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Phase I study of AMT-676, an anti-CDH17 antibody-drug conjugate, in patients with advanced CRC and other GI tumors

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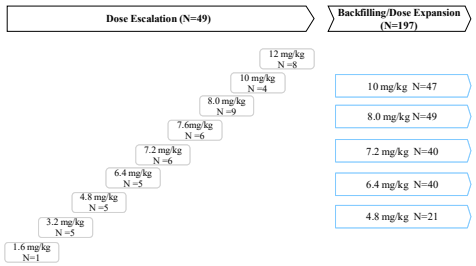
Background

- Cadherin-17 (CDH17) is highly expressed in colorectal cancer (CRC) and multiple gastrointestinal (GI) malignancies.
- AMT-676 is a novel antibody-drug conjugate (ADC) comprising a humanized anti-CDH17 IgG1 antibody conjugated to the topoisomerase I inhibitor exatecan (DAR=4) via a proprietary T-moiety linker.
- AMT-676 demonstrated robust anti-tumor efficacy in preclinical studies representing a wide range of solid tumor indications, including but not limited to colorectal cancer, gastric cancer, esophageal adenocarcinoma, cholangiocarcinoma, pancreatic ductal cancers, and neuroendocrine tumors.
- This first-in-human study evaluated the safety, pharmacokinetics (PK), and preliminary antitumor activity of AMT-676 in patients with advanced GI tumors.

Methods

This ongoing open-label Phase Ia/Ib study (NCT06400485) is being conducted in Australia, China, and the US. AMT-676 was administered IV Q3W at doses from 1.6 to 12 mg/kg using a Bayesian optimal interval (BOIN) design. Primary objectives were safety and tolerability; secondary objectives included PK and preliminary efficacy. Tumor CDH17 expression was retrospectively assessed by IHC. Backfilling enrollment was initiated at selected dose cohorts.

Figure 1: Study Design



Results

- As of May 22, 2026, 246 patients with CRC and other GI tumors have been treated with AMT-676 across AUS (63.0%), CN (27.6%) and US (9.3%). Patient demographics are Caucasian (58.1%), Asian (37.0%) and Others (4.9%).
- Among 191 CRC patients, median prior lines = 3 (range 1–9); 54.5% are Caucasian.
  - 68.6% had liver metastasis and 75.9% had lung metastases at baseline.
  - 92.7% had received prior Irinotecan, 98.4% had received Oxaliplatin, 33.0% had received TAS-102, indicating a heavily pretreated population.

Table 1: Overall Patients Demographics

Characteristics	Colorectal Cancer (N=191)	Others (N=55)	Total (N=246)
Age in years, median (range)	56.0 (27-78)	61.0 (34-88)	57.0 (25-88)
Sex, n (%)			
Male	106 (55.5%)	39 (70.9%)	145 (58.9%)
Female	85 (44.5%)	16 (29.1%)	101 (41.1%)
ECOG, n (%)2			
0	100 (52.4%)	27 (49.1%)	127 (51.6%)
1	91 (47.6%)	28 (50.9%)	119 (48.4%)
Race, n (%)			
Asian	76 (39.8%)	15 (27.3%)	91 (37.0%)
Caucasian	104 (54.5%)	39 (70.9%)	143 (58.1%)
Others or Unknown	11 (5.8%)	1 (1.8%)	12 (4.9%)
Median number of prior therapies (range)	3.0 (1-9)	2.0 (1-6)	3.0 (1-9)

Table 2: CRC Patients Demographics

Characteristics		Total (N=191) % in all CRC
Primary Location	Colon, left	80 (41.9%)
	Colon, right	37 (19.4%)
	Rectum	71 (37.2%)
	Primary site unknown	3 (1.6%)
Metastatic Site	Lung metastases	145 (75.9%)
	Liver metastases	131 (68.6%)
	Peritoneal metastases	46 (24.1%)
Biomarker	KRAS mutation	104 (54.5%)
	NRAS mutation	12 (6.3%)
	BRAF mutation	13 (6.8%)
	MSS	176 (92.1%)
Prior therapies		**Total (N=191) % in all CRC**
Irinotecan		177 (92.7%)
Oxaliplatin		188 (98.4%)
TAS-102 (tipiracil/trifluridine)		63 (33.0%)
Anti-EGFR antibody (cetuximab, panitumumab)		83 (43.5%)
Anti-VEGF antibody (bevacizumab)		157 (82.2%)

Results

Efficacy

- Among efficacy-evaluable CRC patients across doses 7.2-12 mg/kg (N=100), the objective response rate (ORR) was 20% (17 confirmed partial responses [PRs] and 3 unconfirmed PRs with the patients still on treatment), and the disease control rate (DCR) was 91% (Table 3).
- At 8 mg/kg (N=47), ORR was 26% with 25 patients remaining on treatment. Data for the 10–12 mg/kg cohorts are preliminary.
- Responses were observed irrespective of CDH17 expression levels in CRC patients.
- The half-life of AMT-676 was 4–6 days, consistent with other clinical ADCs and supportive of Q3W administration.
- Patients with RAS wild-type achieve a higher ORR compared with those harboring RAS mutations. (Figure 5).

Figure 2: Best response in CRC

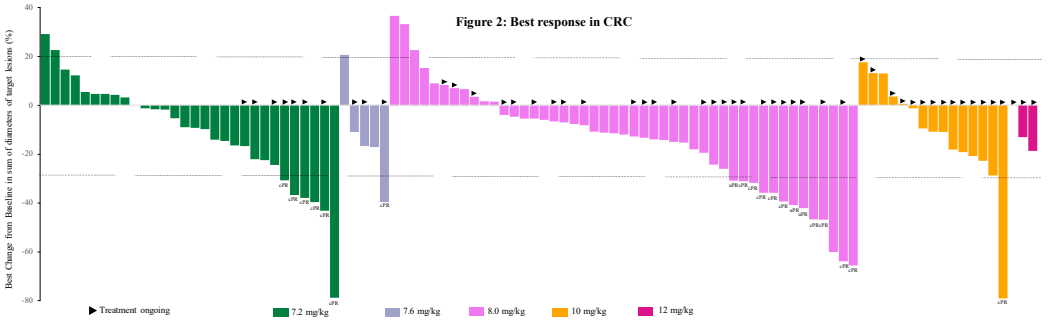


Figure 3: Swimmer plot in CRC

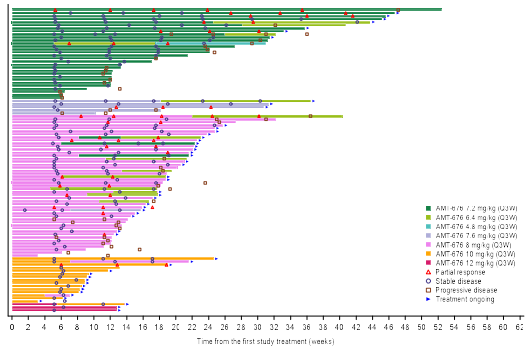


Figure 4: PK profile of AMT-676

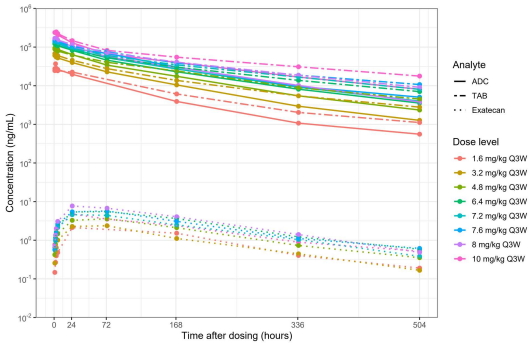
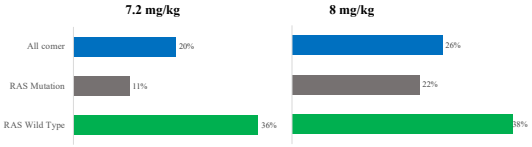


Table 3: Responses in CRC

	7.2 mg/kg (N=30)	7.6 mg/kg (N=5)	8 mg/kg (N=47)	10 mg/kg (N=15)	12mg/kg (N=3)	Total (N=100)
ORR (incl. unconfirmed), n (%)	6 (20)	1 (20)	12 (26)	1 (7)	0	20 (20)
Confirmed ORR, n (%)	6 (20)	1 (20)	9 (19)	1 (7)	0	17 (17)
DCR, n (%)	27 (90)	4 (80)	42 (89)	15 (100)	3 (100)	91 (91)
Median follow-up time, month	4.3	5.6	4	1.4	1.5	3.2

Figure 5: Responses by RAS status



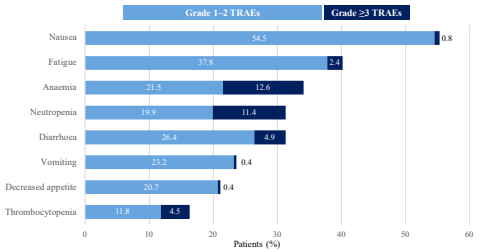
Safety

- The most common TRAEs were gastrointestinal and hematologic toxicities, mostly mild and clinically manageable.
- The most frequent reasons for dose modifications were neutropenia, followed by anaemia and thrombocytopenia.
- One treatment-related Grade 5 event (neutropenic sepsis) occurred at 10 mg/kg after a single 1000 mg dose in a CRC patient.
- Only one Grade 2 pneumonitis event was observed at 8 mg/kg of the entire study.
- One DLT each occurred at the 8 mg/kg and 12 mg/kg cohorts, with Grade 3 colitis and febrile neutropenia in the respective dose groups.
- MTD was not reached after escalated to 12mg/kg.

Table 4: Safety Summary

N (%)	Total (N = 246)
Any TEAE	237 (96.3%)
Grade ≥3	125 (50.8%)
Treatment-related TEAE (TRAE)	230 (93.5%)
Grade ≥3	72 (29.3%)
Grade 4	12 (4.9%)
Grade 5	1 (0.4%)
Any SAE	86 (35.0%)
Treatment-related SAE	28 (11.4%)
TRAEs leading to dose modifications	
Treatment discontinuation	4 (1.6%)
Treatment cycle delay	51 (20.7%)
Dose reduction	28 (11.4%)

Figure 6: TRAEs of Any Grade Occurring in ≥ 10% of Patients



Conclusion

- **AMT-676, a first-in-class CDH17 ADC, is highly differentiated with its DAR4 exatecan payload design to overcome irinotecan resistance while balancing potency and safety.**
- **Dose escalation/optimization ongoing with 246 patients enrolled in predominantly Caucasian population (58.1%). 191/246 are CRC patients.**
- **Favorable safety profile with low Gr3+ TRAE rates supports dose optimization and future combination strategies.**
- **Promising response rates in CRC (≥20% ORR at doses ≥7.2 mg/kg), with a clear dose-response relationship. Emerging response enrichment in RAS wild-type patients (>35% ORR). Preliminary efficacy also observed in other GI tumors.**
- **Data collected so far strongly support continuing clinical development of AMT-676 in the planned randomized Phase 3 trial for CRC.**
- **A clinical trial of AMT-676 in combination with chemotherapy in front-line CRC setting is ongoing.**

Declaration of Interests
Dr. Charlotte Lemech has no conflict of interests to declare

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Contact us at info@multitudetherapeutics.com for questions or comments

Acknowledgments
We would like to thank the patients and their families, as well as the investigators, clinical research personnel and staff for their participation and contributions to the trials. These studies were sponsored by Multitude Therapeutics.

Presented at ESMO Gastrointestinal Cancers Congress, Munich Germany, 1-4 July 2026