

Integrating Clinical Utility Index in Early Phase Oncology Trials: A Case Study With Antibody-Drug Conjugates

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OBJECTIVE

- To calculate the Clinical Utility Index (CUI) distribution between simulated pharmacokinetic exposure and efficacy and safety metrics for three clinically approved and one phase 1 Antibody Drug Conjugate (ADC).
- To determine the sensitivity of dose selection to the ratio of weights between efficacy and safety, and how this differs at different thresholding values for dose selection.

CONCLUSION

- Clinical Utility Indexes provide a quantitative method of combining exposure-response analyses for efficacy and safety to determine optimized dosing strategies.
 - Within clinically approved ADCs the weighting of efficacy to safety varies between 35:65% and 60:40% with an average of 45:55% at a 5% threshold to select the approved dose.
 - Varying the threshold shifted the required weightings by the change in threshold for SG and MIRV but twice that in EV, suggesting individual dose-selection relationships.
- Time invariance and data sparsity both limit the predictive power of the CUI by obfuscating efficacy and safety severity and removing dose specificity, respectively.

PAGE; Thessaloniki, Greece; June 3rd – 6th, 2025

METHODOLOGY

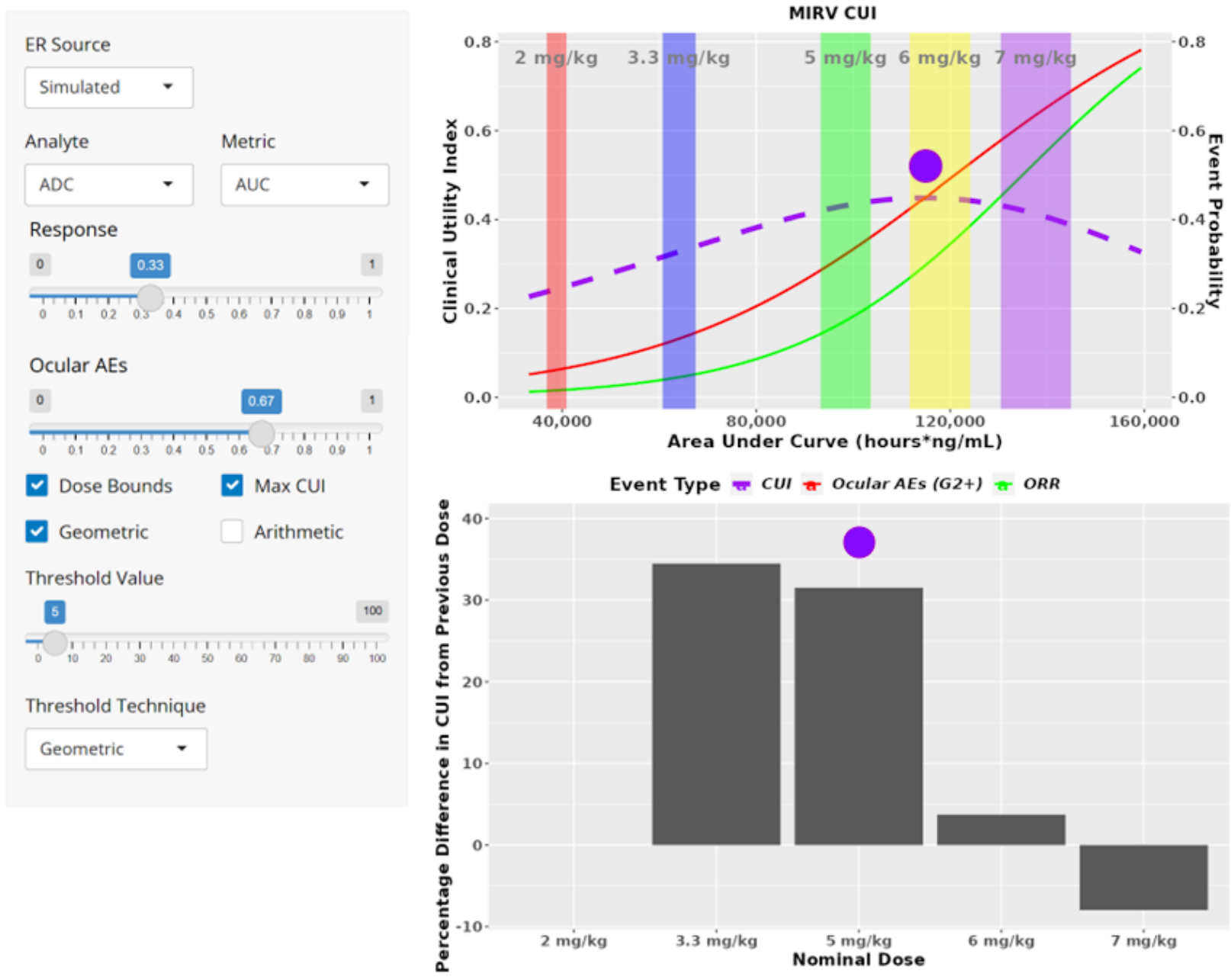
- A Clinical Utility Index is a method of combining exposure-response analyses for efficacy and safety for dose selection, PK and ER data used were digitised from publicly available sources.
- A geometric CUI is calculated by taking the product of all rate-of-efficacy metrics, $E_i(x)$, per an exposure metric, x , simulated from population pharmacokinetic models, raised to weights w_i , and multiplied by the product of 1 minus all rate-of-safety metrics, $AE_j(x)$, raised to weights w_j , where $\sum w_i + \sum w_j = 1$.

$$CUI(x) = \prod_{i=1}^n E_i(x)^{w_i} \times \prod_{j=1}^m (1 - AE_j(x))^{w_j}$$

- The CUI for a dose level, CUI_D , is calculated by taking the integral of the CUI values over the dosing interval, $x_{upper}(D)$ to $x_{lower}(D)$, and dividing this by the range of exposure metric values for that dose.

$$CUI_D = \frac{1}{x_u(D) - x_l(D)} \int_{x_l(D)}^{x_u(D)} CUI(x) dx$$

- The maximum value of this suggests the optimum dose if the percentage difference between it and all previous dose CUI values is greater than a given percentage threshold.



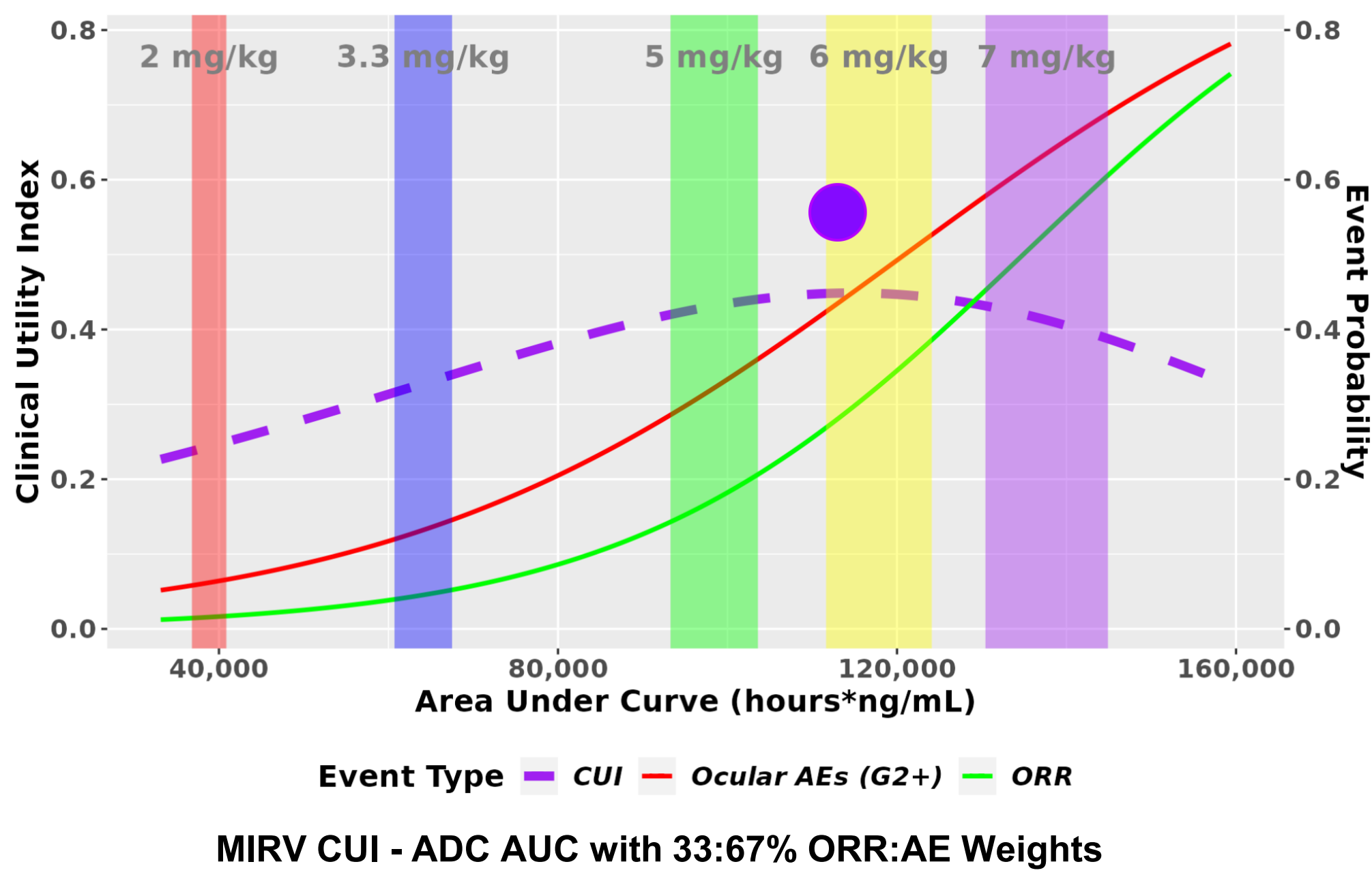
An R Shiny App built to calculate CUI values for ADCs

MIRVETUXIMAB SORAVTANSINE¹⁻²

Mirvetuximab CUI was parameterised from a combination of overall response rate and G2+ ocular adverse events

Weightings for approved 6 mg/kg AIBW Q3W dose:

- 0%: 0.29-0.42 w_{ORR}
- 5%: 0.35-0.48 w_{ORR}
- 10%: 0.40-0.53 w_{ORR}



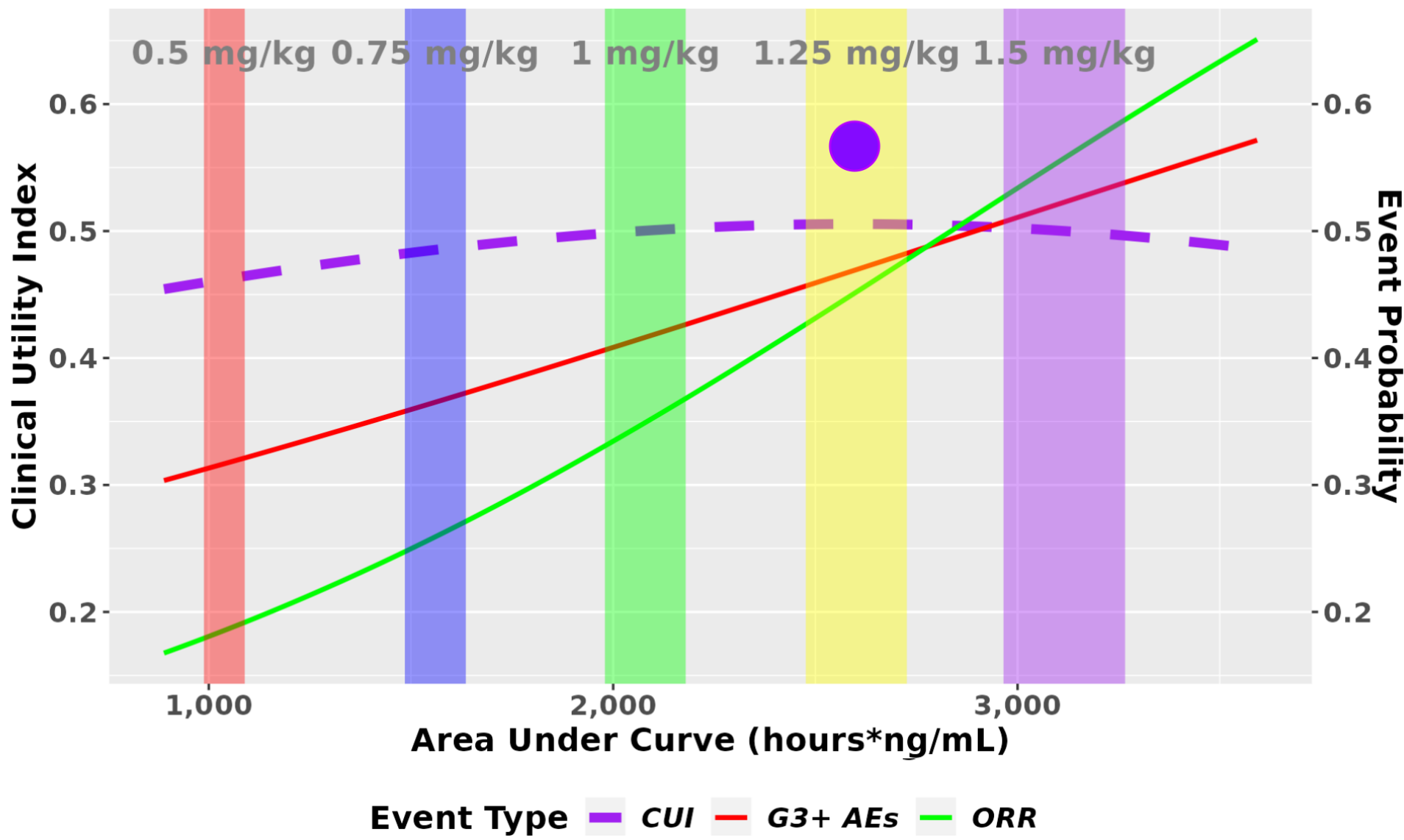
MIRV CUI - ADC AUC with 33:67% ORR:AE Weights

ENFORTUMAB VEDOTIN³⁻⁴

Enfortumab CUI was parameterised with overall response rate and rate of any G3+ adverse event

Weightings for approved D1/D8 per 21D cycle 1.25 mg/kg TBW dose:

- 0%: 0.28-0.33 w_{ORR}
- 5%: 0.41-0.49 w_{ORR}
- 10%: 0.55-0.63 w_{ORR}



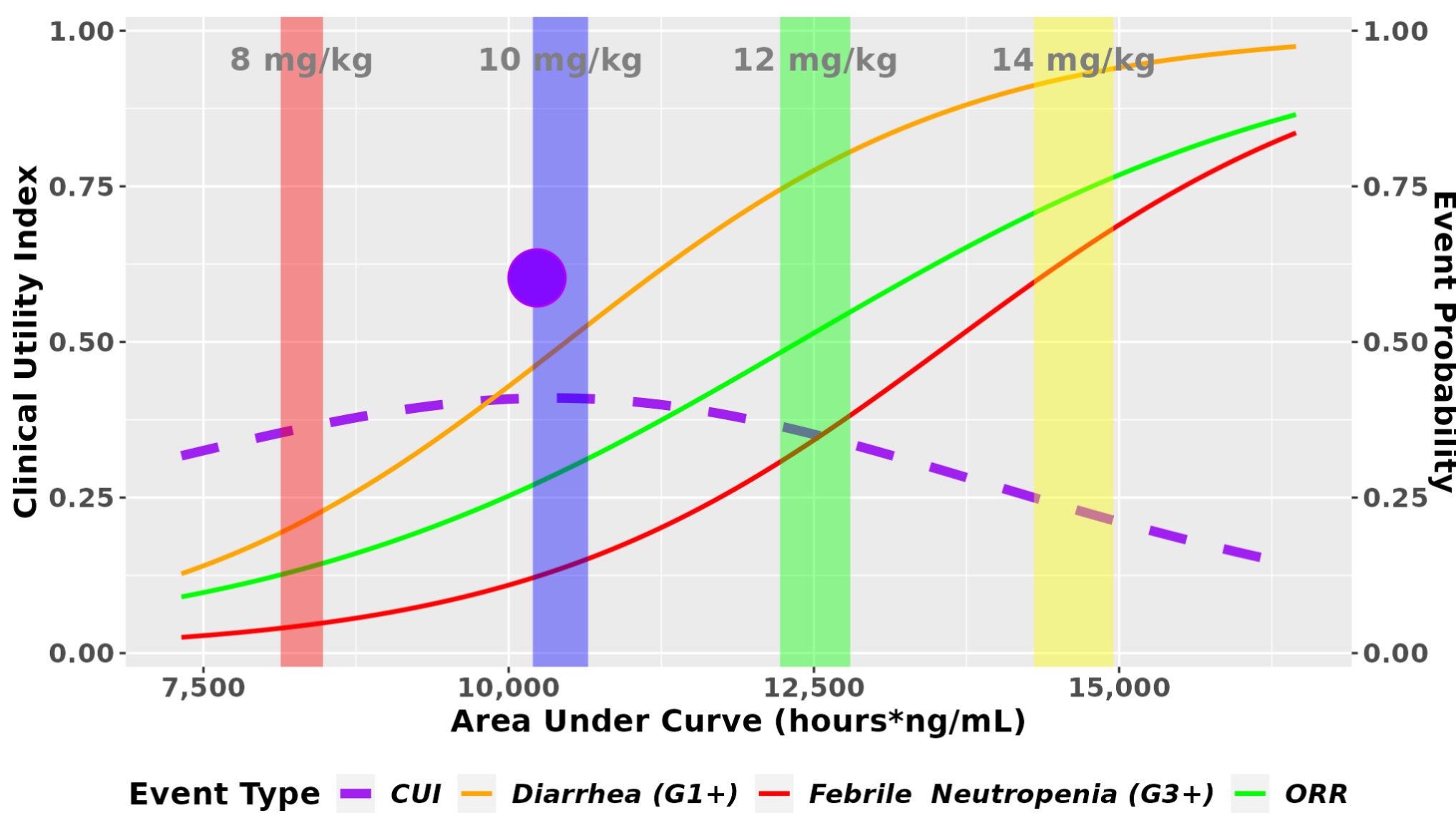
EV CUI - ADC AUC with 30:70% ORR:AE Weights

SACITUZUMAB GOVITECAN⁵⁻⁶

Sacituzumab CUI was parameterised with overall response rate, G3+ febrile neutropenia and G1+ diarrhea adverse events (7:1 AE ratio)

Weightings for approved D1/D8 per 21D cycle 10 mg/kg TBW dose:

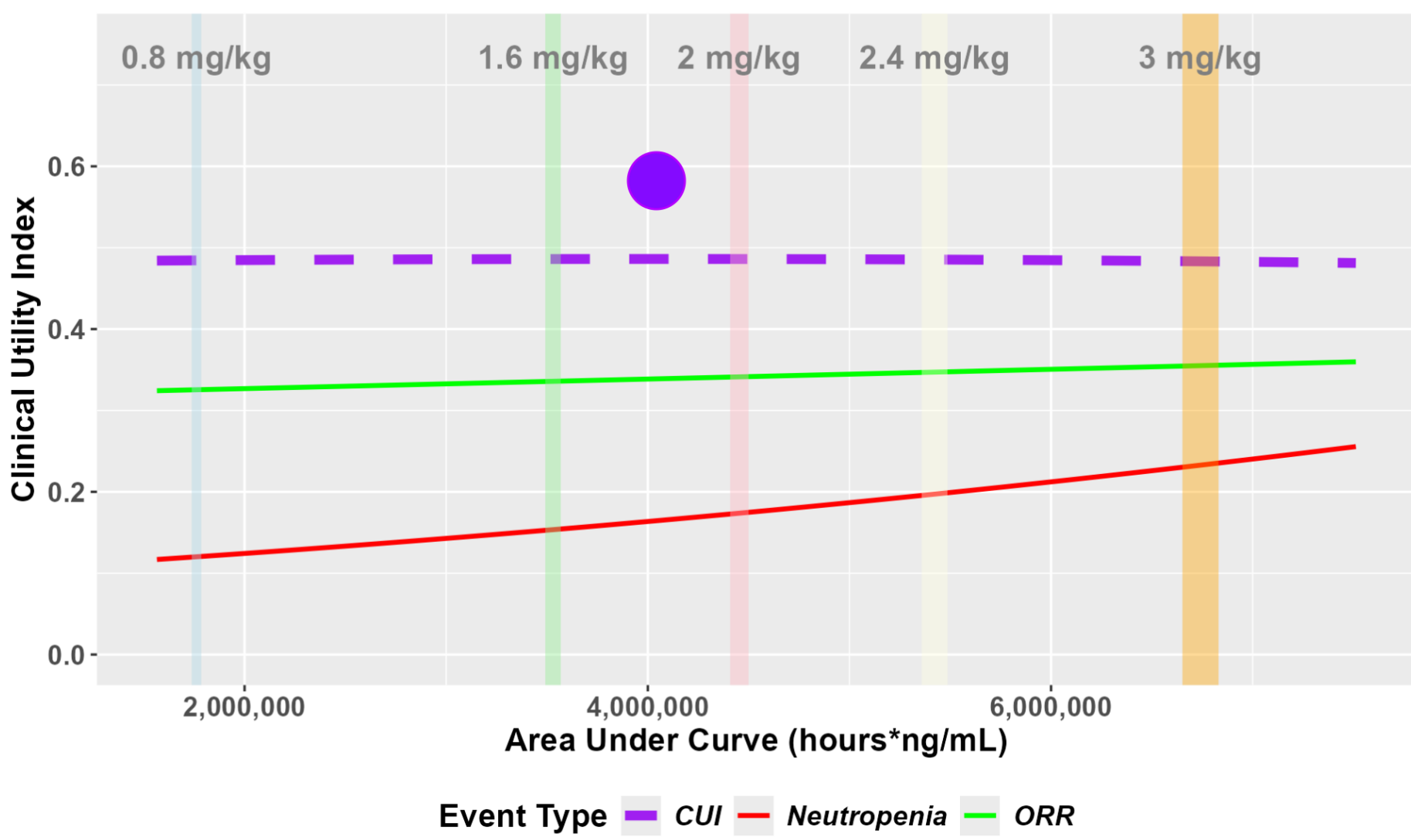
- 0%: 0.34-0.56 w_{ORR}
- 5%: 0.39-0.60 w_{ORR}
- 10%: 0.43-0.64 w_{ORR}



SG CUI - ADC AUC with 45:55% ORR:AE Weights

AZD5335⁷

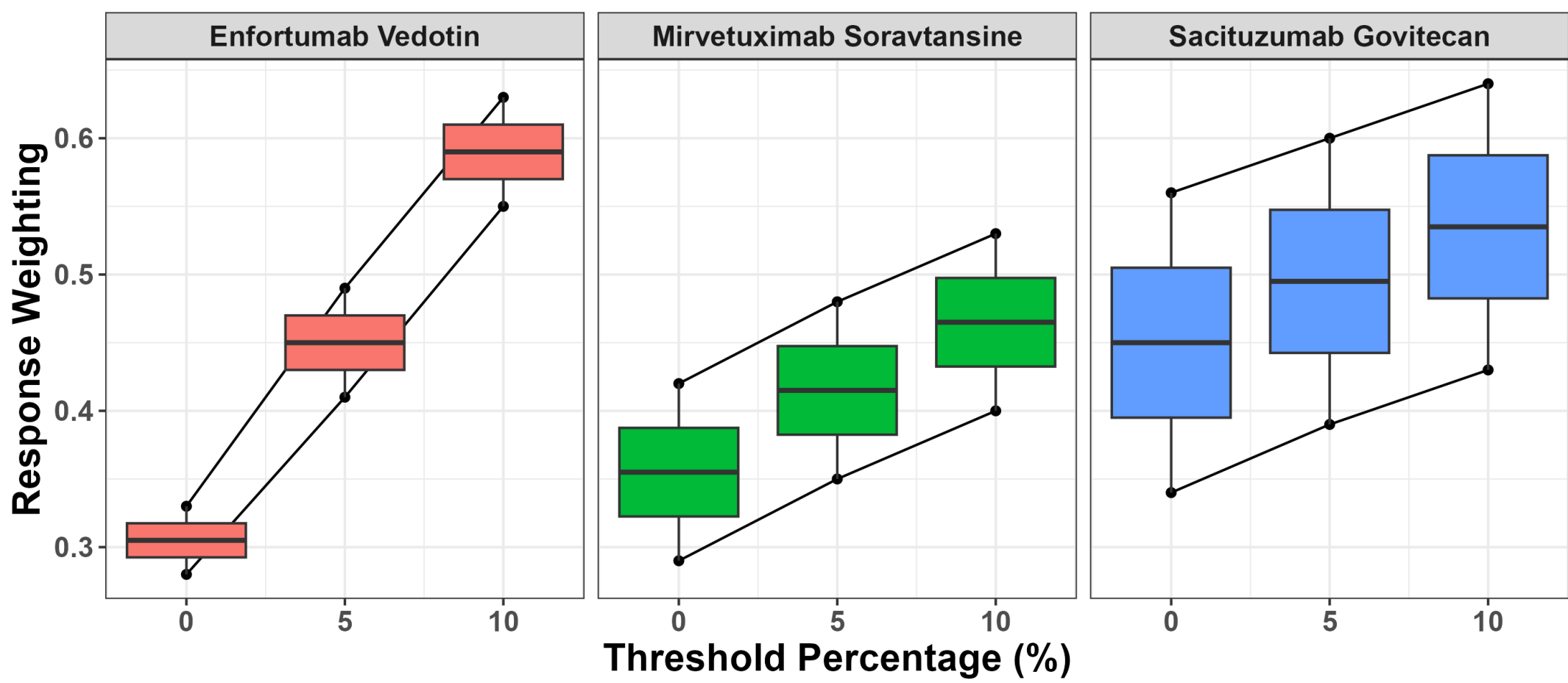
- AZD5335 CUI was Parameterised with overall response rate and rate of G3+ neutropenia
- AZD5335 is currently in phase 1 and has no approved dose
- The displayed CUI plot shows the limitation of insufficient data preventing causal relationships being drawn between dose and event probability



AZD CUI - ADC AUC with 60:40% ORR:AE Weights

DISCUSSION

- The CUI approach was able to predict the approved doses, however this varied inconsistently with the thresholding value, with SG and MIRV weightings increasing at the same rate but with a two-fold higher rate for EV.
- At a 5% thresholding value the response weightings required to select the approved dose were 45:55% between efficacy and safety. This increases to 53:47% at a 10% threshold.



Response Weighting by Threshold required to choose Clinical Dose

FUTURE WORK

- There are two limitations to overcome in the CUI approach, excluding the subjectivity of choosing weights, time invariance and data sparsity.
- Time invariance refers to the use of exposure metrics and the lack of time-to-event and time-of-event measures. This time component is being considered for internal ADC projects.
- Data sparsity is best seen in the AZD5335 CUI, where each dose group had <10 patients. Here Bayesian approaches are being tested within the same ADC class of target/payload to provide prior distributions and improve predictive power.

1. FDA, Multidiscipline Review for NDA 761310, U.S. Food and Drug Administration, 2022.
2. Tu YP et al, Population pharmacokinetics of mirvetuximab soravtansine in folate receptor-α positive ovarian cancer, Br J Clin Pharmacol, 2024.
3. FDA, Multidiscipline Review for NDA 761137, U.S. Food and Drug Administration, 2024.
4. Zuo P et al, Population pharmacokinetic modeling and exposure-response analysis for enfortumab vedotin in urothelial carcinoma, Clin Pharmacol Ther, 2024.
5. FDA, Multidiscipline Review for NDA 761115, U.S. Food and Drug Administration, 2020.
6. Sothe AG et al, Population pharmacokinetics of sacituzumab govitecan in metastatic triple-negative breast cancer and other solid tumors, Clin Pharmacokinet, 2024.
7. Shapiro-Frommer et al., European Society for Medical Oncology (ESMO) congress, Barcelona, Spain, 13–17 Sep, 2024.