg/m^2 Q3W to EOX (arm 2) demonstrated a statistically significant and clinically meaningful improvement in PFS and OS compared with EOX alone (arm 1) in participants with advanced G/GEJ adenocarcinoma whose tumors were CLDN18.2-positive.

Using the PopPK model, efficacy/safety simulations were performed to compare the 800/600 mg/m^2 Q3W regimen with an alternative 800/400 mg/m^2 every 2 weeks (Q2W) regimen. On the basis of model predictions, zolbetuximab C_{max} using the 800/400 mg/m^2 Q2W regimen would be comparable to C_{max} using the 800/600 mg/m^2 Q3W regimen during the initial 42-day dosing interval but about 21% lower at steady state. AUC_{21d} for the 800/400 mg/m^2 Q2W regimen was predicted to be about 12% higher than AUC_{21d} for the 800/600 mg/m^2 Q3W

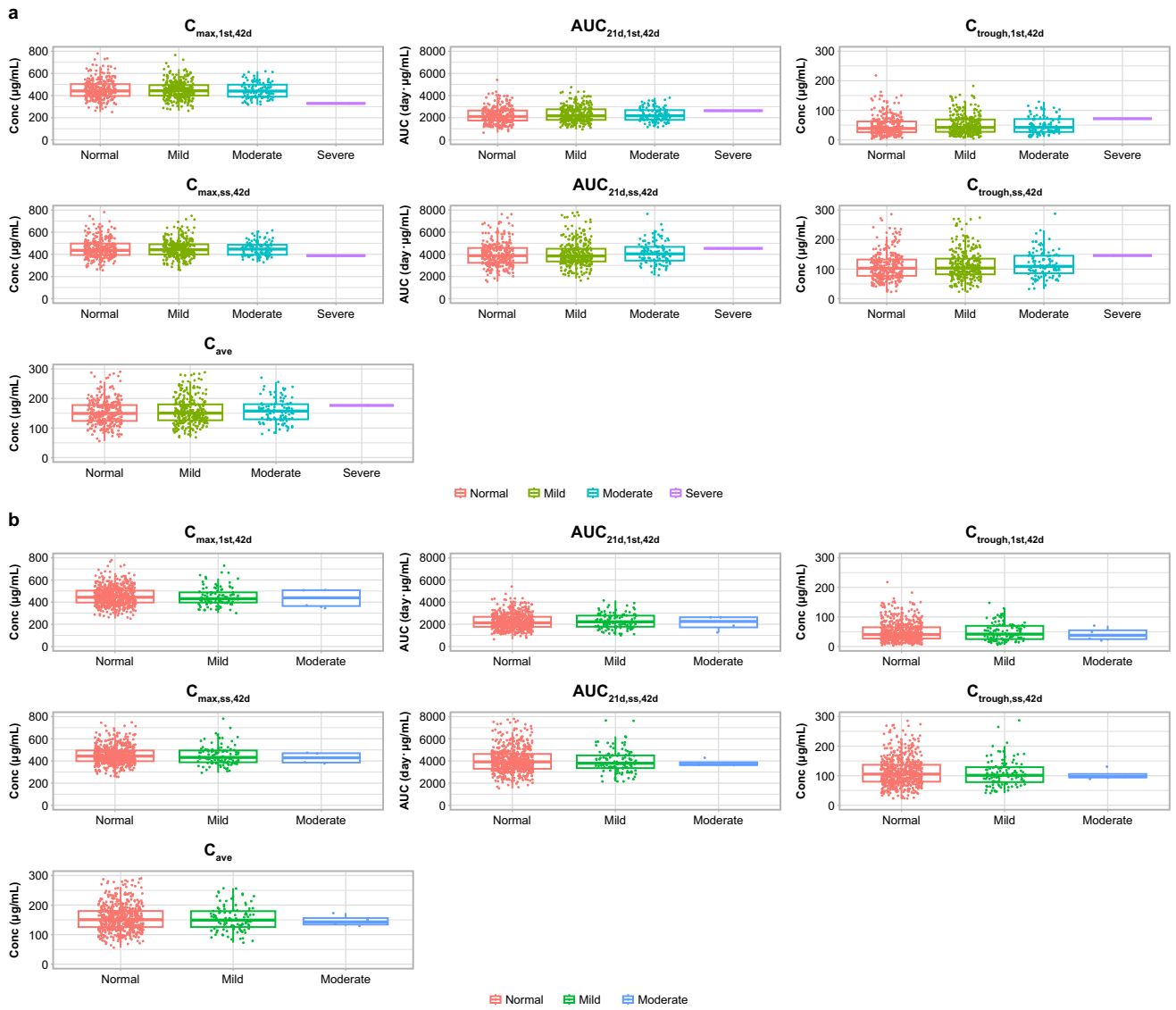

Fig. 1 Zolbetuximab exposure metrics for study participants with renal (**a**) and hepatic (**b**) impairment relative to those with normal function. *AUC* area under the concentration-time curve, $AUC_{21d,1st,42d}$ area under the concentration-time curve from the time of dosing to 42 days after the first dose divided by 2, $AUC_{21d,ss,42d}$ area under the concentration-time curve from the time of dosing to 42 days after dosing at steady state divided by 2, C_{ave} average concentration, $C_{max,1st,42d}$ maximum concentration during 42 days after the first dose, $C_{max,ss,42d}$ maximum concentration during 42 days at steady state, *Conc* concentration, $C_{trough,1st,42d}$ trough concentration during 42 days after the first dose, $C_{trough,ss,42d}$ trough concentration during 42 days at steady state

regimen during the first 42-day dosing interval but comparable at steady state. C_{trough} for the 800/400 mg/m^2 Q2W regimen was predicted to be 19–40% higher than C_{trough} for the 800/600 mg/m^2 Q3W regimen throughout treatment. However, C_{ave} throughout treatment was predicted to be similar between the two regimens (Fig. 3). Overall, these differences in zolbetuximab exposure were not considered clinically meaningful and the two regimens are expected to have similar efficacy and safety profiles, a conclusion confirmed by the simulations from the exposure-response models for efficacy and safety (Figs. 4 and 5).

9 ADAs

Across all nine zolbetuximab clinical studies, the rate of ADA positivity in individual studies ranged from 0 to 12.7%. In the phase 3 studies SPOTLIGHT [15] and GLOW [16], which used an 800/600 mg/m^2 Q3W dosing regimen of zolbetuximab plus chemotherapy (mFOLFOX6 in SPOTLIGHT; CAPOX in GLOW), ADAs were detected in 9.5% (46/485) of participants. Among the 46 ADA-positive participants, a single ADA-positive timepoint was recorded for 31 participants and recurring ADA-positive timepoints were

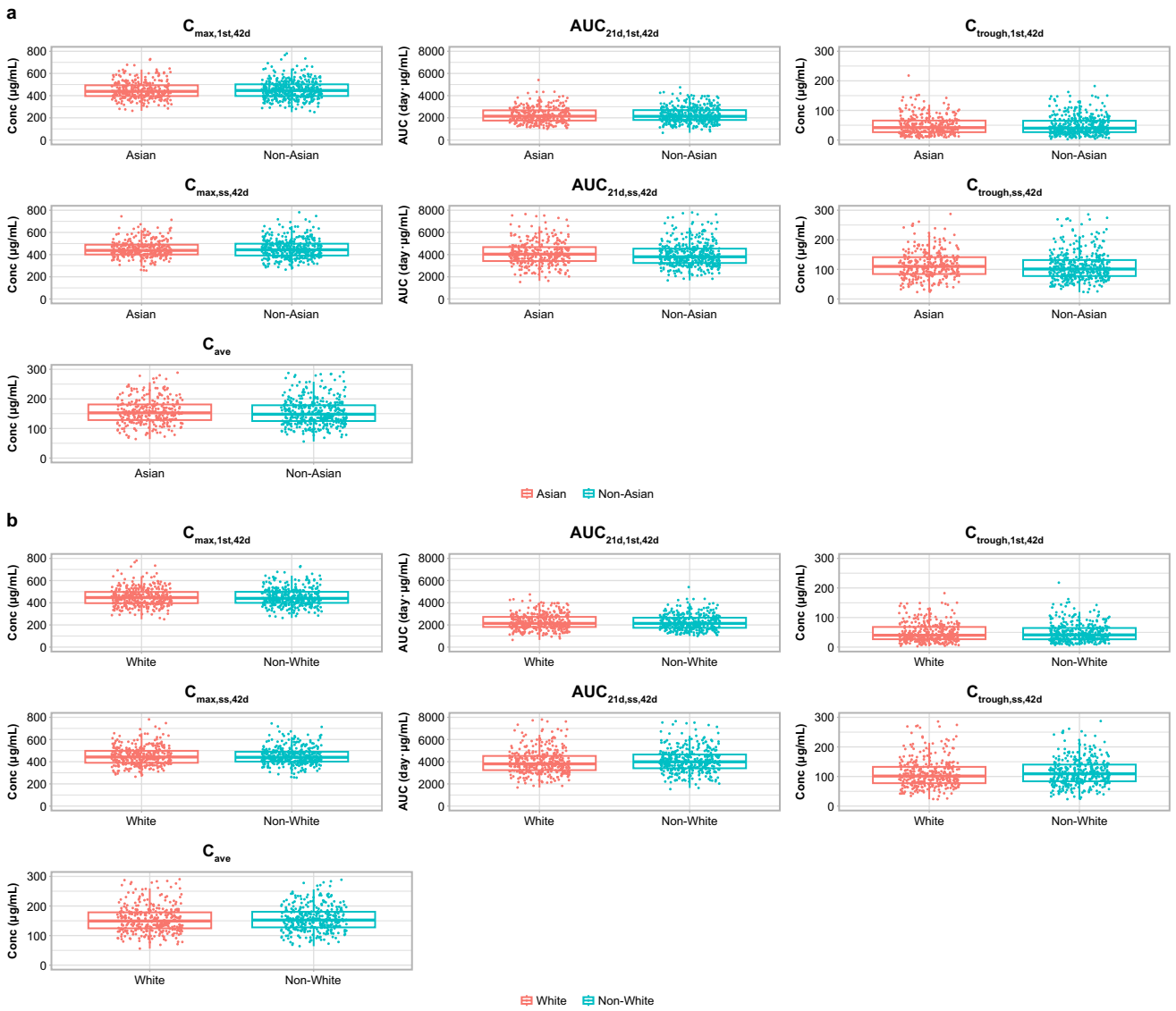

Fig. 2 Zolbetuximab exposure metrics by ethnicity for Asian versus non-Asian (**a**) and White versus non-White (**b**) study participants. *AUC* area under the concentration-time curve, $AUC_{21d,1st,42d}$ area under the concentration-time curve from the time of dosing to 42 days after the first dose divided by 2, $AUC_{21d,ss,42d}$ area under the concentration-time curve from the time of dosing to 42 days after dosing at steady state divided by 2, C_{ave} average concentration, $C_{max,1st,42d}$ maximum concentration during 42 days after the first dose, $C_{max,ss,42d}$ maximum concentration during 42 days at steady state, *Conc* concentration, $C_{trough,1st,42d}$ trough concentration during 42 days after the first dose, $C_{trough,ss,42d}$ trough concentration during 42 days at steady state

recorded for 15 participants. To assess the effect of ADAs on zolbetuximab PK, zolbetuximab serum concentration-time profiles were plotted and overlayed for ADA-positive and ADA-negative participants who had matched PK information. The resulting plots showed no clear differences in zolbetuximab concentrations between ADA-positive and ADA-negative participants (data not shown). The efficacy (PFS, OS, objective response rate, and disease control rate) and safety (all TEAEs, treatment-related TEAEs, systemic IRRs, and immunologically based AEs, such as hypersensitivity) data for ADA-positive participants were generally similar to data for ADA-negative participants. These findings, despite being limited by the low incidence of ADAs overall, suggest that ADA positivity does not have a clinically relevant impact on zolbetuximab efficacy or safety.

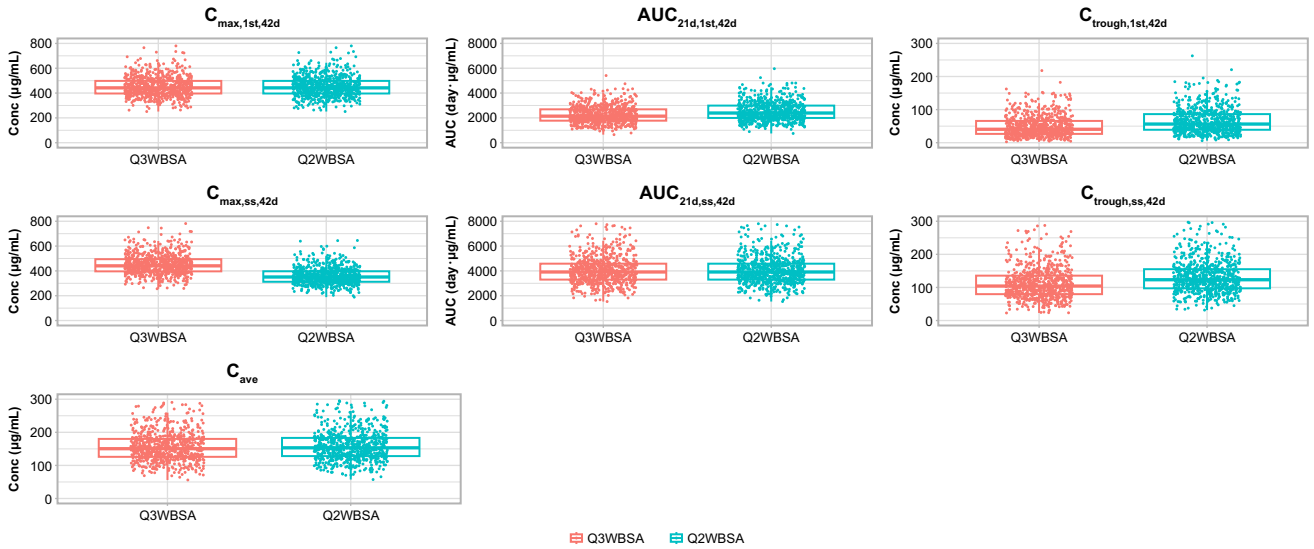

Fig. 3 Simulated exposure metrics of zolbetuximab administered Q3W (800/600 mg/m^2) or Q2W (800/400 mg/m^2). *AUC* area under the concentration-time curve, $AUC_{21d,1st,42d}$ area under the concentration-time curve from the time of dosing to 42 days after the first dose divided by 2, $AUC_{21d,ss,42d}$ area under the concentration-time curve from the time of dosing to 42 days after dosing at steady state divided by 2, *BSA* body surface area, C_{ave} average concentration, $C_{max,1st,42d}$ maximum concentration during 42 days after the first dose, $C_{max,ss,42d}$ maximum concentration during 42 days at steady state, *Conc* concentration, $C_{trough,1st,42d}$ trough concentration during 42 days after the first dose, $C_{trough,ss,42d}$ trough concentration during 42 days at steady state, *Q2W* every 2 weeks, *Q2WBSA* every 2 weeks dosing for the BSA-normalized regimen, *Q3W* every 3 weeks, *Q3WBSA* every 3 weeks dosing for the BSA-normalized regimen

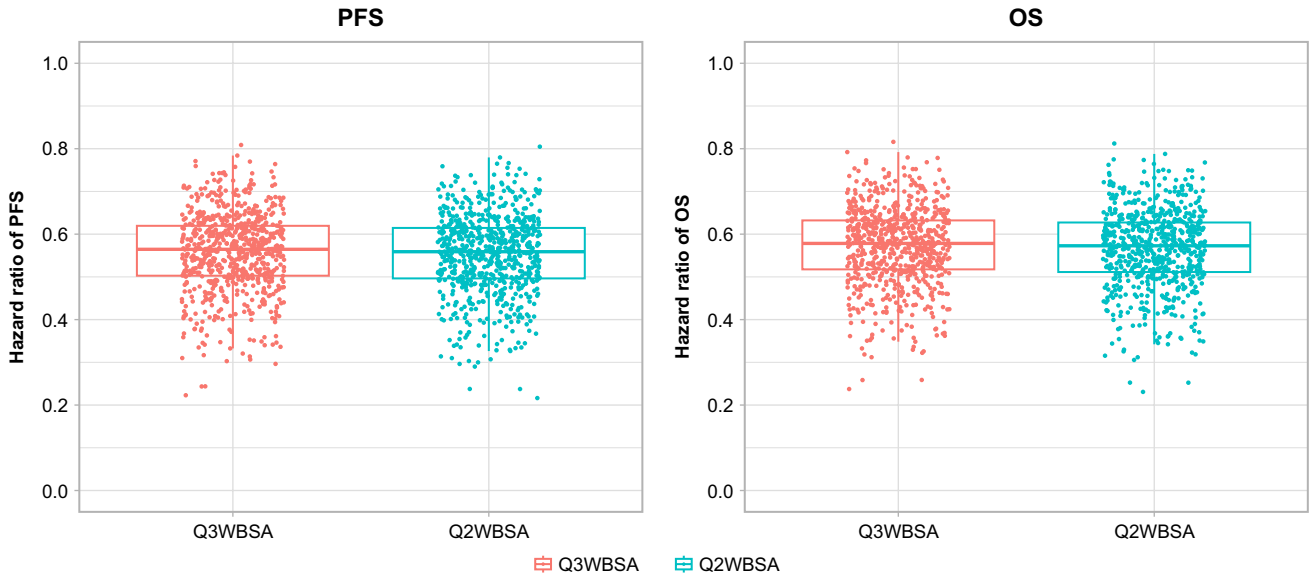

Fig. 4 Model-estimated hazard ratios of PFS and OS: comparison of zolbetuximab 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W regimens. *BSA* body surface area, *OS* overall survival, *PFS* progression-free survival based on evaluation by independent review committee, *Q2W* every 2 weeks, *Q2WBSA* every 2 weeks dosing for the BSA-normalized regimen, *Q3W* every 3 weeks, *Q3WBSA* every 3 weeks dosing for the BSA-normalized regimen

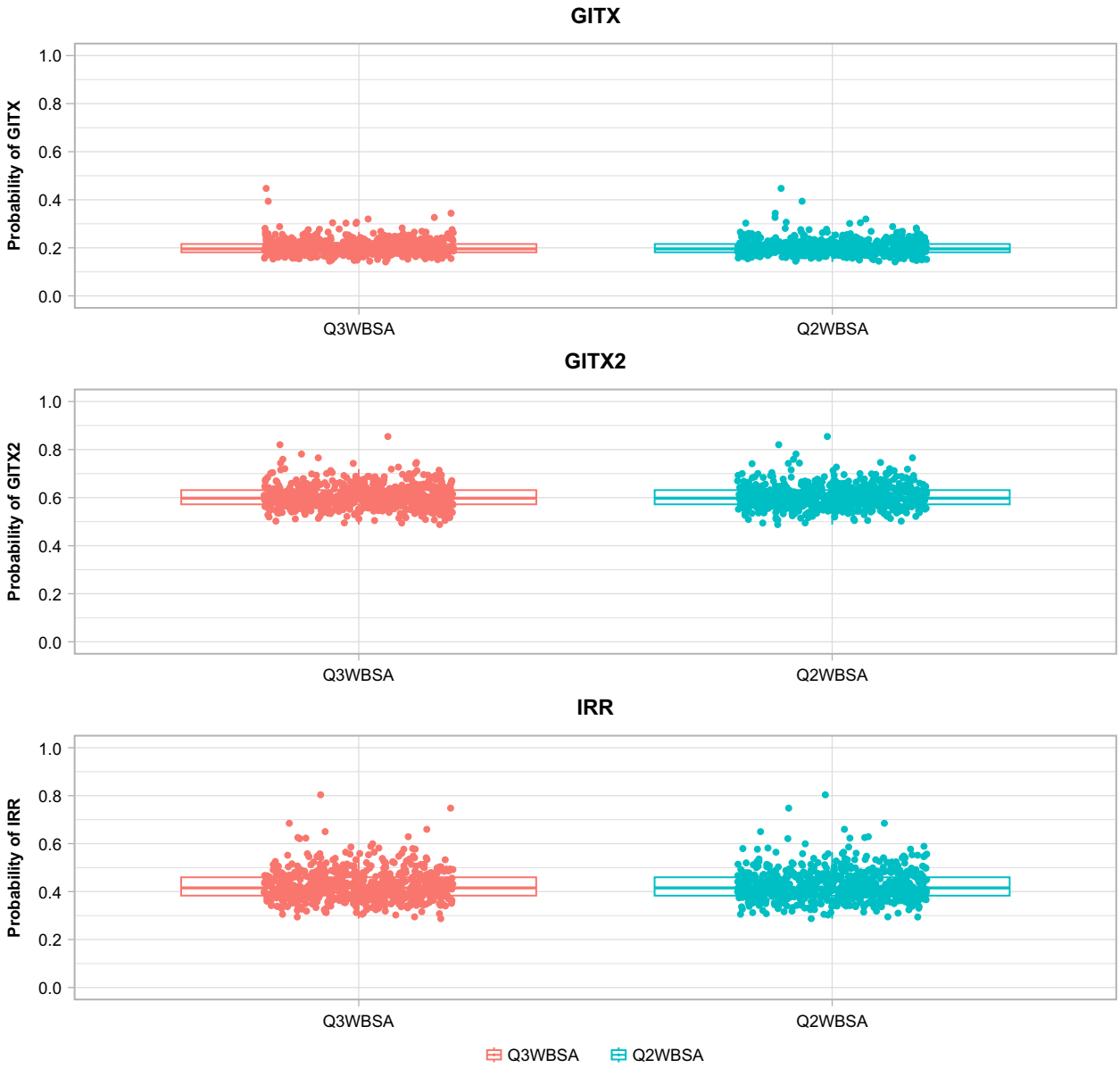

Fig. 5 Model-estimated probabilities of toxicities: comparison between zolbetuximab 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W regimens. *BSA* body surface area, *GITX* combined gastrointestinal toxicity (nausea, vomiting, and abdominal pain) of grade ≥ 3, *GITX2* combined gastrointestinal toxicity (nausea, vomiting, and abdominal pain) of grade ≥ 2, *IRR* infusion-related reaction flagged by investigator, *Q2W* every 2 weeks, *Q2WBSA* every 2 weeks dosing for the BSA-normalized regimen, *Q3W* every 3 weeks, *Q3WBSA* every 3 weeks dosing for the BSA-normalized regimen

10 Discussion

The clinical pharmacology of zolbetuximab has been well characterized using data from nine clinical trials in individuals with advanced adenocarcinoma of the stomach, esophagus, or GEJ. The PopPK analysis evaluated various intrinsic and extrinsic factors relevant to zolbetuximab PK using a two-compartment model with linear and time-dependent CL components. The only variable with a notable PK impact was gastrectomy status (prior gastrectomy versus no prior gastrectomy); prior gastrectomy was predicted to increase zolbetuximab C_{trough}, AUC, and C_{ave} but have a negligible effect on C_{max}. The projected increases in C_{trough}, AUC, and C_{ave} are not anticipated to increase the safety risk of zolbetuximab. In clinical trials, there was no apparent effect of gastrectomy status on AE incidence or study drug discontinuation rate, and study participants with prior gastrectomy actually trended toward greater benefit compared with those without. Thus, no dose adjustment is deemed necessary in individuals with gastrectomy.

No dose adjustments are necessary for patients with mild/moderate renal impairment or mild hepatic impairment [19]. The numbers of clinical study participants with severe renal impairment or moderate/severe hepatic impairment were too small to evaluate the effects of these clinical scenarios on zolbetuximab PK. Ethnicity does not appear to have any meaningful effect on zolbetuximab PK, although ethnicities represented in sufficient numbers for meaningful analysis were limited to White, Asian, Chinese, Japanese, and Korean. These data are relevant given that the highest rates of stomach cancer are reported in Eastern Asia and Eastern Europe [1].

Coadministration of zolbetuximab with mFOLFOX6 did not result in clinically meaningful changes in any drug exposure metrics [18], suggesting that no dose adjustments are required when using zolbetuximab and mFOLFOX6 in combination. This finding is also expected to be applicable to CAPOX, which contains capecitabine (prodrug of 5-FU) and oxaliplatin. Thus, no dose adjustments are necessary for the combination of zolbetuximab and CAPOX. In phase 3 clinical studies, there were no clinically relevant differences in chemotherapy-related safety outcomes between participants treated with zolbetuximab plus chemotherapy and those treated with chemotherapy only, which suggests clinical confirmation of the PK findings and conclusions.

The phase 3 SPOTLIGHT [15] and GLOW [16] studies demonstrated statistically significant and clinically meaningful benefits with a zolbetuximab regimen of 800/600 mg/m^2 Q3W and an overall favorable benefit–risk profile in individuals with G/GEJ adenocarcinoma. In these studies, the risk of disease progression or death was reduced by 25% in participants who received zolbetuximab plus mFOLFOX6 versus those who received placebo plus mFOLFOX6 and by 31% in participants who received zolbetuximab plus CAPOX versus those who received placebo plus CAPOX. Compared with participants in placebo groups, participants receiving zolbetuximab had a higher incidence of nausea and vomiting. These events were commonly observed during the first zolbetuximab infusion in the first cycle but were observed with lower frequency during subsequent doses/cycles and were manageable. Nausea and vomiting are considered related to inhibition of CLDN18.2 in normal gastric mucosa and are on-target toxicities. Preclinical data indicate that damage to the gastric mucosa may contribute to these AEs [21]. Exposure-response analysis suggested that higher zolbetuximab exposure could prolong PFS and OS but may also increase the probability of experiencing gastrointestinal safety events (e.g., nausea, vomiting, and abdominal pain) and IRRs.

The integrated data indicate that a proposed 800/400 mg/m^2 Q2W regimen will be comparable to the 800/600 mg/m^2 Q3W regimen used in zolbetuximab phase 3 studies in terms of both efficacy and safety [19]. Differences in zolbetuximab exposure metrics are not anticipated to affect the benefit–risk profile of zolbetuximab, and this assumption is corroborated by the exposure-response analysis for efficacy and safety. Thus, the Q2W regimen will be a valuable alternative to the Q3W regimen because it can be used in synchrony with chemotherapy regimens dosed on a Q2W basis (e.g., mFOLFOX6). This approach can help alleviate the logistical burdens on patients by streamlining dosing visits for zolbetuximab and chemotherapy and enhance overall treatment convenience.

Despite the murine origin of its variable domains, zolbetuximab is considered to have a low risk of immunogenicity in patients, given its intended clinical use. In the USA and other regions, zolbetuximab is approved for use in combination with fluoropyrimidine- and platinum-containing chemotherapy as first-line treatment in patients with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumors are CLDN18.2-positive. Such patients may have become immunocompromised for reasons including advanced age, perioperative chemotherapy, radiation therapy, or surgery. Furthermore, concomitant fluoropyrimidine- and platinum-containing chemotherapy may lead to myelosuppression and impaired function of immune cells when patients are exposed to zolbetuximab. Data from clinical studies confirmed a low incidence of ADA positivity. ADAs to zolbetuximab did not seem to have any clinically relevant impact on PK, efficacy, or safety in clinical studies. However, owing to the low incidence of ADAs in clinical studies, the ability to draw definitive conclusions from the current data is limited.

11 Conclusions

The recommended dose of zolbetuximab is 800/600 mg/m^2 IV Q3W. Analysis of available PK and clinical data supports the appropriateness of this regimen, regardless of patient ethnicity, mild/moderate renal impairment or mild hepatic impairment, or concomitant chemotherapy. ADAs to zolbetuximab appear to be uncommon and of no apparent clinical consequence. An 800/400 mg/m^2 Q2W regimen is an alternative and convenient dosing strategy for use in combination with chemotherapy administered on a similar schedule. Zolbetuximab, the first and only approved therapy targeted to CLDN18.2, is a valuable new treatment option for patients with CLDN18.2-positive, locally advanced unresectable or metastatic G/GEJ cancer.

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Declarations

Conflicts of Interest Kohei Shitara received personal fees for consulting and advisory roles from ALX Oncology, Amgen, Arcus Biosciences, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline K.K., Guardant Health Japan, Healios K.K., Janssen, Merck, Moderna, Novartis, Ono Pharmaceutical, Takeda, and Zymeworks; honoraria from Astellas, AstraZeneca, Bristol Myers Squibb, Janssen, and Ono Pharmaceutical; and research funding (all to institution) from Amgen, Astellas, AstraZeneca, Chugai Pharma, Daiichi Sankyo, Eisai, Merck, Ono Pharmaceutical, PPD-SNBL K.K., PRA Health Sciences, Taiho Pharmaceutical, and Toray, outside the submitted work. Rui-Hua Xu has nothing to report. David Ilson has nothing to report. Sara Lonardi served as consultant/advisor for Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, GSK, Helion, Incyte, Lilly, Merck Serono, MSD, Nimbus Therapeutics, Rottapharm, Servier, and Takeda; and invited speaker for Amgen, AstraZeneca, Bristol Myers Squibb, GSK, Incyte, Lilly, Merck Serono, MSD, Pierre Fabre, Roche, and Servier. Samuel J. Klempner served as consultant/advisor for Astellas, AstraZeneca, Bristol Myers Squibb, Coherus BioSciences, Daiichi Sankyo, Merck, Mersana Therapeutics, Natera, Novartis, Roche, Sanofi-Aventis, Scandion Oncology, and Servier; and reports prior stock/equity in Nuvalent and Turning Point Therapeutics. Jianning Yang, Akihiro Yamada, Yoko Ueno, Masato Takeuchi, Janet Pavese, Maria Matsangou, and Srinivasu Poondru are employees of Astellas. Tomasz Wojtkowski was an employee of Astellas at the time the study was conducted.

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Consent to Participate Not applicable.

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Availability of Data and Material Details for how researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials can be found at https://www.clinicaltrials.astellas.com/transparency/.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Wagner AD, Syn NLX, Moehler M, Grothe W, Yong WP, Tai BC, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;8(8):CD004064.
3. Jim MA, Pinheiro PS, Carreira H, Espey DK, Wiggins CL, Weir HK. Stomach cancer survival in the United States by race and stage (2001–2009): findings from the CONCORD-2 study. Cancer. 2017;123(Suppl 24):4994–5013.
4. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 2016;388(10060):2654–64.
5. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer. 2023;26(1):1–25.
6. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(10):1005–20.
7. Angerilli V, Ghelardi F, Nappo F, Grillo F, Parente P, Lonardi S, et al. Claudin-18.2 testing and its impact in the therapeutic management of patients with gastric and gastroesophageal adenocarcinomas: a literature review with expert opinion. Pathol Res Pract. 2024;254:155145.
8. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol. 2023;16(1):57.
9. Cao W, Xing H, Li Y, Tian W, Song Y, Jiang Z, et al. Claudin18.2 is a novel molecular biomarker for tumor-targeted immunotherapy. Biomark Res. 2022;10(1):38.
10. Baek JH, Park DJ, Kim GY, Cheon J, Kang BW, Cha HJ, et al. Clinical implications of claudin18.2 expression in patients with gastric cancer. Anticancer Res. 2019;39(12):6973–9.
11. Waters R, Sewastjanow-Silva M, Yamashita K, Abdelhakeem A, Iwata KK, Moran D, et al. Retrospective study of claudin 18 isoform 2 prevalence and prognostic association in gastric and gastroesophageal junction adenocarcinoma. JCO Precis Oncol. 2024;8:e2300543.
12. Kim HD, Choi E, Shin J, Lee IS, Ko CS, Ryu MH, et al. Clinicopathologic features and prognostic value of claudin 18.2 overexpression in patients with resectable gastric cancer. Sci Rep. 2023;13(1):20047.
13. Rohde C, Yamaguchi R, Mukhina S, Sahin U, Itoh K, Türeci Ö. Comparison of Claudin 18.2 expression in primary tumors and lymph node metastases in Japanese patients with gastric adenocarcinoma. Jpn J Clin Oncol. 2019;49(9):870–6.
14. Sahin U, Türeci Ö, Manikhas G, Lordick F, Rusyn A, Vynnychenko I, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann Oncol. 2021;32(5):609–19.
15. Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2023;401(10389):1655–68.

16. Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133–41.
17. Türeci Ö, Sahin U, Schulze-Bergkamen H, Zvirbule Z, Lordick F, Koeberle D, et al. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. Ann Oncol. 2019;30(9):1487–95.
18. Klempner SJ, Lee KW, Shitara K, Metges JP, Lonardi S, Ilson DH, et al. ILUSTRO: phase II multicohort trial of zolbetuximab in patients with advanced or metastatic claudin 18.2-positive gastric or gastroesophageal junction adenocarcinoma. Clin Cancer Res. 2023;29(19):3882–91.
19. Yamada A, Takeuchi M, Komatsu K, Bonate PL, Poondru S, Yang J. Population PK and exposure-response analyses of zolbetuximab in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma. Clin Transl Sci. 2025;18(7):e70280.
20. Ramanathan RK, Egorin MJ, Takimoto CHM, Remick SC, Doroshow JH, LoRusso PA, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol. 2008;26(4):563–9.
21. Kinugasa F, Kajikawa S, Weng J, Ugawa T, Fushiki H, Yamanaka Y, et al. Effect of antiemetics on zolbetuximab-induced gastric injury and emesis in ferrets. J Pharmacol Sci. 2024;156(3):161–70.