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Cadonilimab plus chemotherapy versus chemotherapy as first-line treatment for unresectable locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (COMPASSION-15): a randomized, double-blind, phase 3 trial.

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COI Disclosure

Jiafu Ji

I have no financial conflicts of interest to disclose concerning the presentation.

Background

- Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer mortality worldwide[1].
- PD-1 inhibitors plus chemotherapy (chemo) have shown efficacy in first-line treatment of advanced G/GEJ adenocarcinoma; however, survival benefits are limited in patients with low PD-L1 expression[2-8].
- Cadonilimab is a PD-1/CTLA-4 bispecific antibody; in the phase Ib/II (AK104-201, COMPASSION-03) study cadonilimab plus chemo has shown encouraging tumour response and survival benefits in patients with G/GEJ adenocarcinoma regardless of PD-L1 expression (NCT03852251)[9]. The median PFS was 9.20 months. The median OS was 17.41 months. In pts with PD-L1 CPS≥5 and CPS＜5, the median OS was 20.24 months and 17.28 months, respectively.
- This phase III (AK104-302, COMPASSION-15) study evaluated the efficacy and safety of cadonilimab plus chemo vs chemo alone as the first-line treatment in G/GEJ adenocarcinoma (NCT05008783).

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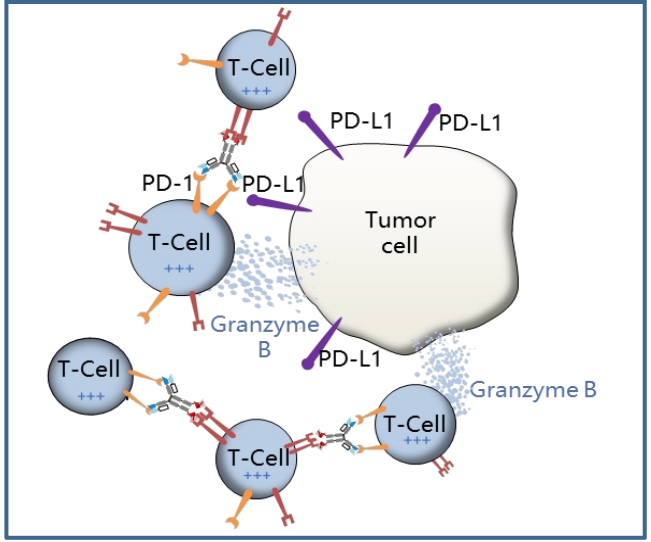
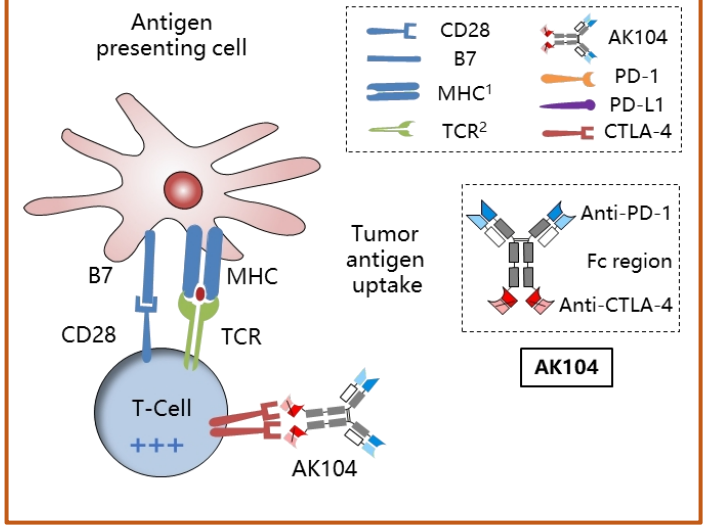
Cadonilimab: PD-1/CTLA-4 bispecific antibody

Tumor microenvironment (high functional affinity or avidity)



Peripheral (lower binding avidity)



- PD-1/CTLA-4 bi-specific may display higher avidity for lymphocytes in the tumor micro-environment versus peripheral sites
- PD-1 and CTLA-4 co-express in tumor infiltrating lymphocytes (TILs), but not in normal peripheral tissue lymphocytes

- AK104 is a first-in-class humanized bi-specific antibody drug candidate targeting PD-1 and CTLA-4 simultaneously;
- AK104 is designed as a novel tetrameric form, which could bind tetravalently to TILs co-expressing PD-1 & CTLA-4 with higher avidity;
- Therefore, AK104 is designed to retain the efficacy benefit of combination of PD-1 and CTLA-4, and offer a better safety profile than the combination therapy.

COMPASSION-15 (AK104-302) Study Design
Randomized, Double-blind, Phase 3 Trial

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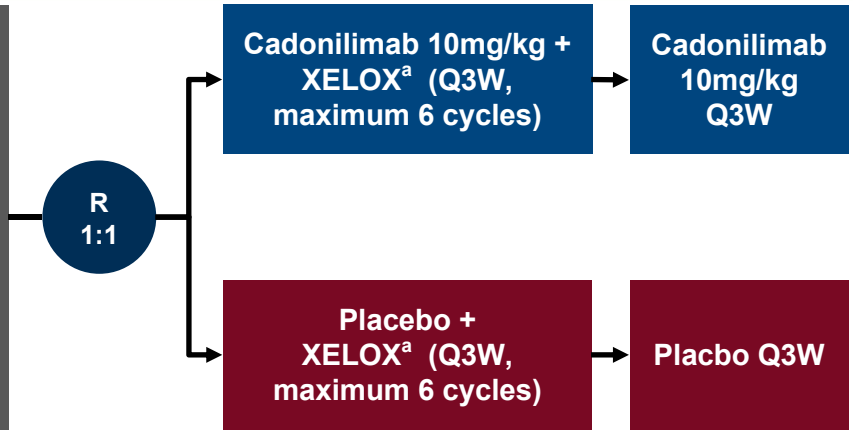
Key Eligibility Criteria

- Histologically confirmed G/GEJ adenocarcinoma
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy
- ECOG PS 0-1
- 18-75 yrs
- Measurable tumor lesion per RECIST v1.1 criteria
- Llife expectancy ≥3 months



Primary Endpoint:

- OS in the ITT[c] population

Secondary Endpoints:

- OS in the CPS ≥ 5[d] population;
- PFS, ORR, DCR, DoR assessed by investigator, in both CPS ≥ 5 population and ITT population;
- Safety, PK, ADA, HRQoL

Stratification Factors

- ECOG PS (0 vs 1)
- PD-L1 expression[b] (vCPS ≥ 5%, vCPS < 5%/NE)
- Liver metastases (with vs. without)

Interim analysis

- Data cutoff date: August 18, 2023
- # of OS events: 341
- One-sided P-value boundaries in the ITT population: 0.0106

Sample size

- Planned: 588
- Actually enrolled: 610

Planned OS analyses	Time (Months)	# OS events	P-value boundary (1-sided)	HR boundary
OS Interim Analysis	28	354	0.012	0.787
OS Final Analysis	39	443	0.021	0.825

[a] XELOX: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
[b] vCPS is an indicator to detect PD-L1 expression levels in tumor tissues using Ventana SP263.
[c] ITT: intent-to-treat
[d] CPS is an indicator to detect PD-L1 expression levels in tumor tissues using 22C3 assay (DAKO).

Patient Flow

871 participants screened

610 randomly allocated and included in the ITT population

Cadonilimab + XELOX
- 305 allocated
- 305 treated (median, 7.0 cycles)

239 discontinued treatment
- 143 clinical or radiographic progression
- 36 adverse event
- 25 subject request
- 17 death
- 2 physician decision
- 3 start new anti-tumor therapy
- 13 other

66 remain on treatment

- 305 included in the efficacy analysis
- 305 included in safety analysis

Median Follow-up :
18.69 mo (IQR, 14.19-19.91)

Subsequent Systemic Therapy in ITT Population
- Any: 36.4% vs 50.5%
- PD-1/L1 inhibitor: 11.1% vs 21.6%

Placebo + XELOX
- 305 allocated
- 304 treated (median, 6.0 cycles)

284 discontinued treatment
- 219 clinical or radiographic progression
- 18 adverse event
- 25 subject request
- 17 death
- 1 physician decision
- 1 start new anti-tumor therapy
- 3 other

20 remain on treatment

- 305 included in the efficacy analysis
- 304 included in safety analysis

Baseline Characteristics

	Cadonilimab + XELOX (N=305)	Placebo + XELOX (N=305)
Age, median (range)	63.7 (29, 75)	64.3 (26, 75)
<65, n(%)	170 (55.7)	164 (53.8)
≥65, n(%)	135 (44.3)	141 (46.2)
Sex, n(%)		
Female	66 (21.6)	70 (23.0)
Male	239 (78.4)	235 (77.0)
Baseline ECOG PS, n(%)		
0	70 (23.0)	72 (23.6)
1	235 (77.0)	233 (76.4)
Primary Tumor Location, n(%)		
GEJ Adenocarcinoma	63 (20.7)	74 (24.3)
Gastric Adenocarcinoma	242 (79.3)	231 (75.7)
Disease status, n(%)		
Recurrent Disease	65 (21.3)	59 (19.3)
Locally advanced unresectable	9 (3.0)	14 (4.6)
Primary Metastasis	231 (75.7)	232 (76.1)

	Cadonilimab + XELOX (N=305)	Placebo + XELOX (N=305)
Site of metastases, n(%)		
Liver	144 (47.2)	143 (46.9)
Lung	51 (16.7)	46 (15.1)
Peritoneum	43 (14.1)	38 (12.5)
PD-L1 Expression (22C3), n(%)		
CPS < 1	72 (23.6)	68 (22.3)
CPS 1-4	85 (27.9)	79 (25.9)
CPS 5-9	44 (14.4)	59 (19.3)
CPS ≥ 10	72 (23.6)	81 (26.6)
Missing	32 (10.5)	18 (5.9)
PD-L1 Expression (SP263), n(%)		
vCPS ≥ 5%	122 (40.0)	123 (40.3)
vCPS < 5%	166 (54.4)	173 (56.7)
Missing	17 (5.6)	9 (3.0)

Overall Survival

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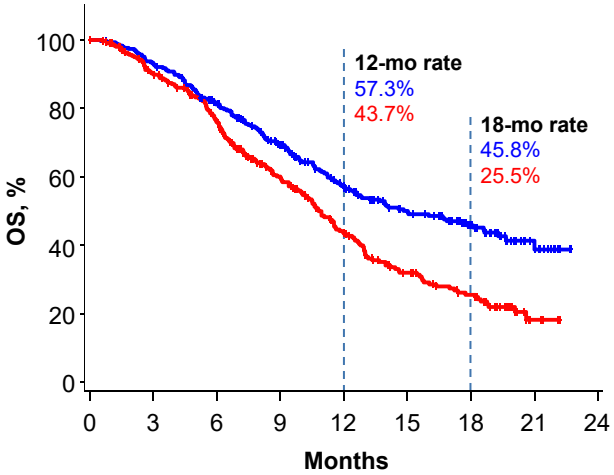
ITT Population

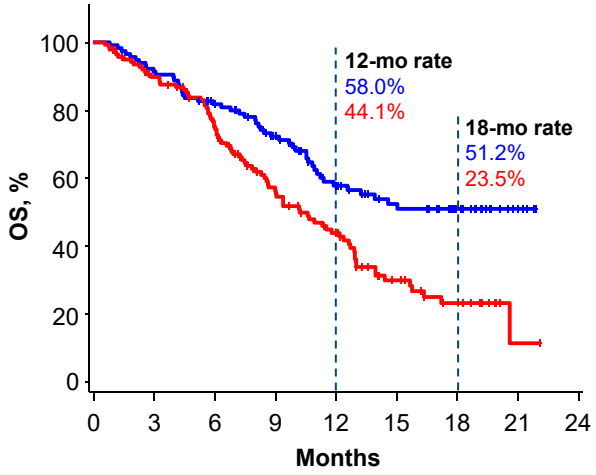
	Cadonilimab+XELOX N=305	Placebo+XELOX N=305
Median, mo (95% CI)	15.0 (12.3,19.3)	10.8 (9.8,12.0)
HR (95% CI)	0.62 (0.50-0.78)	
P value	<0.001	



No. at risk									
Cadonilimab+XELOX	305	283	234	186	136	103	70	15	0
Placebo+XELOX	305	263	212	147	95	59	40	4	0

PD-L1 CPS≥5

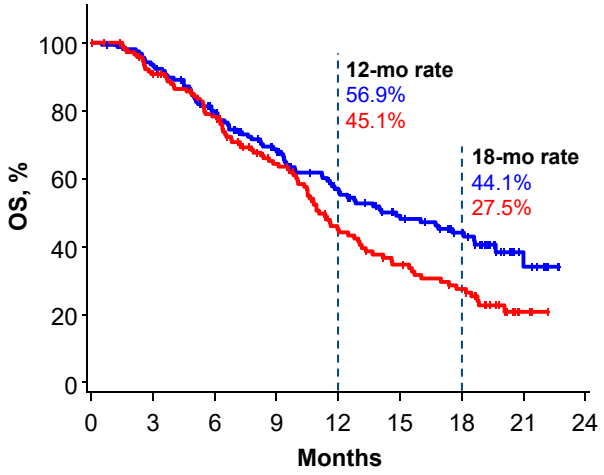
	Cadonilimab+XELOX N=116	Placebo+XELOX N=140
Median, mo (95% CI)	NR# (11.4, NE*)	10.6 (8.6,12.6)
HR (95% CI)	0.56 (0.39-0.80)	
P value	<0.001	



No. at risk									
Cadonilimab+XELOX	116	106	90	72	49	37	21	5	0
Placebo+XELOX	140	121	96	63	42	21	11	1	0

PD-L1 CPS<5

	Cadonilimab+XELOX N=157	Placebo+XELOX N=147
Median, mo (95% CI)	14.8 (11.6, 18.6)	11.1 (10.1, 13.0)
HR (95% CI)	0.70 (0.51-0.95)	
P value	0.011	



No. at risk									
Cadonilimab+XELOX	157	146	116	93	69	52	39	8	0
Placebo+XELOX	147	127	106	78	49	35	26	3	0

NR = not reached * NE = not estimable

Overall Survival in Subgroups

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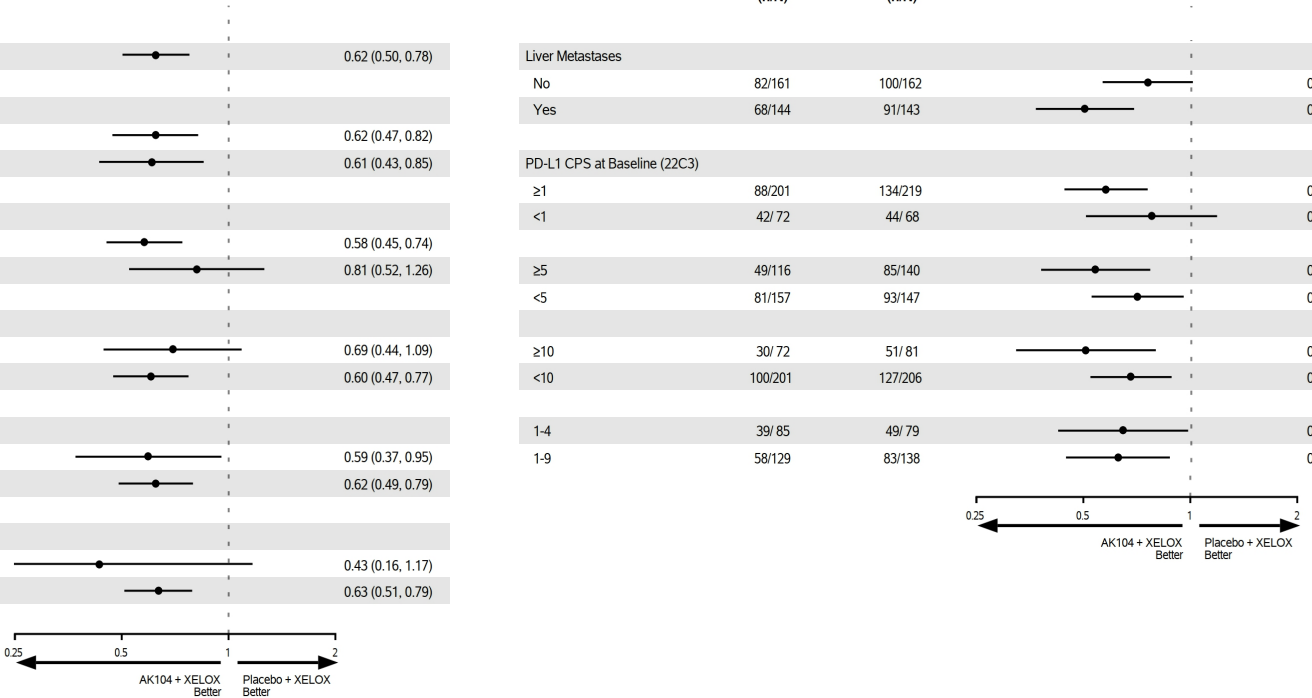
Subgroup	AK104 + XELOX No. Events/ No. Participants (n/N)	Placebo + XELOX No. Events/ No. Participants (n/N)	Hazard Ratio (95%CI)
Overall	150/305	191/305	0.62 (0.50, 0.78)
Age			
<65 years	92/170	111/164	0.62 (0.47, 0.82)
≥65 years	58/135	80/141	0.61 (0.43, 0.85)
Sex			
Male	114/239	146/235	0.58 (0.45, 0.74)
Female	36/ 66	45/ 70	0.81 (0.52, 1.26)
ECOG PS			
0	35/ 70	43/ 72	0.69 (0.44, 1.09)
1	115/235	148/233	0.60 (0.47, 0.77)
Primary Tumor Location			
GEJ	29/ 63	43/ 74	0.59 (0.37, 0.95)
Stomach	121/242	148/231	0.62 (0.49, 0.79)
Metastatic Disease			
No	6/ 12	12/ 18	0.43 (0.16, 1.17)
Yes	144/293	179/287	0.63 (0.51, 0.79)
Liver Metastases			
No	82/161	100/162	0.75 (0.56, 1.01)
Yes	68/144	91/143	0.50 (0.37, 0.69)
PD-L1 CPS at Baseline (22C3)			
≥1	88/201	134/219	0.58 (0.44, 0.75)
<1	42/ 72	44/ 68	0.77 (0.51, 1.18)
≥5	49/116	85/140	0.54 (0.38, 0.77)
<5	81/157	93/147	0.71 (0.52, 0.95)
≥10	30/ 72	51/ 81	0.51 (0.32, 0.79)
<10	100/201	127/206	0.68 (0.52, 0.88)
1-4	39/ 85	49/ 79	0.64 (0.42, 0.98)
1-9	58/129	83/138	0.62 (0.44, 0.87)



Progression-Free Survival

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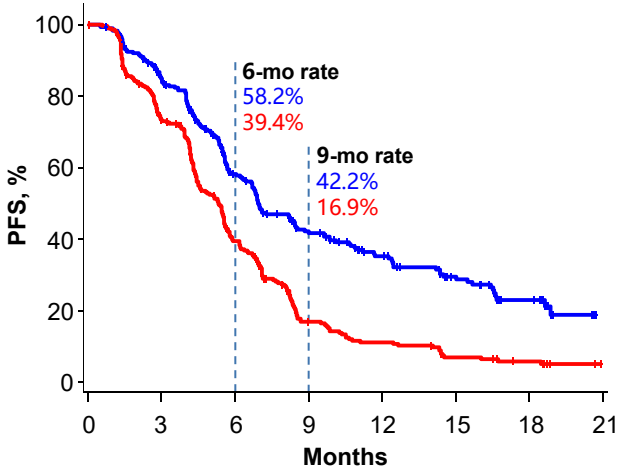
ITT Population

	Cadonilimab+XELOX N=305	Placebo+XELOX N=305
Median, mo (95% CI)	7.0 (6.4,8.4)	5.3 (4.5,5.6)
HR (95% CI)	0.53 (0.44-0.65)	
P value	<0.001	

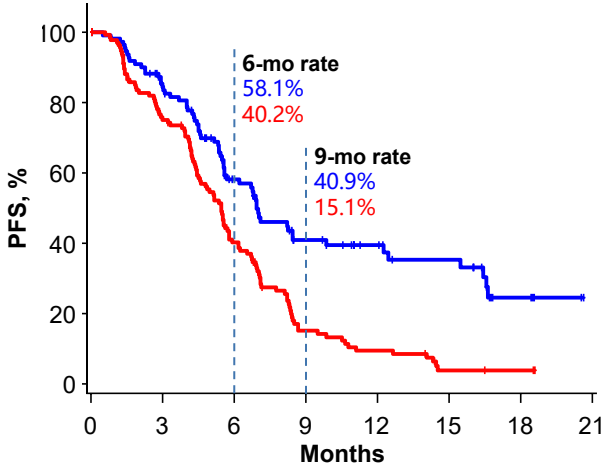


No. at risk

Cadonilimab+XELOX	305	232	137	85	59	40	20	0
Placebo+XELOX	305	207	105	38	25	14	8	0

PD-L1 CPS≥5

	Cadonilimab+XELOX N=116	Placebo+XELOX N=140
Median, mo (95% CI)	6.9 (5.6, 9.9)	5.5 (4.5, 5.8)
HR (95% CI)	0.51 (0.37-0.70)	
P value	<0.001	

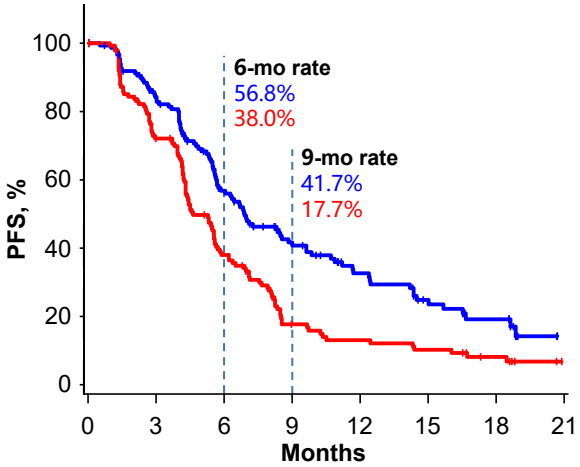


No. at risk

Cadonilimab+XELOX	116	89	50	29	21	16	5	0
Placebo+XELOX	140	97	50	16	10	3	2	0

PD-L1 CPS<5

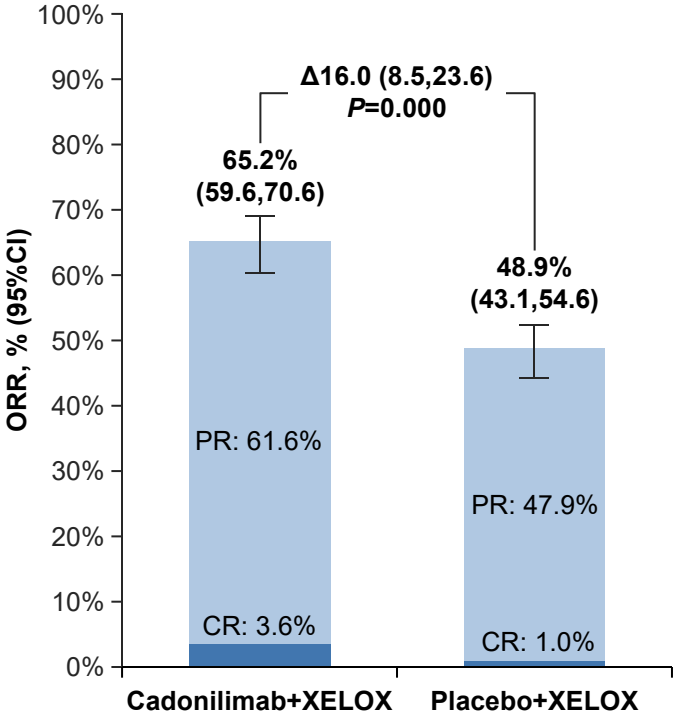
	Cadonilimab+XELOX N=157	Placebo+XELOX N=147
Median, mo (95% CI)	6.9 (5.7, 9.0)	4.6 (4.3, 5.6)
HR (95% CI)	0.60 (0.45-0.79)	
P value	<0.001	



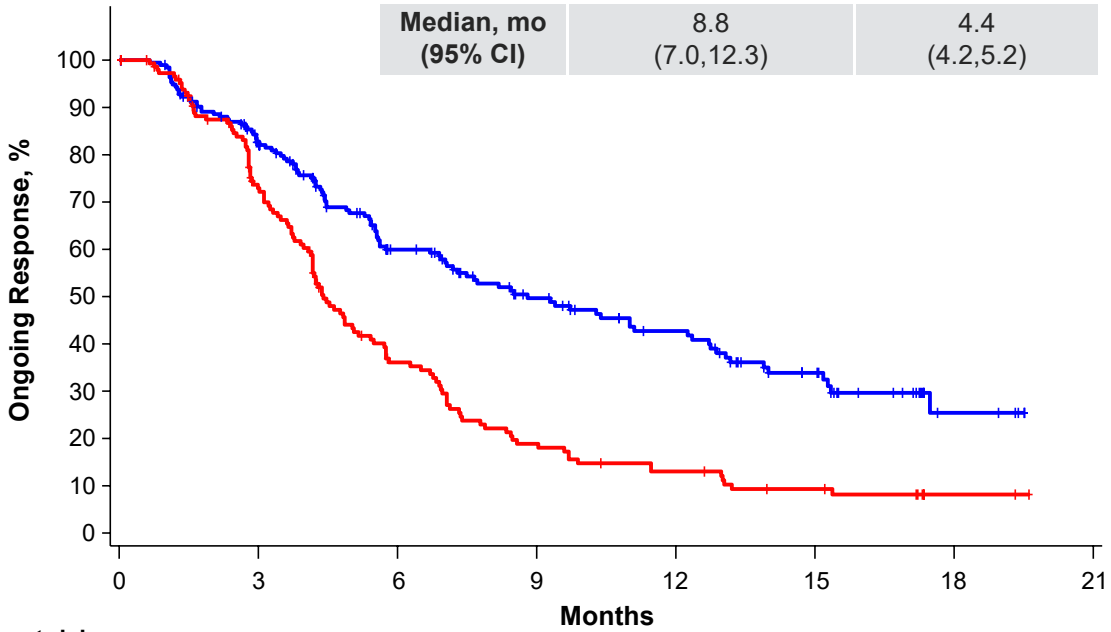
No. at risk

Cadonilimab+XELOX	157	119	71	45	30	19	11	0
Placebo+XELOX	147	98	48	19	14	11	6	0

Response and Duration of Response



	Cadonilimab+XELOX N=199	Placebo+XELOX N=149
Median, mo (95% CI)	8.8 (7.0,12.3)	4.4 (4.2,5.2)



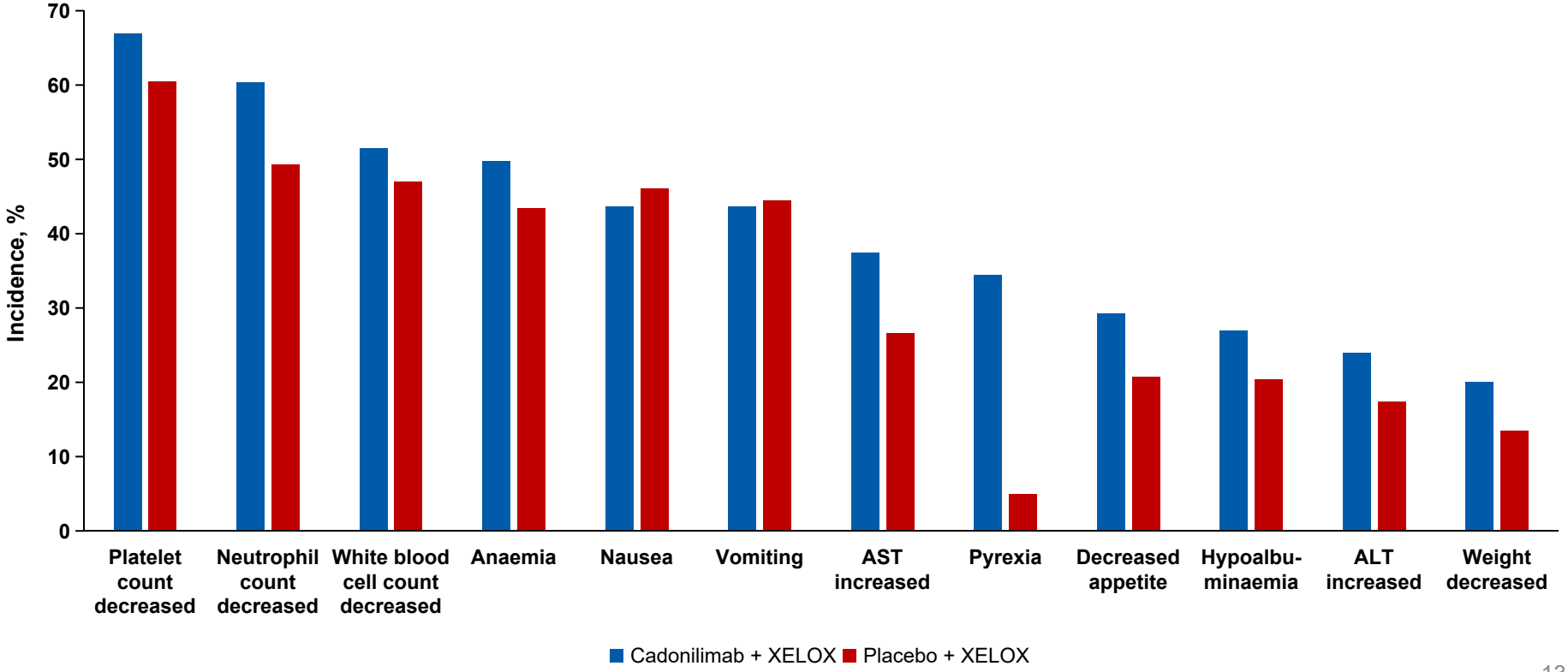
No. at risk								
Cadonilimab+XELOX	199	148	89	62	46	26	5	0
Placebo+XELOX	149	98	44	23	15	9	2	0

Safety Overview

Patients, n (%)	Cadonilimab+XELOX N=305		Placebo+XELOX N=304	
	Any grade	≥ Grade 3	Any grade	≥ Grade 3
TRAEs	302 (99.0)	201 (65.9)	296 (97.4)	163 (53.6)
TRSAEs	117 (38.4)	93 (30.5)	78 (25.7)	66 (21.7)
TRAEs Leading to Discontinuation*	73 (23.9)	47 (15.4)	20 (6.6)	16 (5.3)
AK104/Placebo-related Infusion-related Reactions (IRRs)	67 (22.0)	11 (3.6)	8 (2.6)	0
IRRs leading to AK104/Placebo discontinuation	9 (3.0)	5 (1.6)	0	0
Treatment-related deaths	5 (1.6)		7 (2.3)	
AK104/Placebo-related deaths	5 (1.6)[a]		5 (1.6)[b]	

TRAEs: treatment-related adverse events are defined as "Definitely Related" "Probably Related", or "Possibly Related" to cadonilimab/placebo, at least one chemotherapy component, or both;
TRSAEs: treatment-related severe adverse events;
[a] 2 participants due to death (cause unknown), 1 participant due to immune-mediated lung disease, respiratory failure, and cardiac failure, 1 participant due to acute kidney injury, hyperkalemia, and cardiac failure, 1 participant due to platelet count decreased.
[b] 1 participant each due to cerebral hemorrhage, disease progression, immune thrombocytopenia, respiratory failure, and upper gastrointestinal hemorrhage.
*: TRAEs leading to any drugs including chemotherapy and cadonilimab to discontinuation.

Treatment-Related Adverse Events in ≥20% of patients



Summary and Conclusion

- Cadonilimab is the first PD-1/CTLA-4 bispecific antibody to demonstrate statistically significant and clinically meaningful OS benefit in combination with chemo versus chemo alone in previously untreated patients with advanced G/GEJ adenocarcinoma.
  - Median OS: 15.0 vs 10.8 months; HR 0.62 [95%CI: 0.50-0.78]; P<0.001
  - OS benefits were consistently observed at all pre-specified CPS cutoffs
    - CPS≥5: mOS NR vs 10.6 months; HR 0.56 [95%CI: 0.39-0.80]; P<0.001
    - CPS<5: mOS 14.8 vs 11.1 months; HR 0.70 [95%CI: 0.51-0.95]; P=0.011
- The OS benefit of Cadonilimab plus chemotherapy was accompanied by improvements in PFS, ORR, and DoR compared with chemotherapy alone.
- Cadonilimab showed a survival advantage in GC patients with low PD-L1 expression, which has not been shown in other phase 3 trials with PD-1 antibodies.
- No new safety signals were identified with Cadonilimab + chemo.
- **Cadonilimab + chemo represents a new potential standard 1L treatment for patients with advanced G/GEJ adenocarcinoma, especially in patients with low PD-L1 expression.**

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- All authors contributed to and approved the presentation