Supplementary Data

First-in-human Phase 1 Study of MORAb-202, An Antibody–drug Conjugate Comprising Farletuzumab Linked to Eribulin Mesylate, in Patients with Folate Receptor-α-positive Advanced Solid Tumors

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Table S1. Additional patient characteristics

Characteristic	MORAb-202 dose					
	0.3 mg/kg (n=3)	**0.45 mg/kg (n=3)**	**0.68 mg/kg (n=6)**	**0.9 mg/kg (n=7)**	**1.2 mg/kg (n=3)**	**Total (N=22)**
Weight (kg), median (IQR)	51.80 (48.0–73.8)	46.80 (44.7–58.1)	62.40 (55.7–73.4)	53.80 (50.9–68.9)	52.10 (47.1–56.6)	54.75 (48.0–67.8)
Tumor type, n (%)						
Ovarian	1 (33)	3 (100)	2 (33)	4 (57)	2 (67)	12 (55)
Endometrial	2 (67)	0	0	1 (14)	0	3 (14)
Breast	0	0	1 (17)	1 (14)	0	2 (9)
Non-small cell lung cancer	0	0	3 (50)	1 (14)	0	4 (18)
Fallopian tube	0	0	0	0	1 (33)	1 (5)
Number of previous anticancer medications, n (%)						
0	0	0	0	1 (14)	0	1 (5)
1	1 (33)	0	0	1 (14)	0	2 (9)

2	1 (33)	1 (33)	2 (33)	2 (29)	0	6 (27)
≥3	1 (33)	2 (67)	4 (67)	3 (43)	3 (100)	13 (59)

IQR, interquartile range

Table S2. Summary of treatment-emergent adverse events according to MORAb-202 dose and adverse event grade

n (%)	0.3 mg/kg (n=3)				0.45 mg/kg (n=3)				0.68 mg/kg (n=6)				0.9 mg/kg (n=7)				1.2 mg/kg (n=3)			
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Any treatment-related adverse event	1 (33)	1 (33)	1 (33)	0	2 (67)	0	0	0	1 (17)	4 (67)	0	1 (17)	1 (14)	5 (71)	1 (14)	0	1 (33)	2 (67)	0	0
Leukopenia	0	2 (67)	0	0	0	0	0	0	1 (17)	2 (33)	0	0	2 (29)	1 (14)	0	0	0	2 (67)	0	0
Neutropenia	1 (33)	1 (33)	0	0	0	0	0	0	0	3 (50)	0	0	0	3 (43)	0	0	0	2 (67)	0	0
ALT increased	1 (33)	0	1 (33)	0	0	0	0	0	1 (17)	0	0	0	2 (29)	1 (14)	1 (14)	0	0	0	0	0
Anemia	0	1 (33)	0	0	0	0	0	0	1 (17)	1 (17)	0	0	0	2 (29)	0	0	0	1 (33)	0	0
AST increased	1 (33)	1 (33)	0	0	0	0	0	0	0	0	0	0	1 (14)	3 (43)	0	0	0	0	0	0
Nausea	1 (33)	0	0	0	0	0	0	0	2 (33)	0	0	0	1 (14)	0	0	0	1 (33)	0	0	0
Pyrexia	1 (33)	0	0	0	0	0	0	0	1 (17)	0	0	0	2 (29)	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	1 (17)	0	0	0	0	1 (14)	0	0	1 (33)	0	0	0
Fatigue	0	0	0	0	0	0	0	0	1 (17)	0	0	0	2 (29)	0	0	0	0	0	0	0
GGT increased	0	0	1 (33)	0	0	0	0	0	0	0	0	0	1 (14)	0	1 (14)	0	0	0	0	0
Malaise	0	0	0	0	1 (33)	0	0	0	1 (17)	0	0	0	0	0	0	0	1 (33)	0	0	0
Nasopharyngitis	0	0	0	0	0	0	0	0	1 (17)	0	0	0	1 (14)	0	0	0	1 (33)	0	0	0
Pneumonitis	0	0	0	0	0	0	0	0	0	0	0	0	1 (14)	2 (29)	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0	0	0	0	0	1 (14)	0	0	0	1 (33)	0	0	0
Cough	0	0	0	0	0	0	0	0	0	0	0	0	2 (29)	0	0	0	0	0	0	0
Eye disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (67)	0	0	0
Hypoalbuminemia	1 (33)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (33)	0	0

Ileus	0	0	1 (33)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (33)	0	0
Lipase increased	0	0	1 (33)	0	0	0	0	0	0	0	0	0	1 (14)	0	0	0	0	0	0	0
Lymphopenia	0	1 (33)	0	0	0	0	0	0	0	0	0	0	0	1 (14)	0	0	0	0	0	0
Oropharyngeal pain	1 (33)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (33)	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0	1 (33)	0	0
Vomiting	0	0	0	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0	1 (33)	0	0
Amylase increased	0	0	0	0	0	0	0	0	0	0	0	1 (17)	0	0	0	0	0	0	0	0

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.

If a subject had two or more adverse events in the same preferred term with different Common Terminology Criteria for Adverse Events (CTCAE) grades, then the event with the highest grade was used for that subject.

Adverse events of grade 3 or 4 are all listed. Grade 1 or 2 events are listed by preferred term for events occurring in at least 5% of all subjects.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4

Table S3. Summary of preliminary pharmacokinetic parameters of released eribulin

Parameter	MORAb-202 dose, mg/kg									
	Cycle 1					Cycle 2				
	0.3 (n=3)	**0.45 (n=3)**	**0.68 (n=6)**	**0.9 (n=7)**	**1.2 (n=3)**	**0.3 (n=3)**	**0.45 (n=3)**	**0.68 (n=6)**	**0.9 (n=6)**	**1.2 (n=3)**
C_{max}[a] (ng/mL)	0.2[c]	0.3 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.2[c]	0.4 ± 0.2	0.4 ± 0.1	0.6 ± 0.3	0.5 ± 0.1
t_{max}[b] (h)	71[c]	71 (71–71)	71 (71–167)	71 (71–71)	71 (71–71)	71[c]	71 (71–167)	71 (71–71)	71 (71–71)	71 (71–71)
$AUC_{(0-t)}$[a] (ng.h/mL)	4.9[c]	9.2 ± 7.0	53.2 ± 32.8	101.5 ± 47.6	65.4 ± 26.6	12.3[c]	21.1 ± 14.0	56.8 ± 16.5	120.2 ± 88.6	91.3 ± 57.8

[a]Mean ± standard deviation; [b]median (range) time elapsed from the end of infusion; [c]n=1.

Pharmcokinetic parameters were calculated by noncompartmental analysis method using preliminary concentration data and nominal time/dose (lower limit of quantification = 0.200 ng/mL).

$AUC_{(0-t)}$, area under the concentration–time curve extrapolated from 0 h to time of last quantifiable concentration; C_{max}, maximum plasma concentration; t_{max}, time at which C_{max} was achieved

Table S4. Tumor responses and duration of treatment

	MORAb-202 dose, mg/kg					
Best overall response[a], n	**0.3 (n=3)**	**0.45 (n=3)**	**0.68 (n=6)**	**0.9 (n=7)**	**1.2 (n=3)**	**Total (n=22)**
Complete response	0	0	0	1	0	1 (5)
Partial response	1	0	4	2	2	9 (41)
Stable disease	2	1	2	2	1	8 (36)
Progressive disease	0	2	0	2	0	4 (18)
Unknown/not evaluable	0	0	0	0	0	0
Duration of treatment, days, median (IQR)	84.0 (63–111)	42.0 (42–64)	90.0 (85–106)	84.0 (43–85)	84.0 (65–84)	84.0 (64–85)

[a]According to Response Evaluation Criteria In Solid Tumours version 1.1 per investigator review.

IQR, interquartile range

Figure S1.

Structure of MORAb-202, a cysteine-based conjugation of farletuzumab and enzyme-cleavable eribulin as the payload

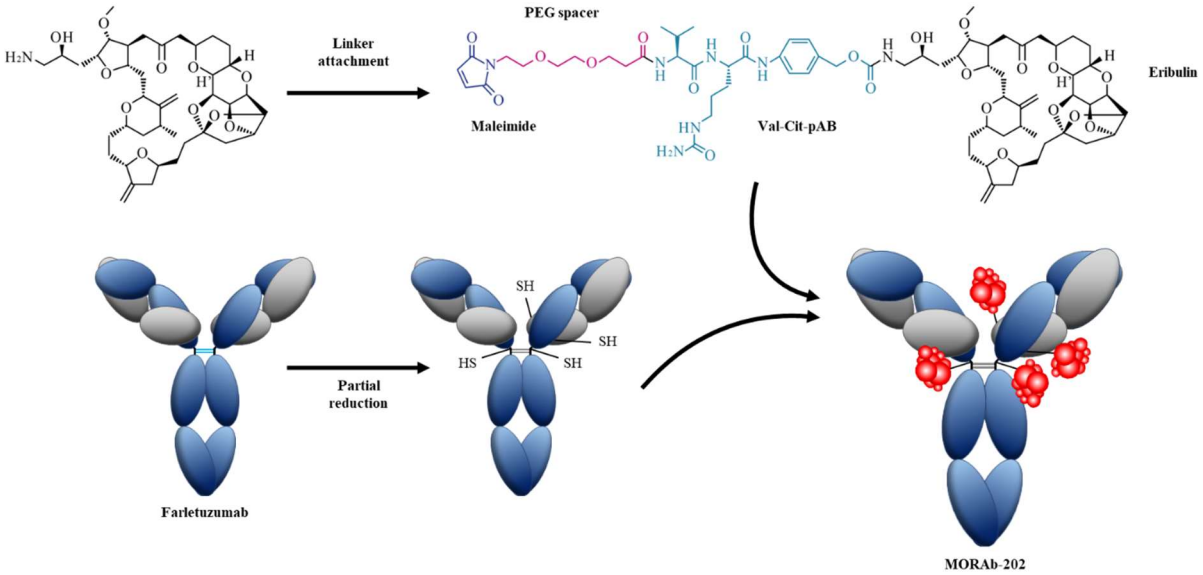
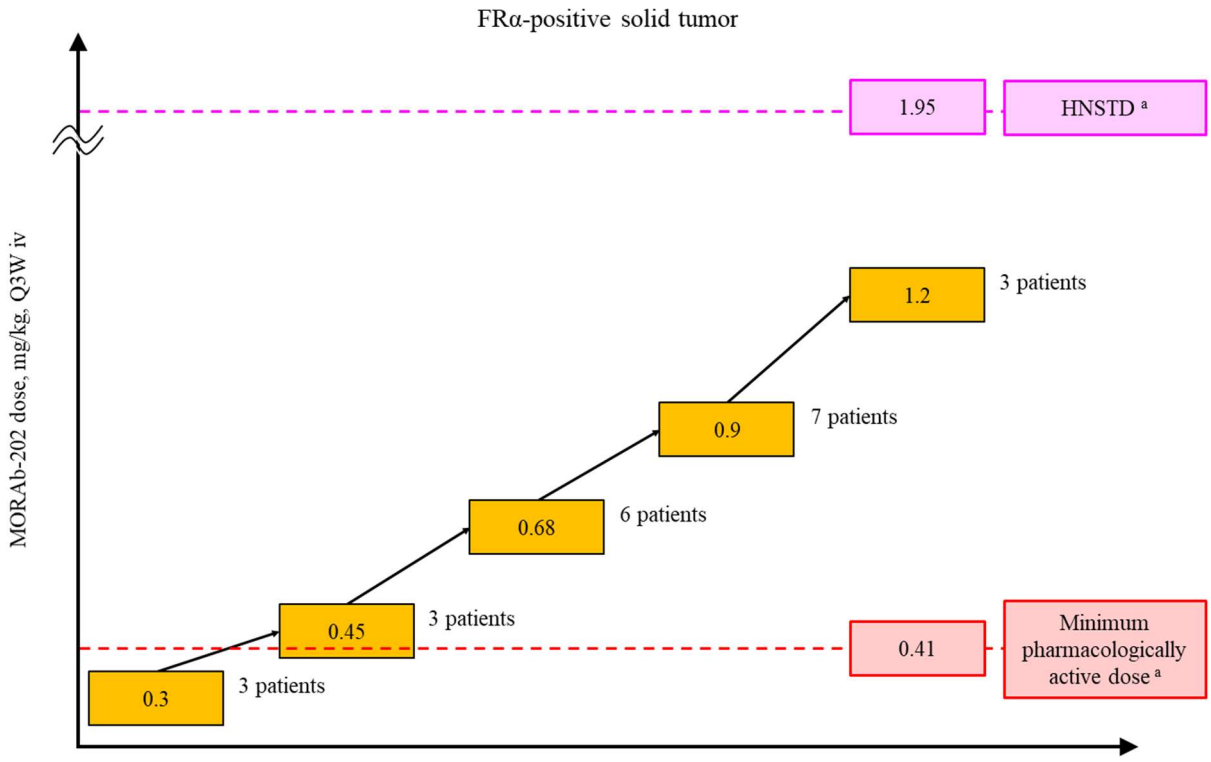


Figure S2.

Study design



[a]The minimum pharmacologically active dose and HNSTD were estimated by extrapolating data from prior studies of mice (1) and monkeys (2), respectively, in accordance with FDA Guidance for Industry (3).

FRα, folate receptor-α; HNSTD, highest non-severely toxic dose; iv, intravenous; Q3W, every 3 weeks

1. Cheng X, Li J, Tanaka K, Majumder U, Milinichik AZ, Verdi AC, et al. MORAb-202, an antibody-drug conjugate utilizing humanized anti-human FRalpha farletuzumab and the microtubule-targeting agent eribulin, has potent antitumor activity. *Mol Cancer Ther* 2018; **17**: 2665-75
2. Furuuchi K, Cheng X, Rybinski KA, Moriyama T, Fulmer J, Maddage C, et al. MORAb-202, a folate receptor-alpha (FRA)-targeting antibody-eribulin drug conjugate (ADC), exhibits durable antitumor activity and payload-mediated bystander effects on

the tumor microenvironment in triple-negative breast cancer. Abstract 952. AACR Annual Meeting, April 14–18, 2018, Chicago, IL. Available at: https://www.abstractsonline.com/pp8/#!/4562/presentation/2977.

3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers. Accessed January 27, 2021.