Zolbetuximab – Assessment of Alternative Dosing Regimens

Summary

- A PopPK and exposure-response analysis predicted similar efficacy and safety between the zolbetuximab 800/600 mg/m^2 Q3W regimen and 800/400 mg/m^2 Q2W for use in combination with chemotherapy.[1]
- Fixed-dosing was predicted to have higher variabilities in exposure, efficacy, and safety than BSA-normalized dosing in the PopPK and exposure-response analysis.[1]

PopPK and exposure-response analysis[1]

A PopPK analysis used data from eight clinical studies to characterize the PK of zolbetuximab in adult patients with advanced, CLDN18.2-positive G/GEJ adenocarcinoma.

The PopPK analysis was used to assess differences in zolbetuximab exposure with alternative dosing regimens and to characterize exposure-response relationships for safety and efficacy. The following dosing regimens were compared:

- Q3W dosing (800 mg/m^2 loading dose on C1D1 followed by 600 mg/m^2 Q3W) used in the Phase 3 clinical trials vs. Q2W dosing (800 mg/m^2 loading dose on C1D1 followed by 400 mg/m^2 Q2W)
- BSA-normalized dosing used in the Phase 3 clinical trials vs. fixed-dosing (1400 mg loading dose followed by 1000mg Q3W regardless of body size)

Results: Q3W vs. Q2W dosing

In the PopPK model, the relatively modest predicted differences in certain zolbetuximab exposure metrics between Q2W and Q3W dosing regimens were not considered clinically meaningful (Table 1).

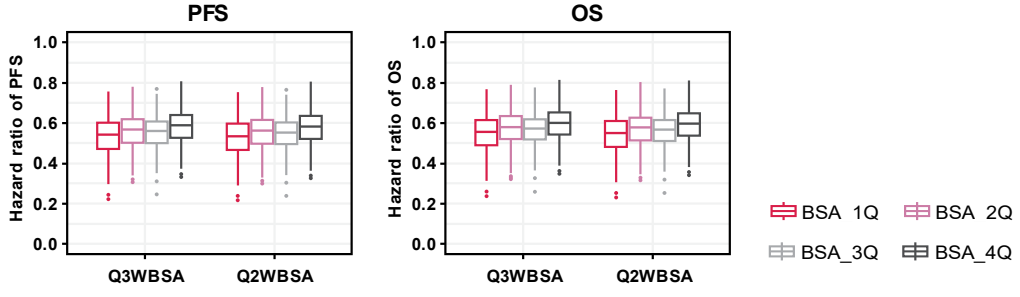
Table 1. GMRs for zolbetuximab exposure metrics for Q2W regimen (800/400 mg/m^2) relative to Q3W regimen (800/600 mg/m^2)[1]

Parameter	GMRs (90% CI) 800/400 mg/m^2 Q2W vs. 800/600 mg/m^2 Q3W	
	First 42-day dosing interval	Steady-state 42-day dosing interval
C_{max}	1.000 (0.984, 1.016)	0.792 (0.779, 0.804)
AUC_{21d}	1.119 (1.089, 1.115)	1.000 (0.976, 1.024)
C_{trough}	1.404 (1.329, 1.484)	1.192 (1.150, 1.235)
C_{ave}	1.018 (0.992, 1.044)	

Adapted from: Yamada et al., Clin Transl Sci 2025.

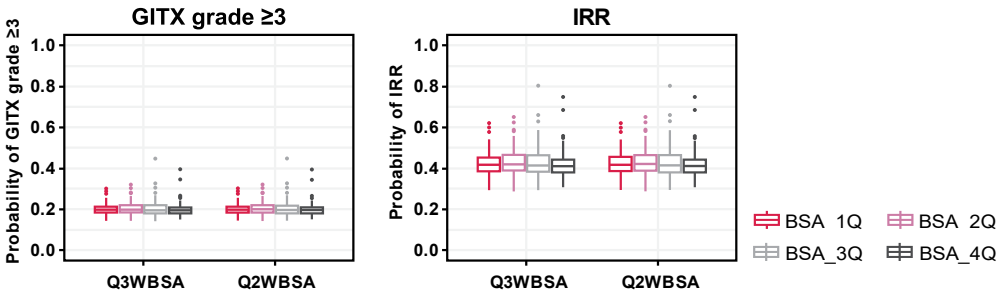
The exposure-response models also suggested similar efficacy and safety outcomes for Q2W and Q3W dosing regimens. The model-predicted hazard ratios for efficacy outcomes (PFS and OS) and safety events (GITX Grade ≥ 3 and IRRs) were similar between both dosing regimens (Figures 1 and 2).

Figure 1. Model-predicted hazard ratios of PFS and OS for zolbetuximab 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W regimens[1]



Adapted from: Yamada et al., Clin Transl Sci 2025.

Figure 2. Model-predicted probabilities of GITX Grade ≥ 3 and IRRs for zolbetuximab 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W regimens[1]

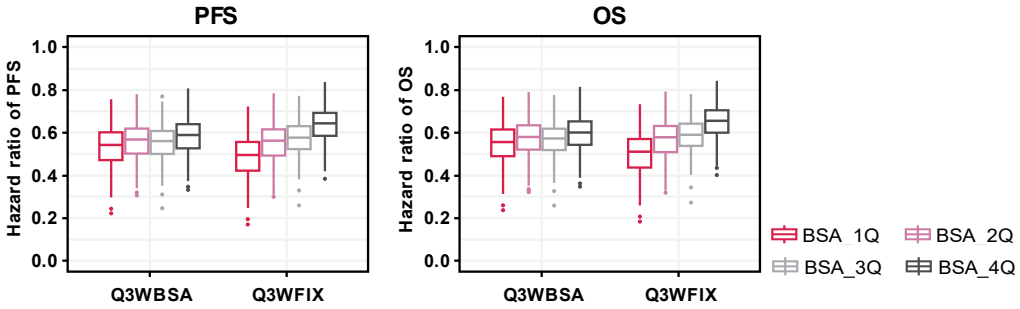


Adapted from: Yamada et al., Clin Transl Sci 2025.

Results: BSA-normalized vs. fixed-dosing[1]

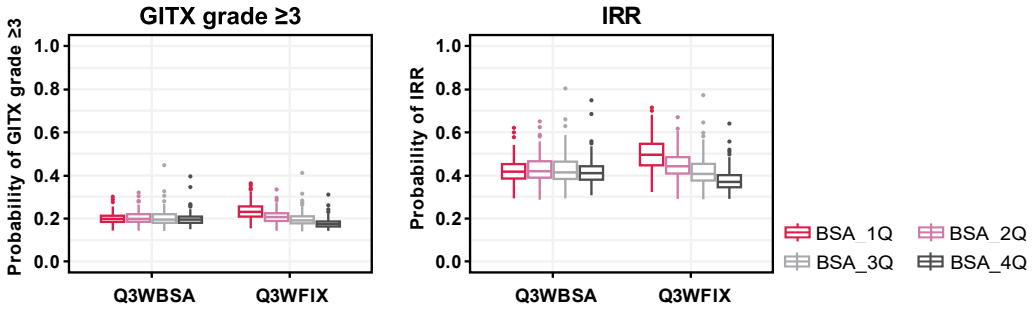
Across different BSA quartiles, a fixed-dosing regimen was predicted to have higher variabilities in drug exposure, efficacy outcomes (PFS and OS) and safety events (GITX Grade ≥3 and IRRs).

Figure 3. Model-predicted hazard ratios of PFS and OS for BSA-normalized and fixed-dosing regimens by BSA quartile[1]



Adapted from: Yamada et al., Clin Transl Sci 2025.

Figure 4. Model-predicted probabilities of GITX Grade ≥ 3 and IRRs for BSA-normalized and fixed-dosing regimens by BSA quartile[1]



Adapted from: Yamada et al., Clin Transl Sci 2025.

Abbreviations

AUC$_{21d}$: area under the concentration-time curve from the time of dosing to Day 21 postdosing; **BSA**: body surface area; **C1D1**: Cycle 1, Day 1; **C$_{ave}$**: average concentration throughout the treatment; **CLDN18.2**: claudin 18.2; **C$_{max}$**: maximum concentration; **C$_{trough}$**: trough concentration immediately prior to dosing at multiple dosing; **G/GEJ**: gastric/gastroesophageal junction; **GITX**: combined gastrointestinal toxicity (nausea, vomiting, and abdominal pain); **GMR**: geometric mean ratio; **IRR**: infusion related-reaction flagged by investigator; **OS**: overall survival; **PFS**: progression free survival; **PK**: pharmacokinetic; **PopPK**: population PK; **Q**: quartile; **Q2W**: every two weeks; **Q3W**: every three weeks; **Q3WBSA**: 800/600 mg/m^2 Q3W; **Q3WFIX**: 1400/1000 mg Q3W; **vs.**: versus.

References:

1. Yamada A, Takeuchi M, Komatsu K, et al. 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. Available at: https://doi.org/10.1111/cts.70280.