First-in-human study of DM002, an anti-MUC1-C/HER3 bispecific antibody-drug conjugate, in patients with advanced solid tumors

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Background

Figure 1: DM002 Molecular Design

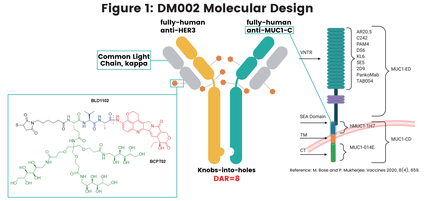
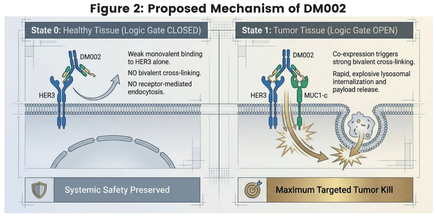


Figure 2: Proposed Mechanism of DM002



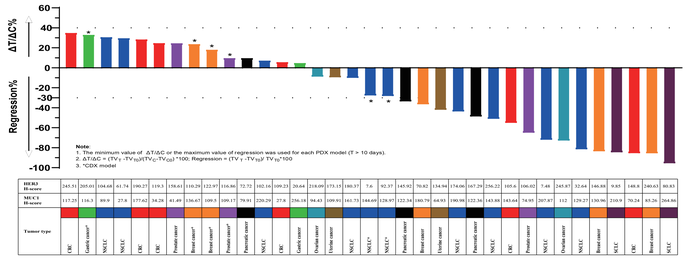
DM002 is a novel bispecific antibody-drug conjugate (BsADC) that targets the proteins MUC1-C and HER3, which are frequently co-expressed in advanced solid tumors and are involved in tumor growth, metastasis, and therapeutic resistance (**Figure 2**).

DM002 utilizes a fully humanized bispecific antibody conjugated to a topoisomerase I inhibitor payload via a cleavable linker, enabling selective delivery of cytotoxic payloads to tumor cells (**Figure 1**).

Dual targeting of MUC1-C and HER3 may enhance tumor selectivity and overcome resistance mechanisms associated with HER-family signaling. In preclinical studies, DM002 demonstrated robust antitumor activity across multiple PDX/CDX tumor models(**Figure 3**).

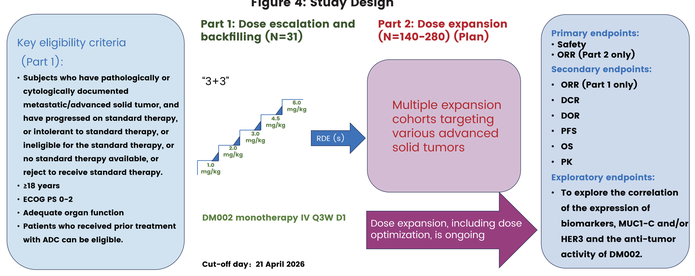
This first-in-human study evaluated the safety, pharmacokinetics, and preliminary antitumor activity of DM002 in patients with advanced solid tumors.

Figure 3: Best Response in PDX&CDX Models



Methods

Figure 4: Study Design



- Patients are treated with DM002 (Q3W D1) IV administration from 1 mg/kg to 6 mg/kg until disease progression or intolerable toxicity.
- The first 10-20 subjects may be randomized at 1:1 to two dose levels in each cohort of Part 2 expansion part to do further dose optimization.

Results

Figure 5: Antitumor activity of DM002 in solid tumors

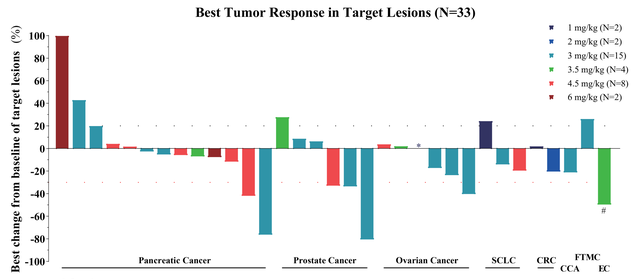
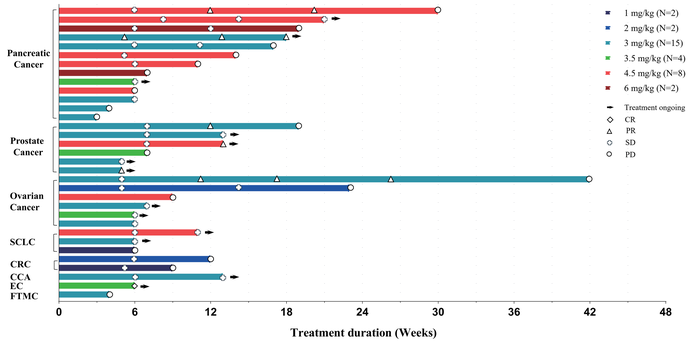


Figure 6: Swimmer plot of treatment time and antitumor activity of DM002 in solid tumors



Efficacy:

- **Encouraging Antitumor Activity:** As of the data cutoff, 33 heavily pretreated patients were evaluable for efficacy. DM002 demonstrated meaningful tumor regression and preliminary clinical benefit across multiple dose cohorts.
- **Deep and Broad Responses:** Meaningful tumor regression was observed across multiple dose cohorts. Highlights include one unconfirmed complete response (CR) in a patient with endometrial carcinoma at 3.5 mg/kg, and six partial responses (PRs; 3 confirmed, 3 unconfirmed) across the 3.0 mg/kg (N=4) and 4.5 mg/kg (N=2) cohorts.
- **Compelling Disease-Specific Efficacy:** DM002 demonstrated notable activity in traditionally recalcitrant solid tumors:
  - **Prostate Cancer**: Highly encouraging response rate with 3 PRs observed among 6 evaluable patients.
  - **Pancreatic Cancer**: 2 confirmed PRs among 13 evaluable patients, with one patient continuing treatment with ongoing, continuous tumor shrinkage.
  - **Ovarian Cancer**: Highly durable response observed; one patient with clear cell ovarian carcinoma achieved a confirmed PR and has remained on treatment for >9 months.

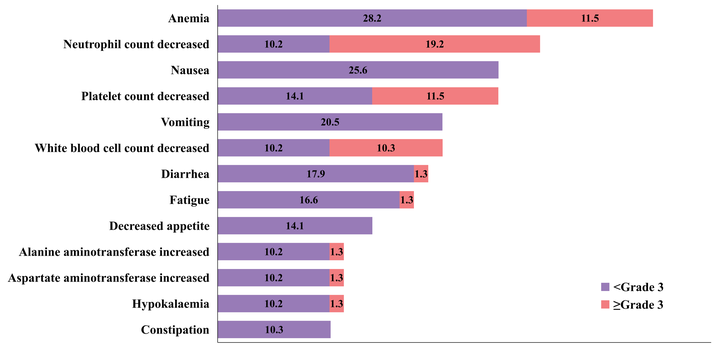
Table 1: Baseline of Characteristics

Median age, years (range)	61 (33-80)
Sex, n	
Female	39
Male	39
Race	
Asian	39
White	31
Other	8
Base line PS, n	
0	19
1	59
Tumor Type, n	
Pancreatic cancer	34
Ovarian cancer	17
Prostate cancer	8
Breast cancer	3
Endometrial cancer	3
Other solid tumors	13
Prior treatment lines, median	
Systemic therapy	2 (1-7)

Table 2: Summary of Safety Profile (N=78)

All TEAEs	55(70.5%)
Grade ≥3	23 (29.5%)
All TRAEs	48 (61.5%)
Grade ≥3	21 (26.9%)
TESAEs	12 (15.4%)
TRSAEs	9 (11.5%)
TEAEs leading to dose delay	15 (19.2%)
TRAEs leading to dose delay	13 (16.7%)
TEAEs leading to dose reduction	8 (10.3%)
TRAEs leading to dose reduction	8 (10.3%)
TEAEs leading to discontinuation	2 (2.6%)
TRAEs leading to discontinuation	2 (2.6%)
TEAEs leading to death	1 (1.3%)
TRAEs leading to death	0

Figure 7: Most common TEAEs (≥10% of all the patients, N=78)



Safety:

- **Manageable Safety Profile**: Overall, DM002 monotherapy demonstrated a predictable and manageable safety profile.
- **Favorable Therapeutic Window**: No dose-limiting toxicities (DLTs) were observed in cohorts up to 4.5 mg/kg. At the 6.0 mg/kg dose level, two patients experienced reversible, hematology-related DLTs (3 episodes).The maximum tolerated dose (MTD) is 4.5 mg/kg.
- **Predictable Adverse Events**: The most frequent treatment-emergent adverse events (TEAEs, all grades) were primarily hematologic and gastrointestinal: anemia (39.7%), decreased neutrophil count (29.4%), decreased platelet count (25.6%), decreased white blood cell count (20.5%), vomiting (20.5%), and diarrhea (19.2%).
- **Manageable High-Grade Events**: Grade ≥3 TEAEs were exclusively hematologic, including decreased neutrophil count (19.2%), anemia (11.5%), decreased platelet count (11.5%), and decreased white blood cell count (10.3%).
- **No Treatment-Related Deaths**: Importantly, there were no treatment-related adverse events (TRAEs) leading to death.

Conclusions

Preliminary results from the first-in-human study of the novel anti-MUC1-C/HER3 bispecific ADC DM002 (NCT06751329) demonstrated:

- A manageable and generally well-tolerated safety profile in patients with previously treated advanced/metastatic solid tumors.
  - -The most common TEAEs were hematologic and gastrointestinal, and were clinically manageable with appropriate supportive care.
  - -No ILD/pneumonitis events were reported.
- Encouraging preliminary antitumor activity across multiple dose levels in heavily pretreated patients with advanced solid tumors.
- Dose expansion and dose-optimization efforts are ongoing, with additional patients across multiple tumor types currently being enrolled.

DM002 exhibited a favorable pharmacokinetic profile

The exposure of DM002 increased approximately proportional to dose with $T_{1/2}$ of 74~99 h. The PK parameters of total antibody were similar to those of DM002, suggesting that DM002 was stable in the circulation. The exposure of BCPT02 in the blood was much lower than that of DM002.

Acknowledgements

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All authors have no conflicts of interest to disclose.