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Efficacy and Safety of LM-108, an Anti-CCR8 Monoclonal Antibody, in Combination With an Anti-PD-1 Antibody in Patients With Gastric Cancer: Results From Phase 1/2 Studies

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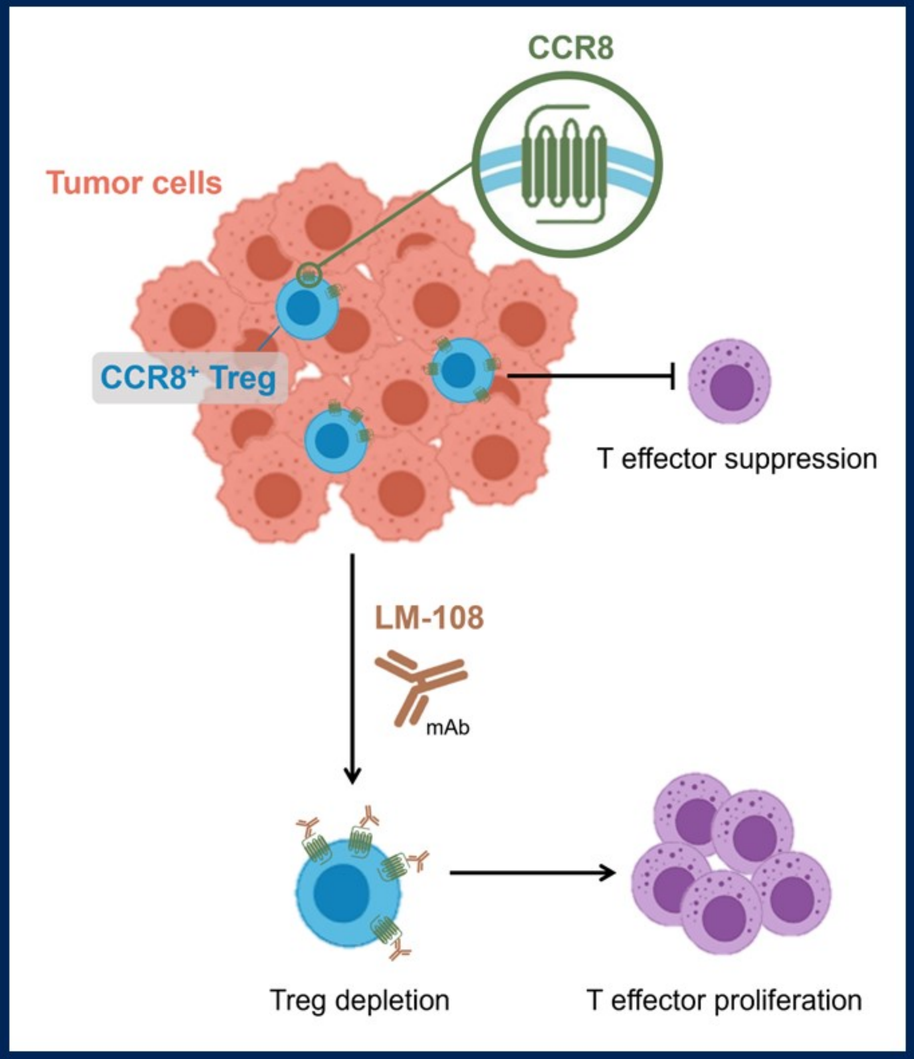
Key Takeaways

- LM-108 is a novel anti-CCR8 monoclonal antibody that selectively depletes tumor-infiltrating Tregs
- The pooled analysis from 3 phase 1/2 studies showed LM-108 plus an anti-PD-1 antibody had promising antitumor activity in GC with a manageable safety profile. Optimal response to treatment was observed in the second-line treatment setting
- Investigation of LM-108 plus anti-PD-1 antibody in various solid tumor types, including GC, is ongoing

CCR8, C-C motif chemokine receptor 8; GC, gastric cancer; PD-1, programmed cell death protein 1; Treg, regulatory T cells.

Background and Rationale

- Infiltration of Tregs in tumor tissues plays a critical role in the resistance to first-line immunotherapy in GC treatment[1]
- CCR8 is selectively expressed on tumor-infiltrating Tregs.[2] Targeting CCR8 can result in reduced accumulation of Tregs within tumors and disruption of their immunosuppressive function[3]
- LM-108 is a novel Fc-optimized, anti-CCR8 monoclonal antibody that selectively depletes tumor-infiltrating Tregs.[4] A previous study showed that LM-108 monotherapy, or in combination with pembrolizumab, had encouraging antitumor activity in patients with advanced solid tumors[5]
- Here we report on a pooled analysis of 3 phase 1/2 studies on the efficacy and safety of LM-108 in combination with anti-PD-1 therapy in patients with GC



mAb, monoclonal antibody.

1. Zhang, et al. Cell Mol Immunol 2020;18:1624-1625. 2. Haruna, et al. Sci Rep 2022;12:5377. 3. Whiteside, et al. Immunology 2021;163:512-520. 4. Luo, et al. Cancer Res 2022;82:6008.
5. Starodub, et al. Immuno-Oncology and Technology 2023;20:100611.

LM-108 Early Phase Study Design

Key eligibility criteria

- Age ≥18 years
- Pathological confirmed advanced solid tumors
- ECOG PS 0-1
- Expected survival ≥3 months
- Adequate organ functions

Primary endpoint:
Investigator-assessed ORR

Secondary endpoints:
Safety, other efficacy endpoints, and biomarker analysis

LM-108 monotherapy dose escalation → **LM-108 + anti-PD-1 dose escalation** → **LM-108 + anti-PD-1 dose expansion**

Patients with GC were included in the pooled analysis

NCT05518045 (China, N=43)*	NCT05255484 (USA, N=1)*	NCT05199753 (Australia, N=4)*
LM-108 6 or 10 mg/kg Q3W	**LM-108** 10 mg/kg Q3W	**LM-108** 3 mg/kg Q2W
Toripalimab 240 mg Q3W	**Pembrolizumab** 200 mg Q3W	**Pembrolizumab** 400 mg Q6W

*The data cut-off date was December 25, 2023 in NCT05199753 and NCT05518045 and November 8, 2023 in NCT05255484 due to the patient-met criteria for early end of study

ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q6W, once every 6 weeks.

Patient Disposition and Baseline Characteristics

- 48 patients with GC were included in the safety analysis set (SS)
  - 12 patients did not have post-treatment tumor assessments as of the data cut-off date and were excluded from the efficacy analysis set (EAS)
- 15 patients discontinued treatment as of the data cut-off date, due to:
  - Disease progression: 10 (20.8%)
  - Intolerable toxicity: 3 (6.3%)
  - Investigator decision: 2 (4.2%)

		SS N=48	EAS N=36
Age (years)	Median (range)	60.5 (34-80)	61 (34-80)
Sex	Male	35 (72.9)	28 (77.8)
	Female	13 (27.1)	8 (22.2)
ECOG PS	0	6 (12.5)	6 (16.7)
	1	42 (87.5)	30 (83.3)
Race	Asian	44 (91.7)	32 (88.9)
	White	4 (8.3)	4 (11.1)
Number of prior treatment lines	≤1*	17 (35.4)	13 (36.1)
	≥2	29 (60.4)	21 (58.3)
	Missing	2 (4.2)	2 (5.6)
Prior anti-PD-1	**Yes**	**43 (89.6)**	**32 (88.9)**
	No	5 (10.4)	4 (11.1)

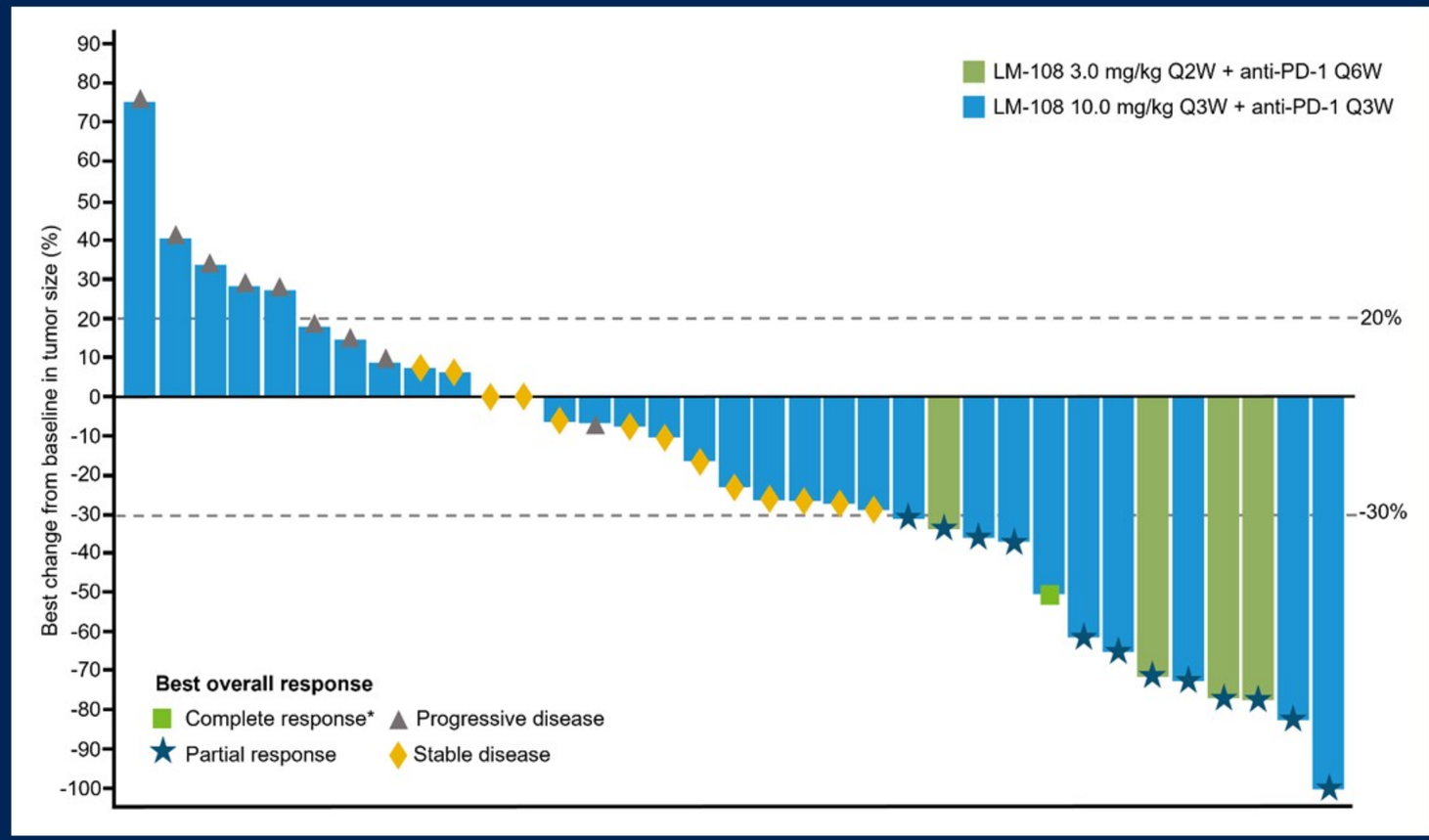
Data are n (%) unless stated otherwise
*2 patients had recurrent disease after adjuvant therapy

EAS, efficacy analysis set; SS, safety analysis set.

Objective Response Rate (Per RECIST v1.1)：All Lines

	Total (EAS) N=36*
Best overall response, n (%)	
Complete response	1 (2.8)
Partial response	12 (33.3)
Stable disease	13 (36.1)
Progressive disease	10 (27.8)
Not evaluable	0
ORR, n (%) [95% CI]	**13 (36.1) [20.8, 53.8]**
DCR, n (%) [95% CI]	26 (72.2) [54.8, 85.8]

Data are n (%) unless stated otherwise
*All lines: Median number of prior treatment lines was 2



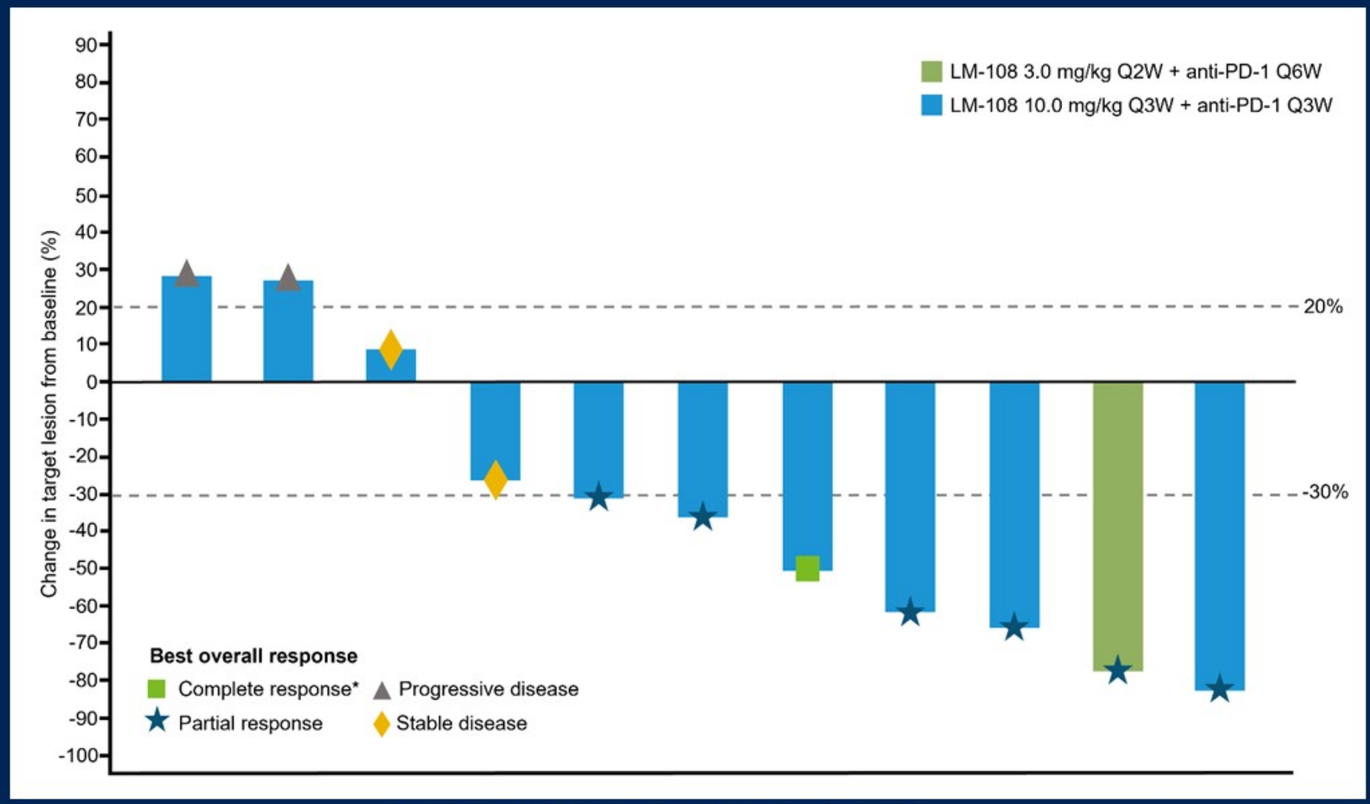
1 patient whose target lesion was not evaluable was not included in the waterfall plot
Treatment responses were confirmed
*CR was assigned based on the patient's target lesion, which was lymph node

CI, confidence interval; CR, complete response; DCR, disease control rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Objective Response Rate (Per RECIST v1.1): Second Line

	Second line (EAS) N=11*
Best overall response, n (%)	
Complete response	1 (9.1)
Partial response	6 (54.5)
Stable disease	2 (18.2)
Progressive disease	2 (18.2)
Not evaluable	0
ORR, n (%) [95% CI]	**7 (63.6) [30.8, 89.1]**
DCR, n (%) [95% CI]	9 (81.8) [48.2, 97.7]

Data are n (%) unless stated otherwise



Treatment responses were confirmed

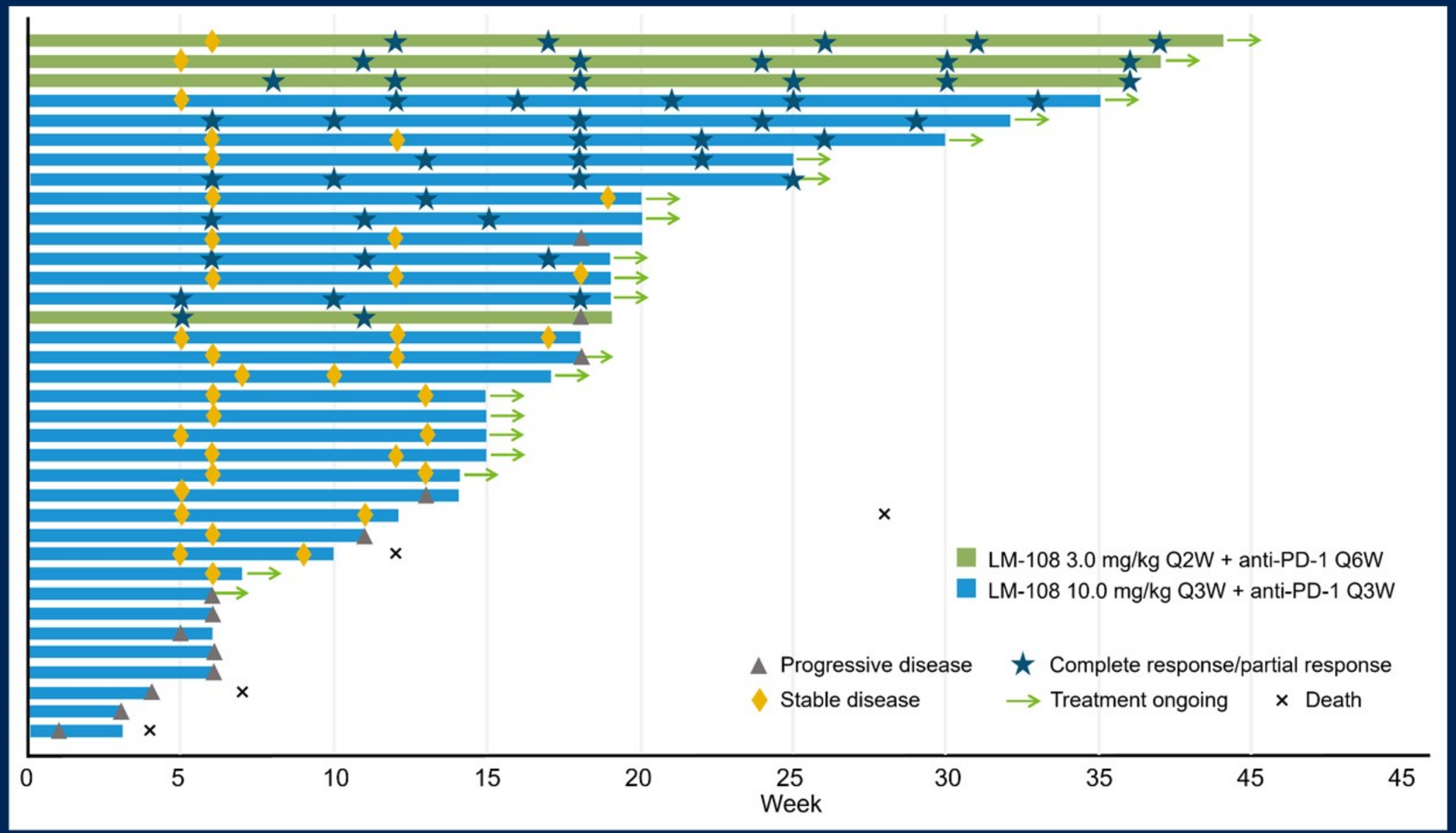
*CR was assigned based on the patient's target lesion, which was lymph node

Treatment Duration and Duration of Response

- Treatment ongoing: 21 patients

	Total (EAS) N=36*
mDOR (95% CI), month	**NE (2.9, NE)**
3 months DOR rate (95% CI)	87.5 (38.7, 98.1)
6 months DOR rate (95% CI)	87.5 (38.7, 98.1)

*All lines: Median number of prior treatment lines was 2

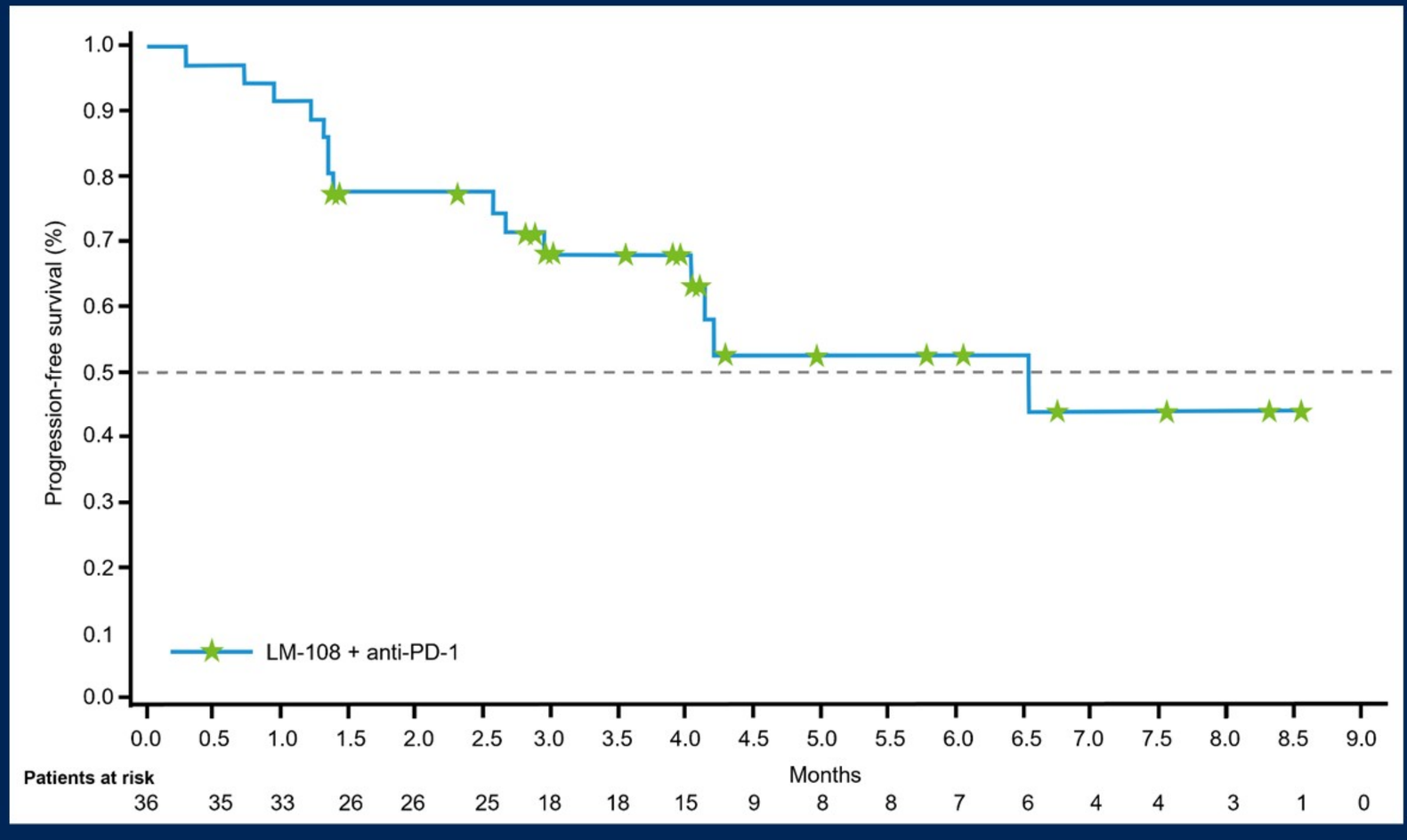


DOR, duration of response; mDOR, median duration of response; NE, not evaluable.

Progression-free Survival (Immature Data)

	Total (EAS) N=36*
PD or death, n (%)	15 (41.7)
mPFS (95% CI), month	**6.5 (3.0, NE)**
3 months PFS rate (95% CI)	68.2 (49.7, 81.0)
6 months PFS rate (95% CI)	53.0 (32.2, 70.1)

*All lines: Median number of prior treatment lines was 2



mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival.

Subgroup Analysis by CCR8 Expression

	Patients with CCR8 results*	All lines		Second line		Other lines	
		CCR8 high#	CCR8 low	CCR8 high#	CCR8 low	CCR8 high#	CCR8 low
	n=31	n=16	n=15	n=8	n=3	n=8	n=12
Best overall response, n (%)							
Complete response	1 (3.2)	1 (6.3)	0	1 (12.5)	0	0	0
Partial response	11 (35.5)	8 (50.0)	3 (20.0)	6 (75.0)	0	2 (25.0)	3 (25.0)
Stable disease	13 (41.9)	6 (37.5)	7 (46.7)	1 (12.5)	1 (33.3)	5 (62.5)	6 (50.0)
Progressive disease	6 (19.4)	1 (6.3)	5 (33.3)	0	2 (66.7)	1 (12.5)	3 (25.0)
ORR, n (%) [95% CI]	12 (38.7) [21.8, 57.8]	9 (56.3) [29.9, 80.2]	3 (20.0) [4.3, 48.1]	**7 (87.5) [47.3, 99.7]**	**0 [0.0, 70.8]**	2 (25.0) [3.2, 65.1]	3 (25.0) [5.5, 57.2]
DCR, n (%) [95% CI]	25 (80.6) [62.5, 92.5]	15 (93.8) [69.8, 99.8]	10 (66.7) [38.4, 88.2]	8 (100) [63.1, 100.0]	1 (33.3) [0.8, 90.6]	7 (87.5) [47.3, 99.7]	9 (75.0) [42.8, 94.5]

Data are n (%) unless stated otherwise
*5 patients did not have CCR8 status due to lack of samples
#The CCR8-positive score was calculated as the number of CCR8-positive cells divided by the total number of cells and multiplied by 100. High CCR8 expression was defined as CCR8-positive score ≥2 by immunohistochemistry staining

Summary of Adverse Events

	Total (N=48) n (%)
TEAE all grade	43 (89.6)
≥grade 3	23 (47.9)
TRAE all grade	39 (81.3)
≥grade 3	18 (37.5)
TEAE leading to treatment interruption	18 (37.5)
TEAE leading to treatment discontinuation	6 (12.5)
TEAE leading to death	2 (4.2)*
irAE	23 (47.9)

Data are n (%)
*The 2 events were gastrointestinal hemorrhage and immune-mediated lung disease. Immune-mediated lung disease was considered related to LM-108 and anti-PD1 treatment

irAE, immune-related adverse events; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Treatment-related Adverse Events in ≥10% of Any Grade or in ≥1 Patient of Grade ≥3

TRAE of any grade (≥10%)	Total (N=48)
Alanine aminotransferase increased	12 (25.0)
Aspartate aminotransferase increased	11 (22.9)
White blood cell count decreased	11 (22.9)
Anemia	8 (16.7)
Hypothyroidism	7 (14.6)
Amylase increased	7 (14.6)
Neutrophil count decreased	6 (12.5)
Rash	6 (12.5)
Platelet count decreased	5 (10.4)
Blood bilirubin increased	5 (10.4)
Activated partial thromboplastin time prolonged	5 (10.4)
Lipase increased	5 (10.4)

Data are n (%)

TRAE grade ≥3 (≥1 patient)	Total (N=48)
Anemia	4 (8.3)
Lipase increased	3 (6.3)
Rash/dermatitis	3 (6.3)
Lymphocyte count decreased	2 (4.2)
Colitis	2 (4.2)
Pancreatitis	2 (4.2)
Hepatitis	2 (4.2)
Hepatic function abnormal	1 (2.1)
Aminotransferase increased	1 (2.1)
Immune-mediated lung disease	1 (2.1)

Data are n (%)

Conclusions

- LM-108 in combination with anti-PD-1 therapy exhibited promising antitumor activity in GC resistant to anti-PD-1 therapy
- Manageable safety profile was observed with LM-108 plus anti-PD-1 therapy
- Trend towards optimal response was seen in second-line therapy. Further exploration is needed to understand the relationship between CCR8 expression and treatment efficacy of the combination therapy
- These results support further evaluation of LM-108 combined with anti-PD-1 therapy in GC. Investigation of LM-108 plus anti-PD-1 antibody in various solid tumor types is ongoing

Acknowledgments

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Thank you