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Comparative Analysis of Background Gastrointestinal Characteristics in Cambodian, Vietnamese, and Mauritian Cynomolgus Monkeys: Optimizing Model Selection in Preclinical Safety Assessment of Antibody-Drug Conjugates

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BACKGROUND

- Antibody-drug conjugates (ADCs) are a growing class of targeted cancer therapies, with 15 FDA approvals. Gastrointestinal (GI) toxicity is a frequent adverse effect, ranging from nausea and diarrhea to colitis and obstruction[1]. These clinical manifestations are due to the ADC cytotoxic payload being released in the GI tract, which can damage the mucosal cells lining the digestive tract, resulting in off-target effects and GI toxicity **(Figure 1)**[2].

- Cynomolgus monkeys (CMs) are a key nonclinical model for evaluating ADC safety. Our studies have shown that the baseline GI variability across geographic origins may confound the interpretation of ADC-related findings and complicate drug development. However, these baseline differences are not well characterized.

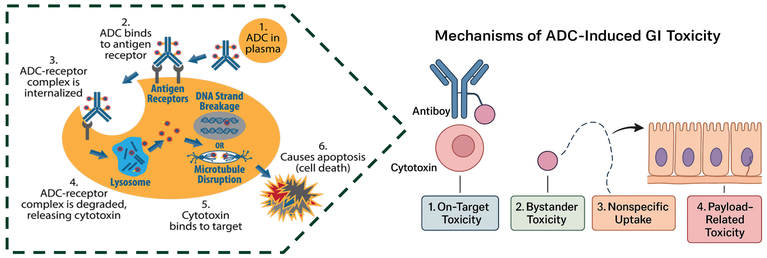

Figure 1. Mechanisms of ADCs-Related Gastrointestinal Toxicity[2]

OBJECTIVE

This study aims to **characterize and compare background GI features,** including microscopic findings, parasite burden, fecal abnormalities, and select clinical pathology (CP) differences, among Cambodian, Vietnamese, and Mauritian CMs, and to evaluate **implications for model selection in ADC toxicology studies.**

METHODS AND KEY RESULTS

- A systematic review of FDA-approved ADCs (*FDA label; Clinical & Nonclinical Reviews*[3]) showed that 9 of 15 were associated with GI toxicity, including mucosal irritation, inflammation, epithelial degeneration, diarrhea, or soft stool, in both clinical settings and CM models **(Table 1).**

- Background GI morphology-related data (lesion location/severity/distribution), parasite burden, fecal abnormalities, and select CP parameters were compiled from **Altasciences Pathology Historical Control Database and Reference Intervals (2020-2025)** for 2–4-year-old male and female CMs in 3–9-month toxicity studies.

- Data extraction, comparative analysis, and visualization were performed on Cambodian, Vietnamese, and Mauritian CMs using Certara's SEND Explorer **(Tables 2 and 3; Figure 2).**

- No notable differences were detected in the selected CP parameters **(Table 3).** Geographic variation was evident **(Table 2)**: Cambodian and Mauritian CMs exhibited comparable background GI morphologic features, whereas **Vietnamese CMs demonstrated a lower incidence of microscopic findings (mostly of inflammatory nature—infiltration, inflammation, granuloma), parasite burden, and fecal abnormalities, suggesting a more predictable background for ADC safety studies.**

Table 1. Comparison of Gastrointestinal (GI) Adverse Events and Nonclinical Findings (CMs) for FDA-Approved ADCs

ADC (Generic Name)	Brand Name	Company	Approval Year	Indication	Target	ROA	mAb	Linker	D-A Ratio#	Payload Class	Payload Action	Key Human GI AEs*	CMs GI Pathology*
Gemtuzumab ozogamicin	Mylotarg	Pfizer	2000	Acute myeloid leukemia	CD33	IV infusion	IgG1	pH-sensitive hydrazone	2-3	**Calicheamicin**	DNA cleavage	Nausea, vomiting, stomatitis/mucositis, diarrhea	Limited GI findings; sporadic mucosal degeneration/erosion only at high exposures[1]
Brentuximab vedotin	Adcetris	Seagen/Takeda	2011	Anaplastic large cell lymphoma	CD30	IV infusion	IgG1	valine-citrulline	4	**MMAE/auristatin**	Microtubule inhibitor	Nausea, diarrhea, vomiting, constipation, abdominal pain	GI mucosal/crypt injury with variable diarrhea (class effect in CMs)[2]
Trastuzumab emtansine	Kadcyla	Roche	2013	Breast cancer	HER2	IV infusion	IgG1	SMCC (non-cleavable)	3.5	**DM1/maytansinoid**	Microtubule inhibitor	Nausea, vomiting, constipation, diarrhea	Limited GI histopathology; soft stool/diarrhea[3]
Inotuzumab ozogamicin	Besponsa	Pfizer	2017	B-cell precursor acute lymphoblastic leukemia	CD22	IV infusion	IgG1	pH-sensitive hydrazone	6	**Calicheamicin**	DNA cleavage	Nausea, vomiting, abdominal pain, stomatitis	Limited GI findings; sporadic mucosal degeneration/erosion only at high exposures[1]
Moxetumomab pasudotox	Lumoxiti	AstraZeneca	2018	Hairy cell leukemia	CD22	IV infusion	IgG1	NA (directly fused to mAb)	1	**PE38/Pseudotoxin**	Inhibition of protein synthesis	Nausea, vomiting, diarrhea	No prominent GI findings
Polatuzumab vedotin-piiq	Polivy	Roche	2019	Large B-cell lymphoma	CD79	IV infusion	IgG1	valine-citrulline	3.5	**MMAE/auristatin**	Microtubule inhibitor	Diarrhea, nausea, constipation, abdominal pain	GI mucosal/crypt injury with variable diarrhea (class effect in CMs)[2]
Enfortumab vedotin	Padcev	Astellas/Seagen	2019	Urothelial cancer	Nectin-4	IV infusion	IgG1	valine-citrulline	3.8	**MMAE/auristatin**	Microtubule inhibitor	Decreased appetite, nausea, diarrhea; vomiting	GI mucosal/crypt injury with variable diarrhea (class effect in CMs)[2]
Trastuzumab deruxtecan	Enhertu	AstraZeneca/Daiichi Sankyo	2019	Breast cancer	HER2	IV infusion	IgG1	maleimide tetrapeptide	8	**DXd/camptothecin**	TOP1 inhibitor	Nausea, vomiting, decreased appetite, diarrhea, stomatitis (common)	GI epithelial degeneration/necrosis with inflammation in monkeys; decreased food intake/diarrhea[4]
Sacituzumab govitecan	Trodelvy	Gilead	2020	Breast cancer	Trop-2	IV infusion	IgG1	pH-sensitive hydrolyzable	7.6	**SN-38/camptothecin**	TOP1 inhibitor	Severe diarrhea (boxed warning); nausea, vomiting, abdominal pain	Crypt cell apoptosis/degeneration with inflammation; diarrhea common in topo-I inhibitor–sensitive species[4]
Belantamab mafodotin-blmf	Blenrep	GSK	2020	Multiple myeloma	BCMA	IV infusion	IgG1	maleimidocaproyl (non-cleavable)	4	**MMAF/auristatin**	Microtubule inhibitor	Nausea, diarrhea, decreased appetite	Limited GI pathology reported
Loncastuximab tesirine-lpyl	Zynlonta	ADC Therapeutics	2021	Large B-cell lymphoma	CD19	IV infusion	IgG1	valine-citrulline	2.3	**SG3199/PBD dimer**	DNA crosslinking	Nausea, constipation, diarrhea	GI lesions generally limited
Tisotumab vedotin-tftv	Tivdak	Seagen	2021	Cervical cancer	Tissue factor	IV infusion	IgG1	valine-citrulline	4	**MMAE/auristatin**	Microtubule inhibitor	Nausea, constipation, diarrhea; stomatitis less frequent	GI mucosal/crypt injury with variable diarrhea (class effect in CMs)[2]
Mirvetuximab soravtansine	Elahere	ImmunoGen	2022	Ovarian cancer	FRα	IV infusion	IgG1	disulfide	3.4	**DM4/maytansinoid**	Microtubule inhibitor	Nausea, vomiting, diarrhea; abdominal pain; decreased appetite	Limited GI histopathology[4]
Datopotamab deruxtecan	Datroway	AstraZeneca/Daiichi Sankyo	2025	Breast cancer	Trop-2	IV infusion	IgG1	maleimide tetrapeptide	4	**DXd/camptothecin**	TOP1 inhibitor	Stomatitis/oral mucositis, nausea, vomiting; diarrhea	GI epithelial degeneration/necrosis with inflammation in monkeys; decreased food intake/diarrhea[4]
Telisotuzumab vedotin	Emrelis	AbbVie	2025	Non-small cell lung cancer	c-Met	IV infusion	IgG1	valine-citrulline	3.1	**MMAE/auristatin**	Microtubule inhibitor	Nausea, diarrhea, decreased appetite, vomiting	GI mucosal/crypt injury with variable diarrhea (class effect in CMs)[2]

Note: *FDA label, Clinical & Nonclinical Reviews; # The specific DAR is achieved by conjugating the payload to the antibody via the protease-cleavable linker.
ADC class effects (payload-driven): 1. Calicheamicin ADCs (Mylotarg®, Besponsa®): FDA reviews highlight hepatotoxicity as dominant; GI findings are limited. **2. Vedotin ADCs** (MMAE): FDA nonclinical reviews consistently describe GI epithelial/crypt injury and diarrhea in NHPs. **3. Maytansinoid ADCs** (DM1 or DM4): GI tract nonclinical findings limited to soft stool/occasional diarrhea. **4. Deruxtecan ADCs** (DXd): FDA pharmacology reviews report GI epithelial degeneration/necrosis with inflammation in NHPs at clinically relevant exposures. **5. SN-38 ADCs** (Trodelvy®): FDA boxed warning for severe diarrhea in humans; NHP studies show crypt apoptosis/degeneration typical of topo-I inhibitors.

❖ This table highlights concordance (green) and divergence (red) between human GI AEs and NHP GI pathology data across FDA-approved ADCs.
❖ Divergence may reflect species-specific mechanisms, exposure differences, or GI system variability across geographic origins in CMs, indicating potential species sensitivity that may confound interpretation.

Table 2. Variability of Baseline GI System Parameters Across CM Geographic Origins

GI Parameter*	Cambodian CMs	Mauritian CMs	Vietnamese CMs
Microscopic Findings	Inflammatory cell infiltration, crypt and gland abscess, inflammation, erosion, ulceration, and hemorrhage (Overall incidence rate or OIR: 19%)	Inflammatory cell infiltration, crypt abscess, granuloma, parasitic granuloma, inflammation, erosion, ulceration, hemorrhage, and depletion (OIR: 11%)	Fewest GI background findings with inflammatory cell infiltration as the most common findings; cleaner baseline histology (OIR: 6%)
Fecal Abnormalities	Frequent soft or liquid stools, mucous content, variable color (black or blue) (OIR: 7%)	Occasional soft or liquid stools, variable color (black or blue); less frequent than Cambodia (OIR: 5%)	Infrequent soft stools; normal fecal consistency predominates (OIR: 3%)
Parasite Burden	High prevalence (OIR: 7%)	Moderate prevalence (OIR: 4%)	Low prevalence (OIR: 1-2%)
Parasite Types (reference data)[4]	Diverse protozoa & helminths; Protozoa (highly prevalent: *Entamoeba coli*, *Endolimax nana*, *Blastocystis sp.* other: *Iodamoeba bütschlii*, *Chilomastix mesnili*, *Balantidium coli*)	Similar to Cambodian with lower burden	Fewer parasite species; often managed in breeding colonies
Interpretation Impact	High variability may confound GI toxicity interpretation	Moderate variability; manageable with controls	More suitable for GI-sensitive ADC toxicology studies

Note: Vietnamese CMs offer the cleanest baseline GI background, making them preferable for GI-focused ADC safety evaluations. *Detailed GI parameter HCD available upon request.

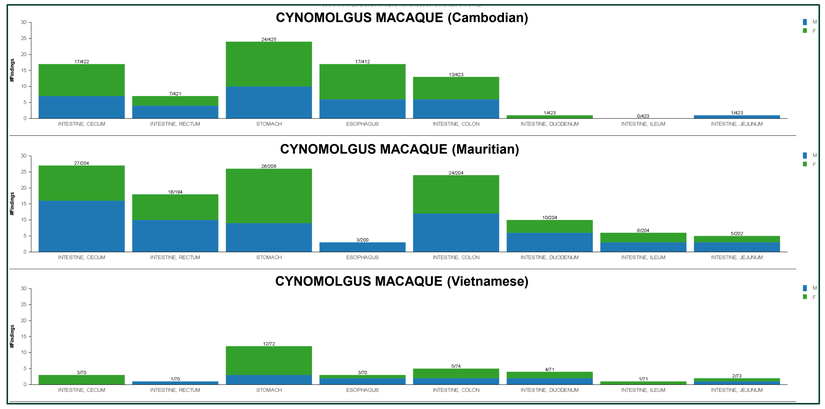

Figure 2. Illustration of Background GI Microscopic Findings Across CM Geographic Origins

Table 3. Select CP Reference Intervals (Baseline) Across CM Geographic Origins

Hematology	Cambodian CM		Mauritian CM		Vietnamese CM	
Hemoglobin (g/dL)	M: 13.5 (11.7-15.0)	F: 13.3 (11.7-14.7)	M: 13.6 (12.0-15.1)	F: 12.8 (11.3-14.3)	M: 13.4 (12.2-15.1)	F: 13.1 (11.7-14.6)
Reticulocyte (^6/µL)	M: 0.068 (0.027-0.164)	F: 0.070 (0.030-0.130)	M: 0.032 (0.012-0.090)	F: 0.041 (0.013-0.121)	M: 0.060 (0.030-0.130)	F: 0.060 (0.030-0.120)
White Blood Cell (^3/µL)	M: 10.68 (5.88-20.07)	F: 10.75 (5.92-20.91)	M: 11.27 (6.24-21.91)	F: 11.85 (6.55-22.88)	M: 12.72 (7.02-24.56)	F: 12.32 (6.83-20.79)
Neutrophils (^3/µL)	M: 4.48 (1.40-12.94)	F: 5.24 (2.04-12.82)	M: 4.07 (1.46-15.10)	F: 5.63 (1.81-15.75)	M: 4.96 (1.97-12.69)	F: 6.00 (2.18-15.04)
Lymphocytes (^3/µL)	M: 5.17 (2.33-11.30)	F: 4.52 (2.07-11.10)	M: 5.63 (2.83-10.61)	F: 5.03 (2.44-9.64)	M: 6.05 (2.63-15.97)	F: 5.03 (2.56-12.31)
Clinical Chemistry						
Albumin (g/dL)	M: 4.3 (3.6-4.9)	F: 4.3 (3.6-4.9)	M: 4.5 (4.1-5.1)	F: 4.4 (3.8-4.9)	M: 4.4 (3.7-4.9)	F: 4.3 (3.5-4.8)
Total Protein (g/dL)	M: 6.9 (6.1-7.9)	F: 7.0 (6.0-7.8)	M: 7.5 (6.8-8.2)	F: 7.5 (6.7-8.2)	M: 7.2 (6.4-8.0)	F: 7.1 (6.3-7.8)
Cholesterol (mg/dL)	M: 130 (85-283)	F: 131 (88-191)	M: 100 (69-144)	F: 102 (72-140)	M: 131 (85-191)	F: 129 (83-183)
Fibrinogen (mg/dL)	M: 236 (165-426)	F: 226 (166-333)	M: 201 (145-275)	F: 187 (130-286)	M: 258 (188-383)	F: 230 (166-366)
Sodium (mEq/L)	M: 148 (143-154)	F: 148 (143-154)	M: 148 (143-154)	F: 147 (143-152)	M: 148 (143-154)	F: 147 (143-152)
Chloride (mEq/L)	M: 107 (102-111)	F: 107 (102-112)	M: 107 (103-112)	F: 108 (103-112)	M: 105 (101-110)	F: 106 (102-110)
Potassium (mEq/L)	M: 4.4 (3.6-5.9)	F: 4.3 (3.6-5.5)	M: 4.3 (3.7-5.3)	F: 4.3 (3.6-5.3)	M: 4.3 (3.6-5.4)	F: 4.2 (3.5-5.4)

Note: Median (2.5%ile - 97.5%ile) value presented for illustration purpose. Complete reference intervals available upon request.

CONCLUSION

- This study highlights the CMs GI system control and baseline data (across geographic origins) curation workflows based on the established Altasciences pathology HCD and reference interval database to populate single-animal data using SEND Explorer.

- Distinct geographic differences were observed: Cambodian and Mauritian CMs had comparable background GI morphologic features, whereas Vietnamese CMs exhibited lower incidences of similar background morphologic features and fecal abnormality, suggesting a more predictable background for ADC safety studies.

- Identifying origin differences offers insights into optimizing model selection to improve data interpretation in pivotal ADCs toxicity studies, enabling more accurate translational outcomes.

- These efforts have produced a unique source of curated control and baseline animal data that in the future may be considered in the development of Virtual Control Groups (VCGs) in nonclinical toxicity studies.

References:
1. Shi, et al., BMC Pharmacol Toxicol 26, 50 (2025). 2. Nguyen, et al., Cancers 15, 713 (2023). 3. FDA website: approved ADCs label and Clinical & Nonclinical Reviews. 4. Zanzani et al., Parasitol Res. 115(1):307 (2016).

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