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Anbenitamab in combination with chemotherapy for previously treated HER2 positive gastric or gastroesophageal junction carcinomas (GC/GEJC): Interim analysis of KC-WISE

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On behalf of the KC-WISE investigators

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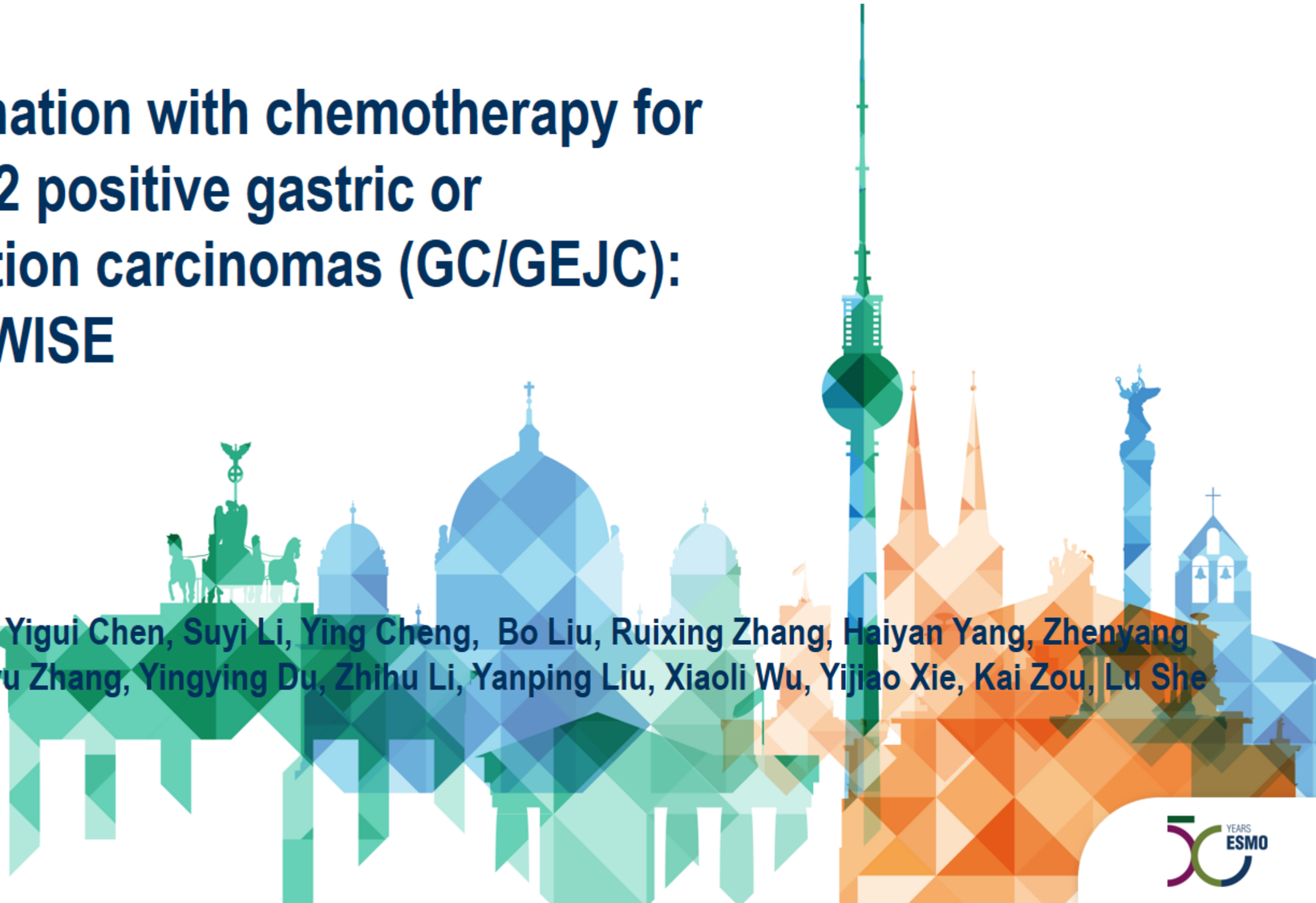

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Declaration of interests

Jianming Xu has nothing to declare.

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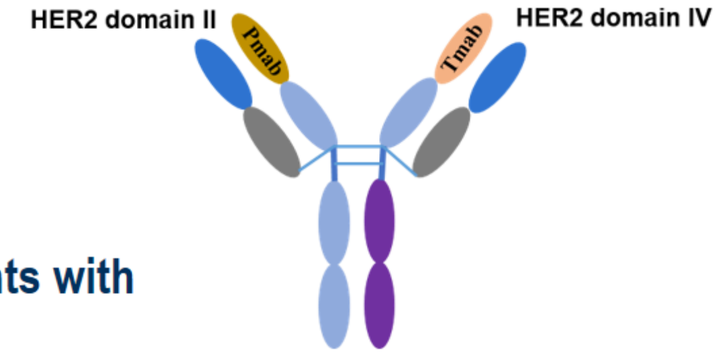
Background

- Gastric cancer remains the fifth most common cancer globally, having 968,000 new cases and close to 660,000 deaths according to the GLOBOCAN 2022[1].
- Human epidermal growth factor receptor 2 (HER2) is overexpressed in 15%-20% of gastric cancer[2].
- Anbenitamab is a novel HER2-targeted bispecific antibody that binds two distinct domains of HER2[3].
- Previous studies have demonstrated promising efficacy of anbenitamab in patients with GC/GEJC as monotherapy or in combination with chemotherapy[4,5].
- KC-WISE was conducted to evaluate anbenitamab plus chemotherapy versus chemotherapy alone in patients with HER2+ GC/GEJC after progression on trastuzumab treatment.



Schematic drawing of anbenitamab

1. Bray F, et al. CA Cancer J Clin 2024;74:229-63. 2. Koopman T, et al. J Cancer Res Clin Oncol 2015;141:1343-51. 3. Wei H, et al. Oncotarget. 2017;8(31):51037-49. 4. Xu J, et al. Eur J Cancer 2023;178:1-12. 5. Xu J, et al. Ann Oncol. 2024;35:S889.

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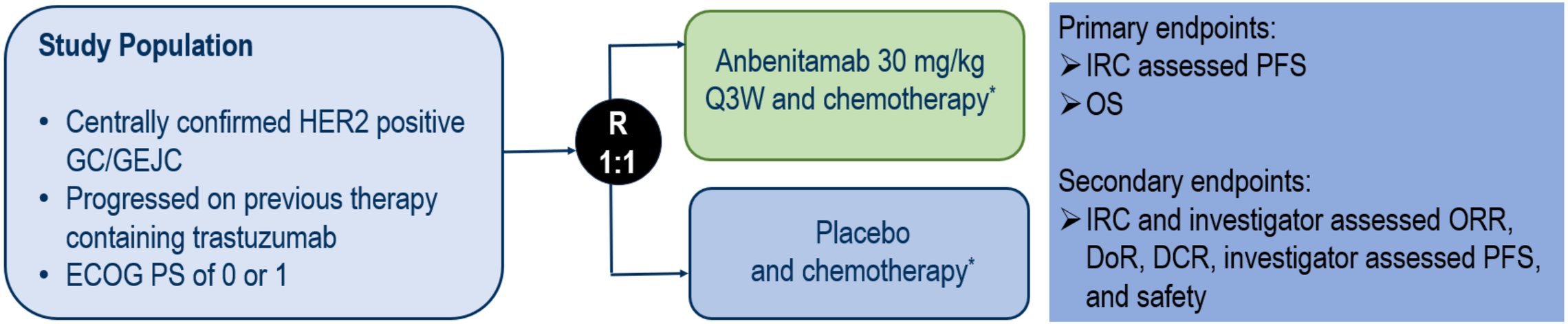
Study design

KC-WISE is a multicenter, randomized, double-blind, phase 3 study conducted at 51 sites in China (NCT05427383).



Stratification factors:
- Chemotherapy type (taxanes [paclitaxel and docetaxel] or irinotecan)
- HER2 expression (IHC 3+ or IHC2+/FISH+)
- Previous lines of therapy (1 or ≥2)

*Before randomisation, the investigators selected one of the chemotherapy regimens (taxane [paclitaxel or docetaxel] or irinotecan) based on the patient's previous treatment history.
DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; GC/GEJC, gastric cancer or gastroesophageal junction carcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRC, independent review committee; ORR, objective response, rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks.

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Statistical considerations

Planned sample size: 246

- PFS and OS were tested hierarchically to control the overall type I error at a one-sided 0.025.
- 201 PFS events were expected to achieve 95% power to detect a PFS hazard ratio of 0.6.
- 174 OS events were expected to achieve 80% power to detect a OS hazard ratio of 0.65.

Interim analyses

- Two interim efficacy analyses were planned, with the first interim analysis planned when approximate 120 PFS events were observed.
- At data cutoff date (April 3, 2025), 121 PFS events were observed and the stopping boundary at one-sided p-value for this interim PFS analysis was set at 0.0039 using the prespecified O'Brien–Fleming alpha-spending function method.
- Conditional on achieving statistical significance in this interim PFS analysis, OS would subsequently be evaluated under an extremely stringent alpha threshold of 0.00001.

one-sided
alpha =0.025

PFS

Two analyses were planned with one interim analysis (IA)

OS

Three analyses were planned with two IAs

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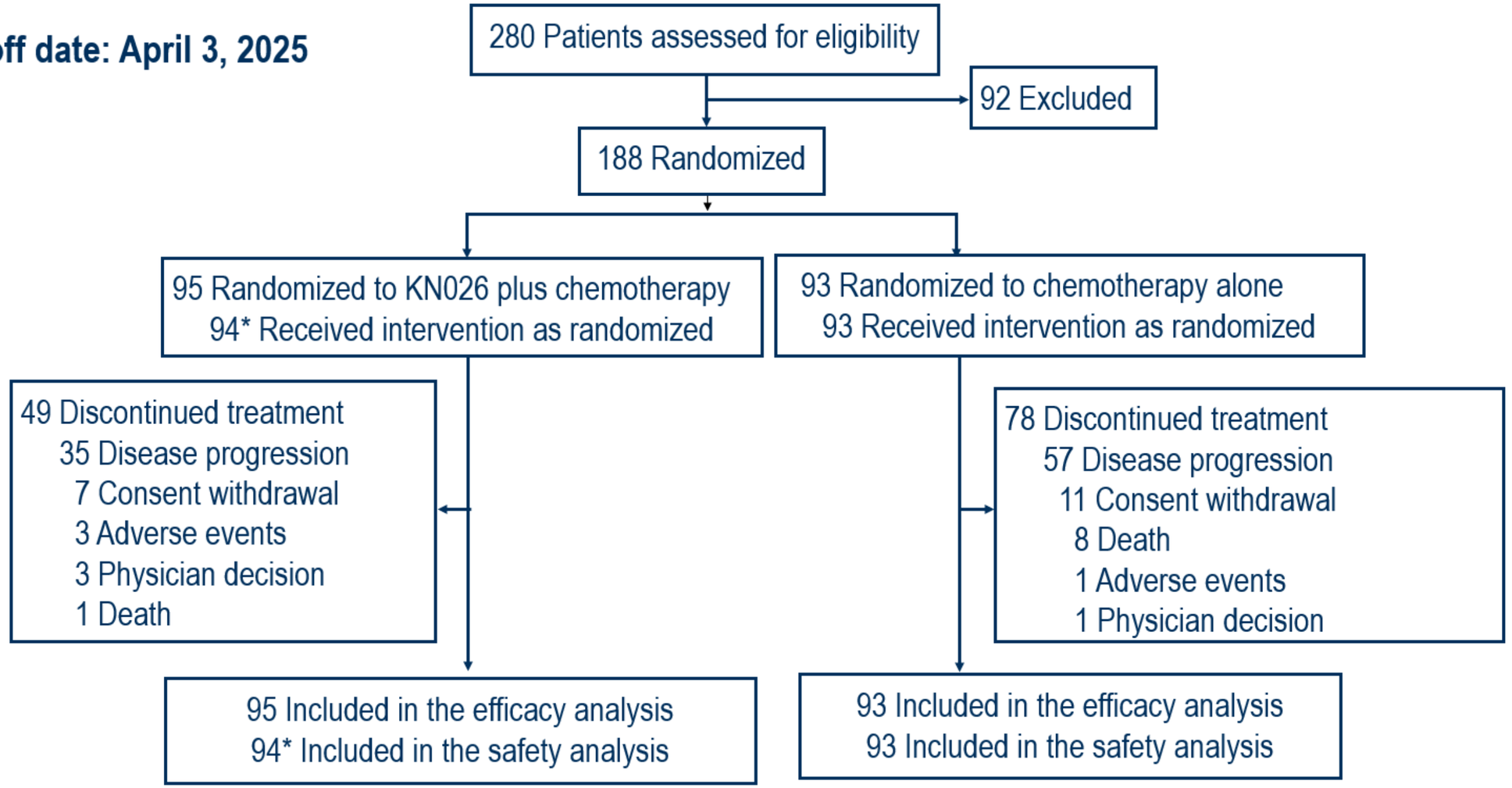
Patient disposition

Cutoff date: April 3, 2025



*At cutoff date of April 3, 2025, one patient in the anbenitamab group enrolled and didn't receive the treatment

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Baseline characteristics

	Anbenitamab(n=95)	Control(n=93)
Median age, range (years)	64 (39, 82)	61 (34, 83)
Male, n (%)	81 (85.3)	69 (74.2)
Race, n (%)		
Asian (Chinese)	95 (100)	93 (100)
ECOG PS*, n (%)		
0	14 (14.7)	18 (19.4)
1	80 (84.2)	75 (80.6)
Primary site, n (%)		
Gastric	72 (75.8)	79 (84.9)
GEJ	23 (24.2)	14 (15.1)
HER2 status, n (%)		
IHC 2+/FISH+	17 (17.9)	17 (18.3)
IHC 3+	78 (82.1)	76 (81.7)
Stage at the enrolment, n (%)		
III	0	2 (2.2)
IVA	0	2 (2.2)
IVB	95 (100)	89 (95.7)

	Anbenitamab(n=95)	Control(n=93)
Presence of metastasis, n (%)	95 (100)	93 (100)
No. of metastatic organs, n (%)		
1-2	72 (75.8)	59 (63.4)
≥3	23 (24.2)	34 (36.6)
Liver metastasis, n (%)	54 (56.8)	48 (51.6)
Previous lines of therapy, n (%)		
1	80 (84.2)	77 (82.8)
≥2	15 (15.8)	16 (17.2)
Previous treatment with immunotherapy, n (%)	52 (54.7)	56 (60.2)
Type of chemotherapy, n (%)		
Taxane (paclitaxel or docetaxel)	68 (71.6)	66 (71.0)
Irinotecan	27 (28.4)	27 (29.0)

Cutoff date: April 3, 2025.

*One patient in the anbenitamab group had a missing ECOG PS.

ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; FISH, fluorescent in situ hybridization.

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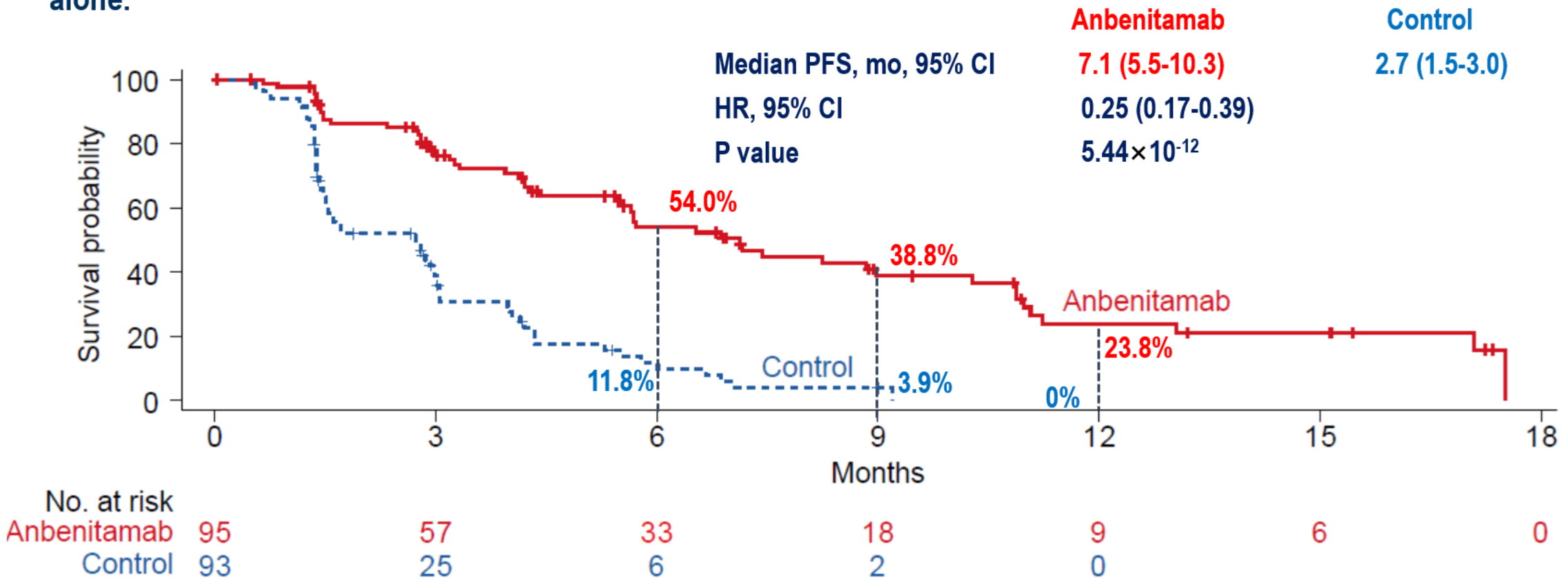
IRC-assessed PFS: primary endpoint

Anbenitamab plus chemotherapy significantly reduced the risk of progression or death by 75% versus chemotherapy alone.



At cutoff date of April 3, 2025, 121 PFS events occurred; The median follow-up duration was 9.7 months (95% CI, 7.2 to 11.9) in the anbenitamab group and 9.8 months (95% CI, 7.4 to 12.9) in the control group. IRC, independent review committee; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.

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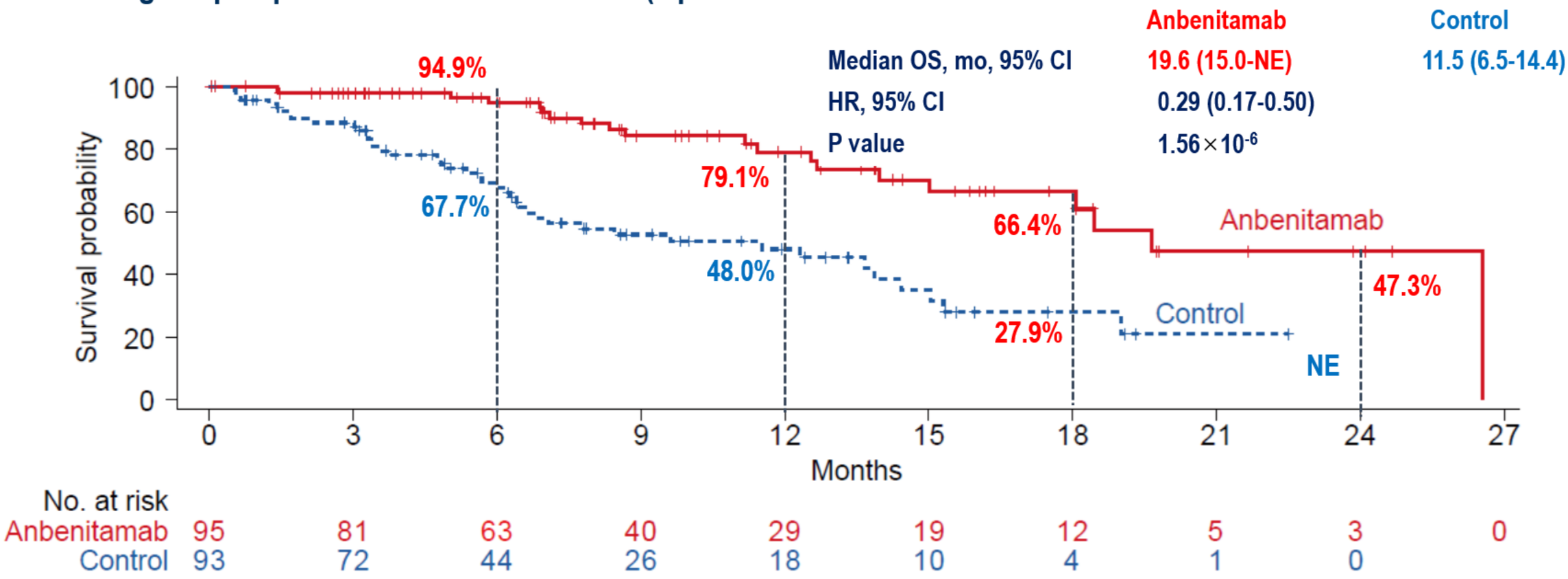
OS: co-primary endpoint

Compared with chemotherapy alone, anbenitamab plus chemotherapy significantly reduced the risk of death by 71%, achieving the prespecified statistical criterion (alpha threshold of 0.00001).



At cutoff date of April 3, 2025, 63 OS events occurred; The median follow-up duration was 9.7 months (95% CI, 7.2 to 11.9) in the anbenitamab group and 9.8 months (95% CI, 7.4 to 12.9) in the control group. HR, hazard ratio; OS, overall survival.

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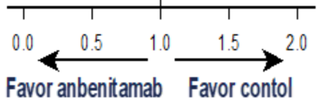
IRC-assessed PFS and OS: subgroup analysis

PFS and OS benefits were consistent across all prespecified subgroups.

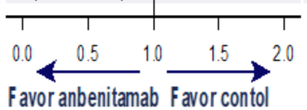
IRC-assessed PFS

	Anbenitamab group	Control group	HR (95% CI)
	Events/Patients	Events/Patients	
Overall	52/95	69/93	0.26(0.17 to 0.39)
Sex			
Male	45/81	49/69	0.26(0.16 to 0.41)
Female	7/14	20/24	0.24(0.09 to 0.64)
Age			
< 65 years	22/49	42/55	0.19(0.10 to 0.34)
≥ 65 years	30/46	27/38	0.36(0.20 to 0.63)
ECOG PS			
0	5/14	12/18	0.14(0.04 to 0.51)
1	47/80	57/75	0.18(0.18 to 0.43)
Combined chemotherapy			
Taxanes (paclitaxel and docetaxel)	39/68	49/66	0.26(0.16 to 0.42)
Irinotecan	13/27	20/27	0.25(0.12 to 0.54)
HER2 expression			
IHC3+	39/78	57/76	0.20(0.12 to 0.32)
IHC2+/FISH+	13/17	12/17	0.59(0.26 to 1.34)
No. of previous therapies			
1	47/80	58/77	0.29(0.19 to 0.44)
≥2	5/15	11/16	0.08(0.02 to 0.36)
Primary site			
Gastric	39/72	58/79	0.28(0.18 to 0.44)
GEJ	13/23	11/14	0.21(0.08 to 0.54)
Number of metastatic organs			
1-2	39/72	41/59	0.28(0.17 to 0.45)
≥3	13/23	28/34	0.23(0.11 to 0.49)



OS

	Anbenitamab group	Control group	HR (95% CI)
	Events/Patients	Events/Patients	
Overall	20/95	43/93	0.29(0.17 to 0.51)
Sex			
Male	17/81	30/69	0.26(0.14 to 0.49)
Female	3/14	13/24	0.41(0.11 to 1.45)
Age			
< 65 years	10/49	27/55	0.31(0.15 to 0.65)
≥ 65 years	10/46	16/38	0.32(0.14 to 0.73)
ECOG PS			
0	3/14	9/18	0.32(0.07 to 1.49)
1	17/80	34/75	0.28(0.16 to 0.51)
Combined chemotherapy			
Taxanes (paclitaxel and docetaxel)	15/68	31/66	0.31(0.16 to 0.58)
Irinotecan	5/27	12/27	0.21(0.07 to 0.66)
HER2 expression			
IHC3+	15/78	33/76	0.27(0.14 to 0.51)
IHC2+/FISH+	5/17	10/17	0.36(0.12 to 1.06)
No. of previous therapies			
1	19/80	37/77	0.32(0.18 to 0.57)
≥2	1/15	6/16	0.11(0.01 to 0.96)
Primary site			
Gastric	17/72	37/79	0.38(0.21 to 0.68)
GEJ	3/23	6/14	0.07(0.01 to 0.58)
Number of metastatic organs			
1-2	13/72	24/59	0.30(0.15 to 0.60)
≥3	7/23	19/34	0.28(0.10 to 0.75)



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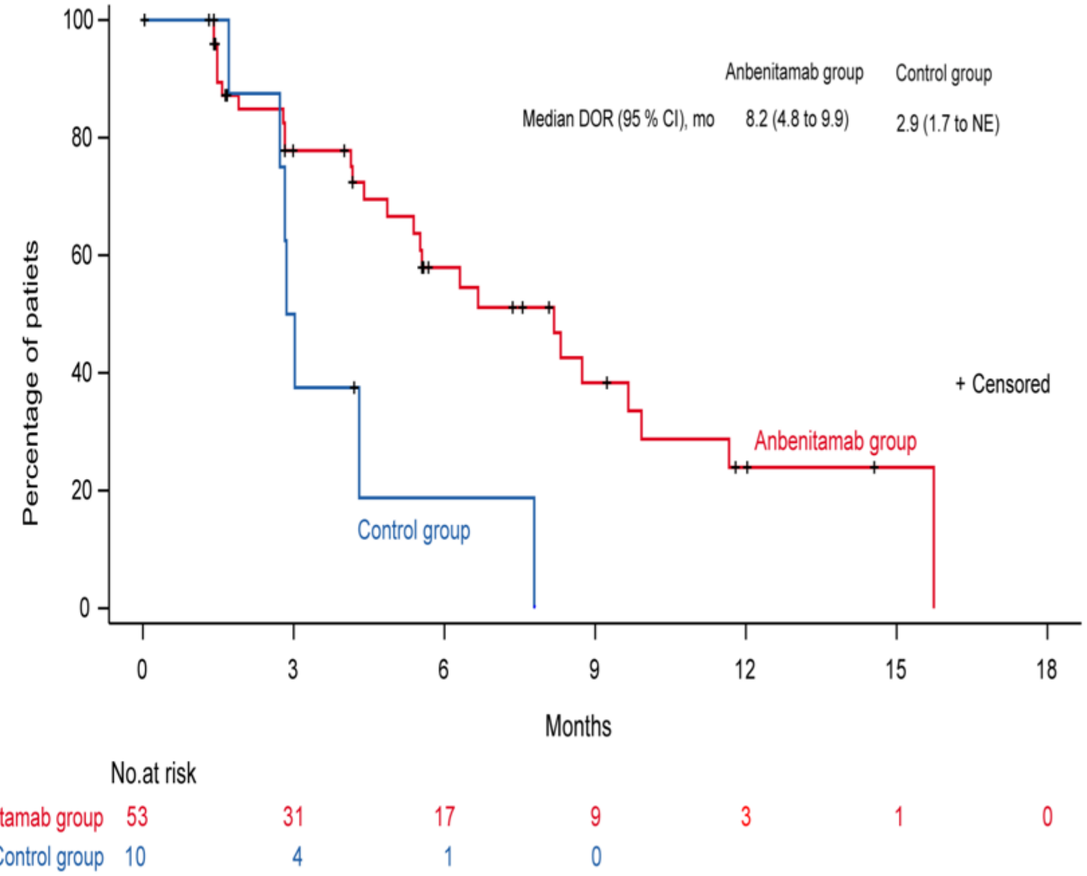
IRC and investigator-assessed ORR and DoR

	Anbenitamab(n=95)		Control(n=93)	
	IRC-assessed	Investigator-assessed	IRC-assessed	Investigator-assessed
BOR, n (%)				
CR	0	1 (1.1)	1 (1.1)	0
PR	53 (55.8)	46 (48.4)	9 (9.7)	15 (16.1)
SD	13 (13.7)	23 (24.2)	25 (26.9)	23 (24.7)
Non-CR/Non-PD	10 (10.5)	10 (10.5)	4 (4.3)	4 (4.3)
PD	14 (14.7)	8 (8.4)	36 (38.7)	32 (34.4)
NE	5 (5.3)	7 (7.4)	18 (19.4)	19 (20.4)
ORR, %, 95% CI	55.8 (45.2-66.0)	49.5 (39.1-59.9)	10.8 (5.3-18.9)	16.1 (9.3-25.2)
DCR, %, 95% CI	80.0 (70.5-87.5)	84.2 (75.3-90.9)	41.9 (31.8-52.6)	45.2 (34.8-55.8)
Median DoR, mo, 95% CI	8.2 (4.8-9.9)	8.3 (5.6-10.2)	2.9 (1.7-NE)	2.9 (2.7-NE)



At cutoff date of April 3, 2025, 63 OS events occurred; The median follow-up duration was 9.7 months (95% CI, 7.2 to 11.9) in the anbenitamab group and 9.8 months (95% CI, 7.4 to 12.9) in the control group.
BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response.

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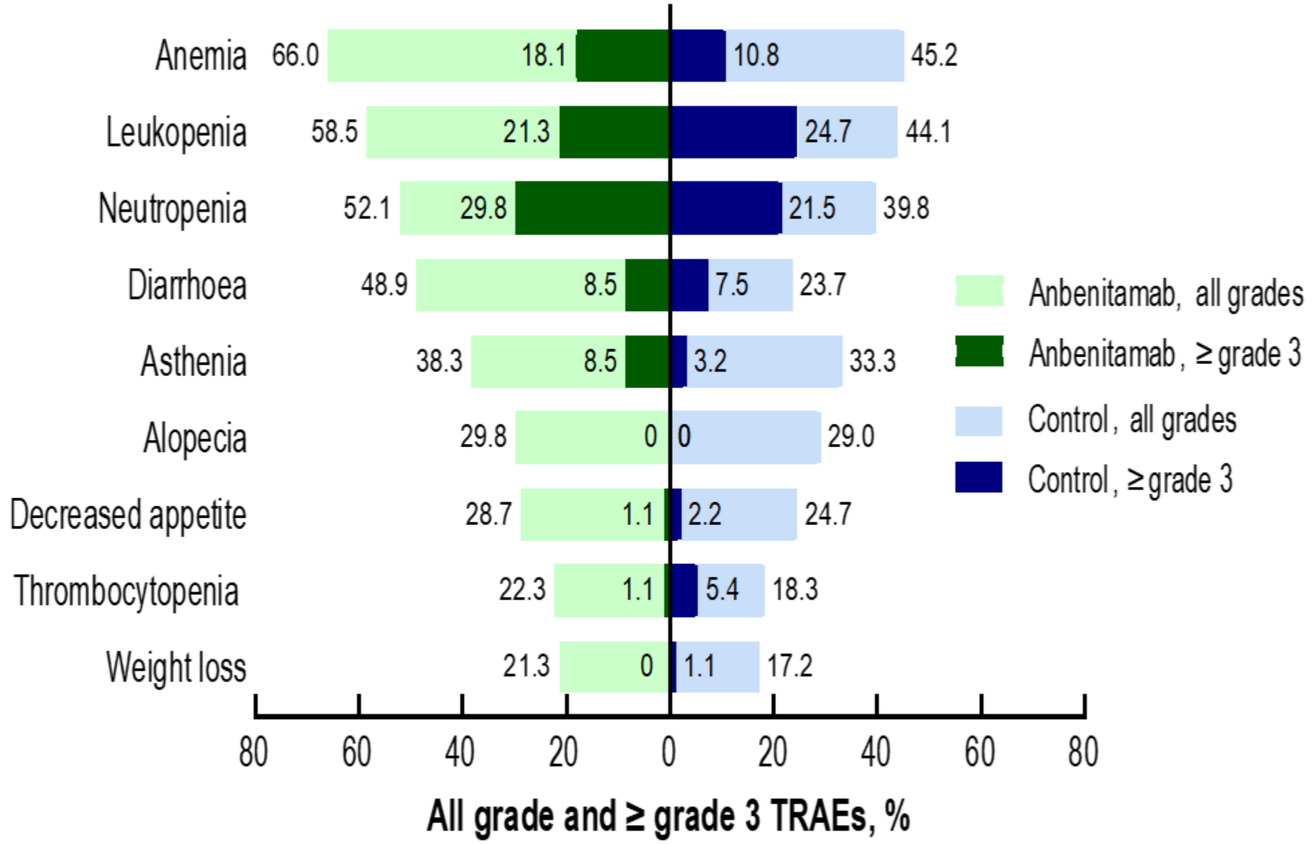
Exposure and safety

	Anbenitamab(n=94*)	Control(n=93)
Median duration of treatment, cycles (IQR)	6.5 (4.0-12.0)	3.0 (2.0-5.0)
TEAEs, n (%)	91 (96.8)	90 (96.8)
≥grade 3 TEAEs, n (%)	57 (60.6)	48 (51.6)
TEAEs leading to dose reduction, n (%)	41 (43.6)	29 (31.2)
TEAEs leading to treatment interruption, n (%)	53 (56.4)	38 (40.9)
TEAEs leading to treatment discontinuation, n (%)	10 (10.6)	3 (3.2)
SAEs, n (%)	30 (31.9)	31 (33.3)
AESI#, n (%)	3 (3.2)	3 (3.2)
TEAEs leading to death, n (%)	1& (1.1)	8 (8.6)



*At cutoff date of April 3, 2025, one patient in the anbenitamab group enrolled and didn't receive the treatment; The median follow-up duration was 9.7 months (95% CI, 7.2 to 11.9) in the anbenitamab group and 9.8 months (95% CI, 7.4 to 12.9) in the control group.

Adverse event of interest in this study was cardiotoxicity (defined as symptomatic left ventricular systolic dysfunction and asymptomatic left ventricular systolic dysfunction meeting the following criteria: ≥ 15% decrease in left ventricular ejection fraction from baseline or ≥ 10% decrease in left ventricular ejection fraction from baseline and left ventricular ejection fraction <50%) that occurred between the first administration and one year after last administration.

&The patient discontinued the treatment due to the emergence of new brain metastases and the disease progression was confirmed by imaging. The patient died within 30 days after the last dose of the study drug. This incident was reported as a Serious Adverse Event (SAE) pre protocol. The investigator determined that the death was related to disease progression and not associated with the study drug.

AESI, adverse events of special interest; IQR, interquartile range; SAEs, serious adverse events; TEAEs, treatment emergent adverse events.

Conclusions

- Anbenitamab plus chemotherapy achieved clinical meaningful and statistically significant PFS and OS benefits compared with chemotherapy alone in patients with HER2-positive GC/GEJC who progressed on trastuzumab.
  - Median PFS 7.1 vs. 2.7 months (HR=0.25; 95% CI, 0.17–0.39; $p=5.44\times10^{-12}$).
  - Median OS 19.6 vs. 11.5 months (HR=0.29; 95% CI, 0.17–0.50; $p=1.56\times10^{-6}$).
  - Similar improvement were observed in ORR, DCR and DoR.
- Anbenitamab plus chemotherapy had a favorable safety profile.
  - ≥Grade 3 TEAEs were 60.6% (anbenitamab plus chemotherapy) vs. 51.6% (chemotherapy alone)
  - The incidence of cardiotoxicity was low (3.2% vs. 3.2%), with fewer cardiac concerns.
- KC-WISE demostrated that anbenitamab in combination with chemotherapy offer a promising treatment option for these patients.

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We thank

The patients, their families

&

Investigators and site personnel from 51 sites who participated in the study

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