ASCO Gastrointestinal Cancers Symposium

AK104-201：
A phase Ib/II, multicenter, open-label study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with chemotherapy (chemo) as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer

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Background

- Gastric cancer ranks fifth of the most common cancers and occupies the fourth leading cause of cancer mortality worldwide[1].
- Two studies demonstrated synergy between immune checkpoint inhibitors and chemo in G/GEJ cancer worldwide[2,3]. Compared to PD-1 monotherapy, the cotreatment of anti-PD-1 and anti-CTLA-4 has consistently shown a higher response rate but higher toxicity.
- AK104 is a PD-1/CTLA-4 bispecific antibody; this phase Ib/II (AK104-201) study evaluated the efficacy and safety of AK104 combined with XELOX (capecitabine combined with oxaliplatin) or modified XELOX (mXELOX) in the first-line setting of G/GEJ cancer treatment [4].

1. Sung H et al. Global Cancer Statistics 2020. GLOBOCAN.
2.Yelena YJ et al. Lancet 2021; 398: 27-40.
3. Jianming Xu et al. Annals of Oncology (2021) 32 (suppl_5): S1331.
4.ClinicalTrials.gov Identifier: NCT03852251

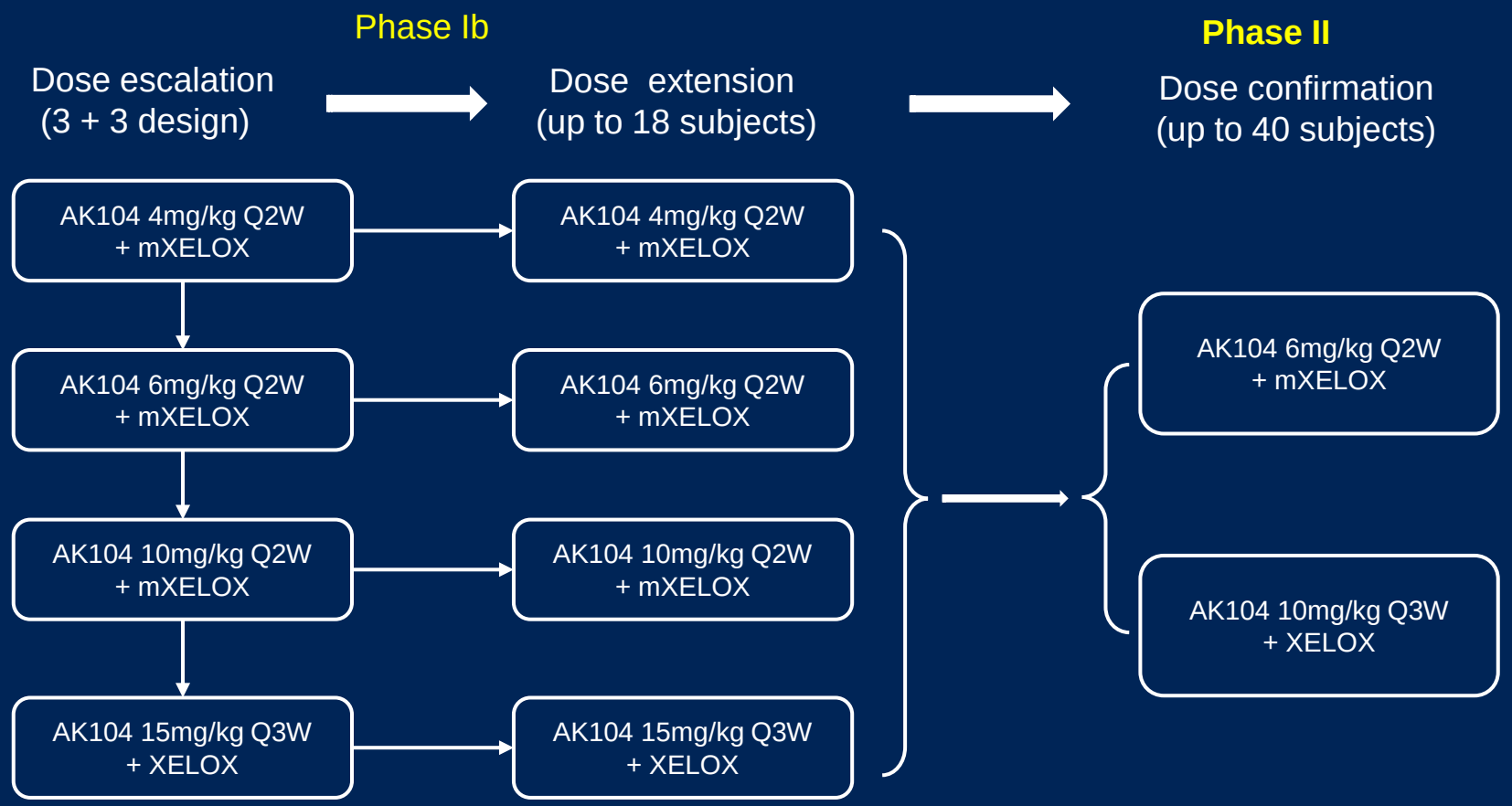
AK104-201: Gastric Cohort Study Design

Key Eligibility Criteria

- Unresectable advanced or metastatic G/GEJ adenocarcinoma
- No prior systemic therapy
- ECOG 0-1
- 18-75 yrs
- Measurable tumor lesion per RECIST v1.1 criteria

Primary Endpoints

- Phase Ib: safety
- Phase II: ORR by investigator



1. Capecitabine plus AK104 Maintenance.
2. Until progressive disease, excessive toxicity, withdrawal of consent or investigator's judgment, or a maximum treatment of 2 years.

mXELOX: Oxaliplatin: 85 mg/m^2, IV, day 1, every 2 weeks; Capecitabine 1000 mg/m^2, orally, twice daily, day 1 to 10, every 2 weeks; up to 12 cycles

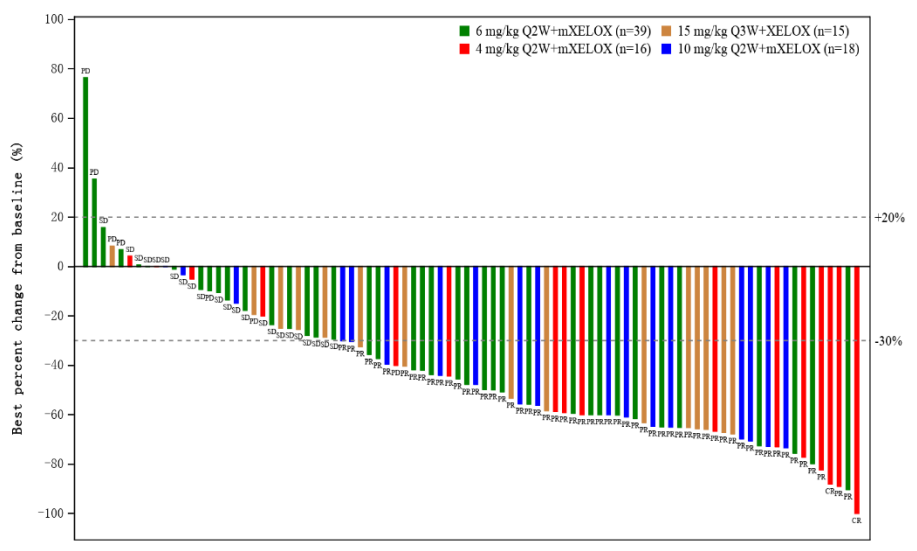
XELOX: Oxaliplatin: 130 mg/m^2, IV, day 1, every 3 weeks; Capecitabine 1000 mg/m^2, orally, twice daily, day 1 to 14, every 3 weeks; up to 6 cycles

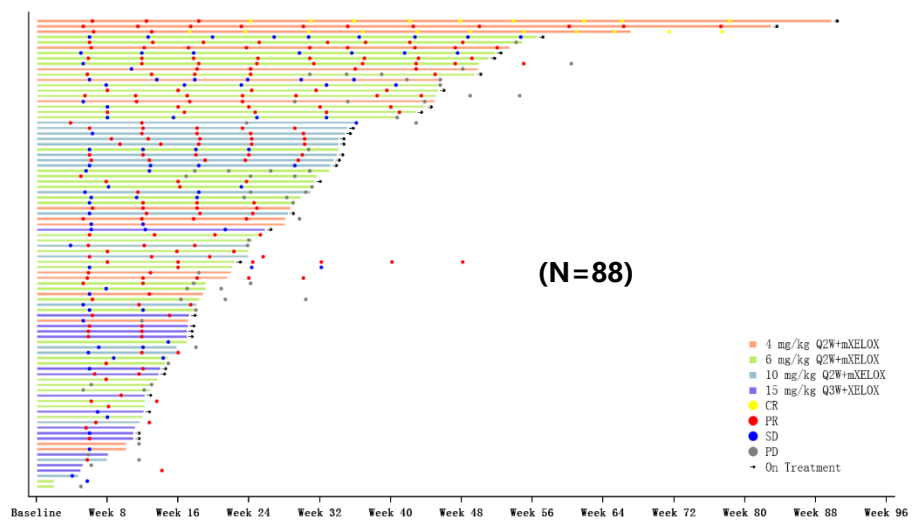
Baseline Characteristics

	4mg/kg Q2W N=18	6mg/kg Q2W N=40	10mg/kg Q2W N=18	15mg/kg Q3W N=18	10mg/kg Q3W N=2	Total N=96
Median age (range), years	65.9 (29, 75)	62.8 (41, 74)	59.9 (30, 73)	62.5 (29, 70)	51.9 (48, 56)	62.7 (29, 75)
Male, n(%)	13 (72.2)	28 (70.0)	15 (83.3)	10 (55.6)	2 (100.0)	68 (70.8)
ECOG PS 1, n(%)	12 (66.7)	26 (65.0)	11 (61.1)	11 (61.1)	0	60 (62.5)
Primary tumor location at initial diagnosis						
GEJ Adenocarcinoma, n(%)	4 (22.2)	5 (12.5)	3 (16.7)	0 (0.0)	0 (0.0)	12 (12.5)
Gastric Adenocarcinoma, n(%)	14 (77.8)	35 (87.5)	15 (83.3)	18 (100.0)	2 (100.0)	84 (87.5)
Disease Stage						
Metastatic, n(%)	15 (83.3)	34 (85.0)	18 (100.0)	17 (94.4)	2 (100.0)	86 (89.6)
Locally Advanced , n(%)	3 (16.7)	6 (15.0)	0 (0.0)	1 (5.6)	0 (0.0)	10 (10.4)
Previous surgery						
No, n(%)	16 (88.9)	32 (80.0)	15 (83.3)	14 (77.8)	1 (50.0)	78 (81.3)
Yes, n(%)	2 (11.1)	8 (20.0)	3 (16.7)	4 (22.2)	1 (50.0)	18 (18.8)
PD-L1 (22c3), n=84						
CPS≥5	4 (22.2)	7 (17.9)	1 (6.3)	2 (18.2)	0	14 (16.7)
CPS<5	14 (77.8)	32 (82.1)	15 (93.7)	9 (81.8)	0	70 (83.3)
Median duration of Follow-up (range),months	20.58 (0.5, 26.8)	10.73 (3.1, 23.1)	7.77 (5.5, 12.7)	3.32 (0.8, 6.0)	0.59 (0.4, 0.8)	9.95 (0.4, 26.8)

Cut off date: 13 Aug. 2021

Response and Duration of Response per RECIST v1.1

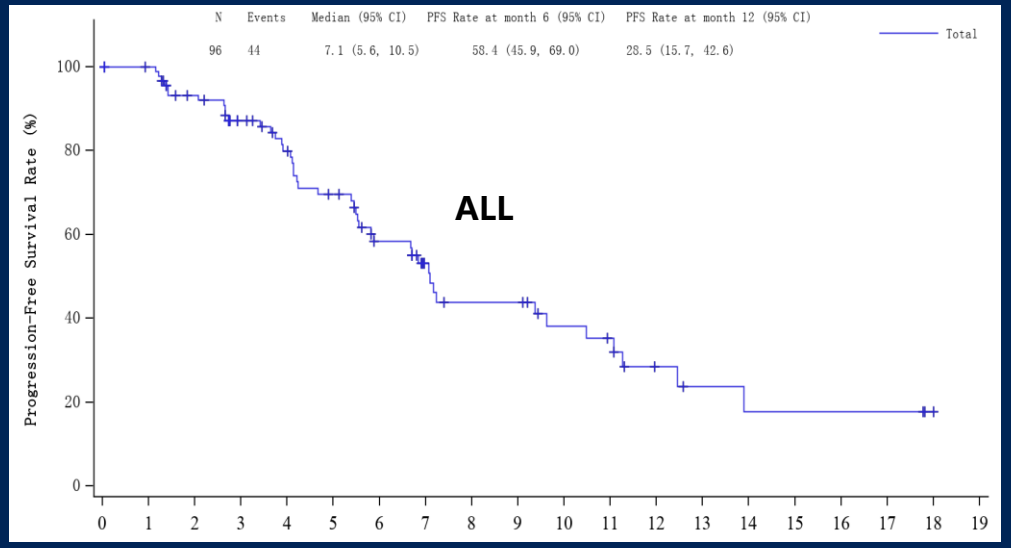


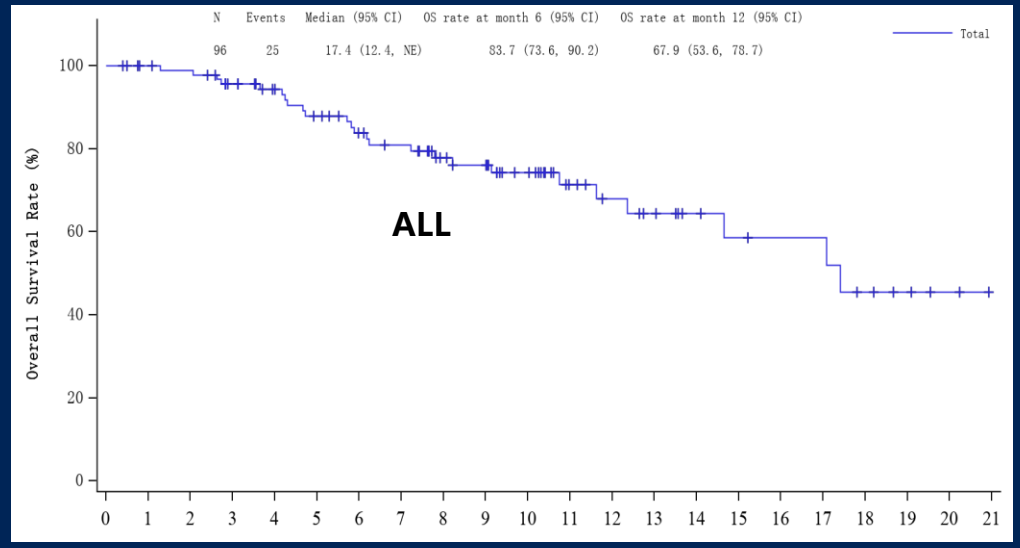


	4mg/kg Q2W (N=16)*	6mg/kg Q2W (N=39)*	10mg/kg Q2W (N=18)*	15mg/kg Q3W (N=15)*	Total (N=88)*
Objective Response Rate#, n(%)	11(68.8)	22(56.4)	15(83.3)	10(66.7)	58(65.9)
Disease Control Rate#, n(%)	81(93.8)	15(89.7)	18(100.0)	13(86.7)	81(92.0)
Best Overall Response#					
Complete Response, n(%)	2(12.5)	0(0.0)	0(0.0)	0(0.0)	2(2.3)
Partial Response, n(%)	9(56.3)	22(56.4)	15(83.3)	10(66.7)	56(63.6)
Stable Disease, n(%)	4(25.0)	13(33.3)	3(16.7)	3(20.0)	23(26.1)
Progressive Disease, n(%)	1(6.3)	4(10.3)	0(0.0)	2(13.3)	7(7.8)
Median DoR, [95%CI], months	6.93 [2.89,NE]	10.05 [2.89,11.20]	NR [2.96,NE]	NR [NE,NE]	6.93 [4.60,11.20]
Median TTR, (range), months	1.45 (1.2-4.2)	1.81 (1.1-3.7)	1.54 (0.9-2.9)	1.41 (1.3-3.3)	1.46 (0.9-4.2)

*: Subjects had at least one post-baseline tumor evaluation
#: All CR and PR were unconfirmed.
DoR: duration of response
TTR: time to response
Cut off date: 13 Aug. 2021

Progression-Free Survival and Overall Survival

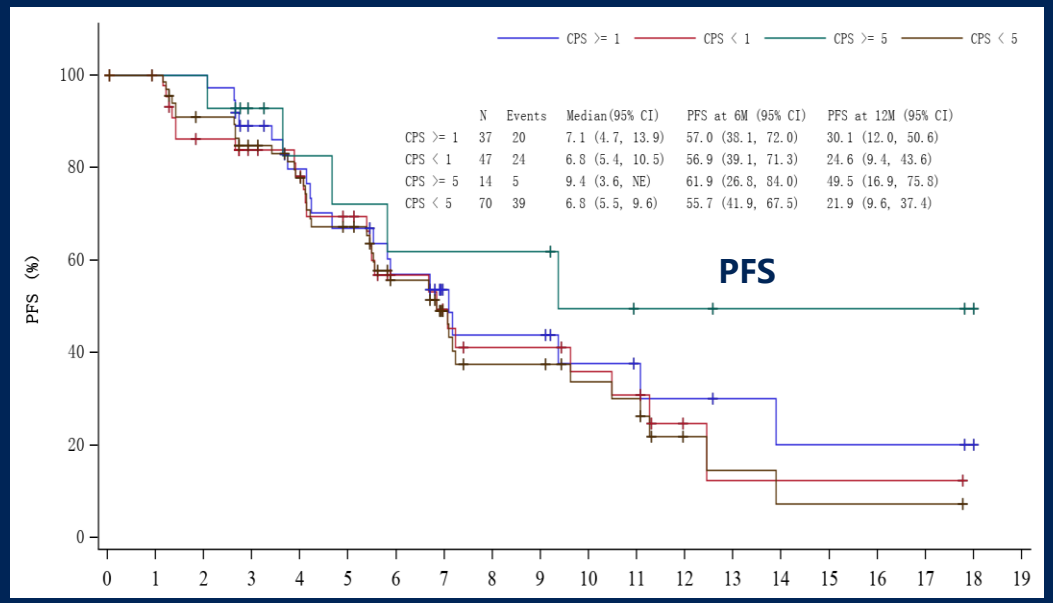


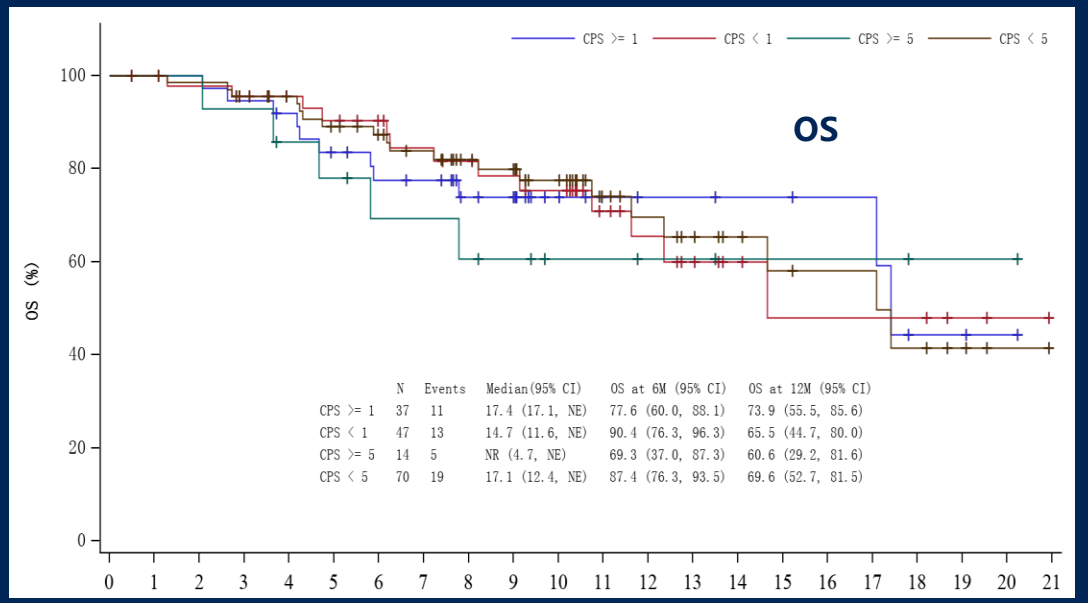


	4mg/kg Q2W (N=18)	6mg/kg Q2W (N=40)	10mg/kg Q2W (N=18)	15mg/kg Q3W (N=18)	Total (N=96)
PFS events, n(%)	10 (55.6)	26 (65.0)	5 (27.8)	3 (16.7)	44 (45.8)
Median PFS, [95%CI], months	7.23[2.73, NE]	7.06 [4.67, 10.48]	NR [5.45, NE]	NR [1.41, NE]	7.10 [5.55, 10.48]
OS events, n(%)	9 (50.0)	12 (30.0)	3 (16.7)	1 (5.6)	25 (26.0)
Median OS, [95%CI], months	17.08[7.23, NE]	NR [12.35, NE]	NR [10.74, NE]	NR [NE, NE]	17.41 [12.35, NE]

There were only 2 subjects in the group of 10mg Q3W and the median follow-up time was 0.59 months; the efficacy data didn't show in the table.
Cut off date: 13 Aug. 2021

Subgroup analysis by PD-L1 expression





PD-L1 Antibody	Cutoff Value	DOR(months) [95% CI]	PFS(months) [95% CI]	OS(months) [95% CI]
Dako-22c3	CPS≥1（n=37）	6.93[2.89,NE]	7.10[4.67, 13.90]	17.41[17.08, NE]
	CPS＜1（n=47）	10.05[4.17, NE]	6.83[5.39, 10.48]	14.65[11.63, NE]
	CPS≥5（n=14）	NR [1.81, NE]	9.36[3.65, NE]	NR[4.67, NE]
	CPS＜5（n=70）	5.82 [4.17, 11.10]	6.83[5.45, 9.63]	17.08[12.35, NE]

84 subjects had the PD-L1 results.

Safety Overview

Patients, n (%)	4mg/kg Q2W (N=18)	6mg/kg Q2W (N=40)	10mg/kg Q2W (N=18)	15mg/kg Q3W (N=18)	Total (N=96)
TRAEs	18 (100.0)	38 (95.0)	18 (100.0)	18 (100.0)	94 (97.9)
≥Grade 3 TRAEs	15 (83.3)	23 (57.5)	12 (66.7)	10 (55.6)	60 (62.5)
TRSAEs	8 (44.4)	14 (35.0)	10 (55.6)	8 (44.4)	40 (41.7)
TRAEs Leading to Permanently Discontinued	2 (11.1)	1 (2.5)	1 (5.6)	2 (11.1)	6 (6.3)
TRAEs Leading to Death	2 (11.1)	1 (2.5)	0 (0.0)	1 (5.6)	4 (4.2)
Infusion-related AEs	8 (44.4)	8 (20.0)	8 (44.4)	5 (27.8)	29 (30.2)
≥Grade 3 Infusion-related AEs	1 (5.6)	1 (2.5)	1 (5.6)	0 (0.0)	3 (3.1)

TRAEs: treatment-related adverse events; TRSAEs: treatment-related serious adverse events; AEs: adverse events;
There were only 2 subjects in the group of 10mg Q3W and the median follow-up time was 0.59 months; the safety data didn't show in the table.

Common Treatment Related Adverse Events (TRAEs)

	4 mg/kg Q2W (N=18)		6 mg/kg Q2W (N=40)		10 mg/kg Q2W (N=18)		15 mg/kg Q3W (N=18)		Total (N=96)	
	Any Grade	Grade≥3	Any Grade	Grade≥3	Any Grade	Grade≥3	Any Grade	Grade≥3	Any Grade	Grade≥3
Platelet count decreased	5 (27.8)	0 (0.0)	11 (27.5)	2 (5.0)	6 (33.3)	3 (16.7)	5 (27.8)	1 (5.6)	27 (28.1)	6 (6.3)
Anemia	1 (5.6)	0 (0.0)	16 (40.0)	3 (7.5)	6 (33.3)	0 (0.0)	2 (11.1)	0 (0.0)	25 (26.0)	3 (3.1)
Aspartate aminotransferase increased	2 (11.1)	0 (0.0)	11 (27.5)	0 (0.0)	9 (50.0)	0 (0.0)	3 (16.7)	0 (0.0)	25 (26.0)	0 (0.0)
Neutrophil count decreased	5 (27.8)	1 (5.6)	10 (25.0)	1 (2.5)	6 (33.3)	0 (0.0)	1 (5.6)	0 (0.0)	22 (22.9)	2 (2.1)
White blood cell count decreased	2 (11.1)	1 (5.6)	12 (30.0)	0 (0.0)	6 (33.3)	2 (11.1)	2 (11.1)	0 (0.0)	22 (22.9)	3 (3.1)
Alanine aminotransferase increased	2 (11.1)	0 (0.0)	8 (20.0)	0 (0.0)	7 (38.9)	0 (0.0)	2 (11.1)	0 (0.0)	19 (19.8)	0 (0.0)
Amylase increased	1 (5.6)	0 (0.0)	7 (17.5)	1 (2.5)	7 (38.9)	1 (5.6)	4 (22.2)	0 (0.0)	19 (19.8)	2 (2.1)
Infusion related reaction	6 (33.3)	0 (0.0)	4 (10.0)	0 (0.0)	3 (16.7)	0 (0.0)	5 (27.8)	0 (0.0)	18 (18.8)	0 (0.0)
Hypothyroidism	3 (16.7)	0 (0.0)	6 (15.0)	0 (0.0)	7 (38.9)	0 (0.0)	1 (5.6)	0 (0.0)	17 (17.7)	0 (0.0)
Pyrexia	1 (5.6)	0 (0.0)	7 (17.5)	0 (0.0)	3 (16.7)	0 (0.0)	2 (11.1)	0 (0.0)	13 (13.5)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	7 (17.5)	0 (0.0)	4 (22.2)	0 (0.0)	1 (5.6)	0 (0.0)	12 (12.5)	0 (0.0)
Asthenia	1 (5.6)	0 (0.0)	4 (10.0)	0 (0.0)	4 (22.2)	2 (11.1)	3 (16.7)	1 (5.6)	12 (12.5)	3 (3.1)
Rash	4 (22.2)	1 (5.6)	3 (7.5)	1 (2.5)	3 (16.7)	1 (5.6)	2 (11.1)	0 (0.0)	12 (12.5)	3 (3.1)
Lipase increased	0 (0.0)	0 (0.0)	7 (17.5)	0 (0.0)	3 (16.7)	1 (5.6)	1 (5.6)	0 (0.0)	11 (11.5)	1 (1.0)
Blood bilirubin increased	0 (0.0)	0 (0.0)	6 (15.0)	0 (0.0)	3 (16.7)	0 (0.0)	1 (5.6)	0 (0.0)	10 (10.4)	0 (0.0)
Blood thyroid stimulating hormone increased	2 (11.1)	0 (0.0)	6 (15.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	10 (10.4)	0 (0.0)

Summary and Conclusion

- ✓ AK104 combined with mXELOX/XELOX showed promising activity and manageable safety in previously untreated pts with advanced G/GEJ adenocarcinoma.
- ✓ AK104 + chemo represented a potential new first-line treatment option for advanced G/GEJ adenocarcinoma.
- ✓ A phase III study of AK104 combined with chemo as first-line therapy for G/GEJ adenocarcinoma is underway (NCT05008783).

Acknowledgments: All patients participating in the trial and their families.