FIH Phase I dose escalation and expansion study of anti-HER2 ADC MRG002 in patients with HER2 positive solid tumors

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BACKGROUND

MRG002 is an antibody-drug conjugate(ADC) composed of a humanized anti-HER2 monoclonal antibody conjugated to monomethyl auristatin E (MMAE), via a valine-citrulline (vc) linker. MRG002 is presently being investigated as monotherapy in an ongoing Phase I study for safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity in patients (pts) with HER2 positive advanced or metastatic solid tumors.

OBJECTIVE

Primary Objectives

- **Phase Ia**: To identify Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)
- **Phase Ib:** safety and tolerability

Secondary Objectives

- **Phase Ia:** Pharmacokinetic (PK), immunogenicity (ADA), antitumor activity
- **Phase Ib:** antitumor activity, PK, ADA

Exploratory Objectives

- Assess HER2 expression and amplification level in tumor specimens and correlation with efficacy indicators of tumor response

METHODS

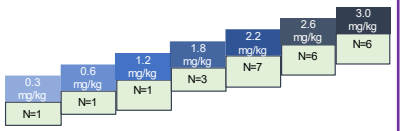
KEY Eligibility Criteria

1.Expected survival time ≥ 12 weeks;
2.Patients with histologically and/or cytologically confirmed HER2-positive solid tumors who have failed standard therapy or for whom no standard therapy exists or standard therapy is not appropriate;
3.Patients must have at least one evaluable lesion (Phase Ia) or measurable lesion (Phase Ib) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1);
4.Score of ECOG for performance status is 0 or 1;
5.Prior anti-tumor treatment-related AEs (NCI CTCAE v5.0 Criteria) have recovered to ≤ Grade 1 (except alopecia);
6.No severe cardiac dysfunction with left ventricular ejection fraction (LVEF) ≥ 50%;
7.Organ functions must meet the basic requirements;
8.Coagulation function must meet the basic requirements;
9.Cumulative anthracycline dose ≤ 360 mg/m^2 doxorubicin or its equivalent, 720 mg/m^2 epirubicin.

RESULTS

In Phase Ia dose escalation utilizing a "3+3" design to identify MTD/RP2D **(Figure1)**, a total of 25 pts with breast cancer (BC) (n=19), salivary gland cancer (SGC) (n=3), gastric cancer (GC) (n=2), and colorectal cancer (CRC) (n=1) were enrolled to identify MTD/RP2D. The starting dose of MRG002 was 0.3 mg/kg, followed by 0.6, 1.2, 1.8, 2.2, 2.6, and 3.0 mg/kg, and all pts with BC and GC were HER2 positive per CAP guidelines. For the other tumor types, pts were IHC 2+ or 3+, regardless of HER2 FISH status. Enrolled pts received MRG002 every three weeks (Q3W) for a maximum of 8 cycles.

Figure 1. Phase Ia **dose escalation**



1 SGC patient in 1.8mg/kg, 1 SGC patient and 1GC patient in 2.2 mg/kg,1CRC patient in 2.6 mg/kg, 1 GC patient and 1SGC in 3.0 mg/kg.

Table 1. Patient demographics and baseline characteristics

Characteristic	Patients (N = 25)
Age	
Median (range) — years	53 (33–66)
Sex	
Males, n (%)	5 (20)
Females, n (%)	20 (50)
ECOG performance -status score , n (%)	
1	25 (100)
The median number of prior therapies	5 (1, 11)

The median age was 53 (30, 66) years. The median number of prior therapies was 5 (1,11) **(Table 1)**. Among 22 pts who had at least one tumor assessment, 10 PR (45%), 8 SD (36%) .The investigator assessed ORR was 45% and the DCR was 82%. Of these 22 pts, 17 pts were breast cancer, 9 PR, 4 SD, and ORR was 53% (9/17), DCR was 76% (13/17) **(Figure 2-3)**.
The terminal elimination half-life ($T_{1/2}$) of MRG002 was approximately 2 days at 2.6 mg/kg.
Commonly observed treatment-emergent adverse events (TRAEs) were neutrophil count decreased (56%), aspartate aminotransferase (AST) increased (56%), white blood cell (WBC) decreased (56%), lactate dehydrogenase increased (44%), alopecia (44%), creatine phosphokinase (CPK) increased (40%), alanine aminotransferase (ALT) increased (36%), triglyceride increased (32%), cholesterol increased (32%), gamma-glutamyl transpeptidase(GGT) increased (32%), appetite decreased (32%), and hypoaesthesia (32%). Majority of AEs were mild to moderate in severity. The most commonly reported TRAEs ≥ Grade 3 were neutrophil count decreased and triglycerides increased in 3 pts (12%), respectively. The treatment-related Serious Adverse Events (SAEs) were reported in 6 pts (24%) including GGT increased, AST/ALT increased, neutrophil count decreased, LEVF decreased, fatigue, peripheral neuropathy.
There were 4 Dose-limiting toxicities events (DLTs) occurred in the dose escalation phase, including 1 DLT (Grade 3 AST/ALT increased) at 2.2 mg/kg, 1 DLT (Grade 3 GGT increased) at 2.6 mg/kg, and 2 DLTs (1 Grade 3 CPK increased and 1 Grade 3 LVEF decreased) at the maximum administered dose level of 3.0 mg/kg, and MTD/RP2D was determined to be 2.6 mg/kg **(Table 3)**.

Figure 2. Duration of treatment by patient

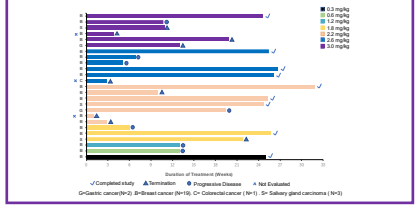


Figure3. Change from Baseline in Tumor Size

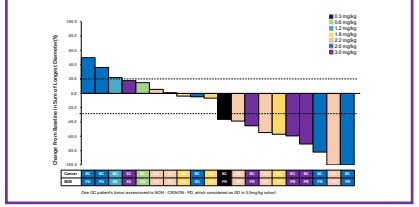


Table 3. Safety Summary

Adverse Events[a]	Dose Cohort (mg/kg) 0.3 (n=1) n (%)	0.6 (n=1) n (%)	1.2 (n=1) n (%)	1.8 (n=3) n (%)	2.2 (n=7) n (%)	2.6 (n=6) n (%)	3.0 (n=6) n (%)	Total (n=25) n (%)
Total Patients with AEs	1 (100)	1 (100)	1 (100)	3 (100)	7 (100)	6 (100)	6 (100)	25 (100)
Grade 1-2	1 (100)	1 (100)	1 (100)	3 (100)	7 (100)	6 (100)	6 (100)	25 (100)
≥ Grade 3	1 (100)	0	0	3 (100)	2 (29)	3 (50)	5 (83)	14 (56)
Death	0	0	0	0	0	0	0	0
SAEs	0	0	0	2 (67)	3 (43)	1 (17)	1 (17)	7 (28)
Treatment Discontinuation	0	0	0	1 (33)	1 (14)	1 (17)	1 (17)	4 (16)
Patients with MRG002 Related AEs[b]	1 (100)	1 (100)	1 (100)	3 (100)	7 (100)	6 (100)	6 (100)	25 (100)
Grade 1-2	1 (100)	1 (100)	1 (100)	3 (100)	7 (100)	6 (100)	6 (100)	25 (100)
≥ Grade 3	1 (100)	0	0	3 (100)	2 (29)	3 (50)	5 (83)	14 (56)
Death	0	0	0	0	0	0	0	0
SAEs	0	0	0	2 (67)	2 (29)	1 (17)	1 (17)	6 (24)
Treatment Discontinuation	0	0	0	1 (33)	1 (14)	1 (17)	1 (17)	4 (16)

Common TRAEs (PT) ≥ 30%	Total (n = 25) 25 (100%)
Neutrophil count decreased	14 (56)
AST increased	14 (56)
WBC decreased	14 (56)
Lactate dehydrogenase increased	11 (44)
Alopecia	11 (44)
CPK increased	10 (40)
ALT increased	9 (36)
Triglyceride increased	8 (32)
Cholesterol increased	8 (32)
GGT increased	8 (32)
Appetite decreased	8 (32)
Hypoaesthesia	8 (32)

≥G3 TRAEs ≥ 10%	6 (24%)
Neutrophil count decreased	3 (12)
Triglycerides increased	3 (12)
Treatment-related SAEs	**6 (24%)**
GGT increased	1 (4)
AST/ALT increased	1 (4)
Neutrophil count decreased	1 (4)
LEVF decreased	1 (4)
Fatigue	1 (4)
Peripheral neuropathy	1 (4)

DLT Events

Dose Cohort (mg/kg)	Patient ID	Preferred Term	Action Taken	CTCAE Grade	Causality
1.8	E01006*	Blood triglycerides increased	Treatment no change	3	Possibly related
2.2	E01007	AST/ALT increased	Study discontinuation	3	Possibly related
2.6	E01014	GGT increased	Study discontinuation	3	Definitely related
3.0	E01020	Creatine kinase increased	Treatment no change	3	Possibly related
	E06002	LEVF decreased	Study discontinuation	3	Possibly related

[a] All AEs reported from the time of first dose of MRG002 in first patient to the date of cutoff (26 Aug 2021).
[b] Investigator assessment of relatedness.
* DLT exception approved by Ethics Committee.
Based on Common Terminology Criteria for Adverse Events(CTCAE) Version 5.0

CONCLUSIONS

The dose escalation of MRG002 showed manageable safety profile and encouraging antitumor activity in pts with HER2 positive solid tumors including BC, GC and other tumor types, the MTD/RP2D was determined to be 2.6 mg/kg. MRG002 is currently being investigated in Phase Ib dose expansion and exploratory Phase II studies.

Acknowledgments:

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Disclosure:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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