CLARITY-Gastric01: a Phase 3 study of sonesitatug vedotin (Sone-Ve, AZD0901) in second or later-line advanced or metastatic Claudin 18.2-positive gastroesophageal carcinoma

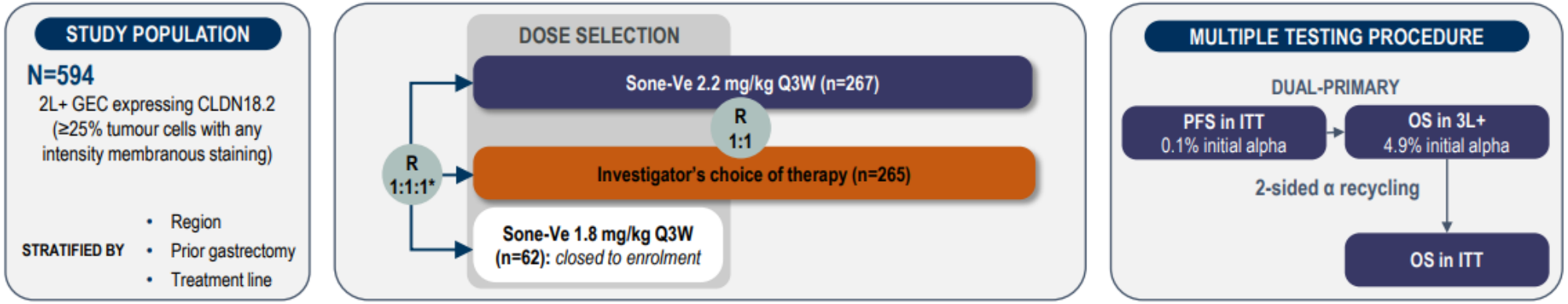
Background

- **CLDN18.2**, a tight junction protein that is expressed in 40–80% of gastroesophageal carcinomas depending on the threshold for positivity assessed, has emerged as a **validated therapeutic target**[1–3]
- In the 2L setting, **median OS is <10 months** with ramucirumab plus paclitaxel, whereas single chemotherapeutic options in the 3L+ setting are associated with an **OS benefit of <6 months**[4,5]
- **No CLDN18.2-targeted therapies** are approved globally for 2L+ therapy
- **Sone-Ve is a first-in-class CLDN18.2-targeted antibody-drug conjugate** comprised of a CLDN18.2-directed antibody conjugated to the microtubule-disrupting payload MMAE via a protease cleavable linker[6]

Here, we present the results of the global Phase 3 CLARITY-Gastric01 trial (NCT06346392) evaluating Sone-Ve versus investigator's choice of therapy in patients with 2L+ advanced or metastatic CLDN18.2-positive (≥25% tumour cells with membranous staining at any intensity) gastroesophageal carcinoma

Study design: CLARITY-Gastric01 (NCT06346392)

Randomised, open-label, sponsor-blinded, global Phase 3 study comparing the efficacy and safety of sonesitatug vedotin (Sone-Ve) to investigator's choice of therapy in patients with 2L+ advanced gastroesophageal carcinoma (GEC) expressing CLDN18.2



Investigator's choice of therapy

2L
- Ramucirumab + paclitaxel
- Paclitaxel (contraindication to ramucirumab only)
- Docetaxel (contraindication to ramucirumab only)

3L+
- Irinotecan
- TAS-102 (except China)
- Apatinib (China only)

Endpoints

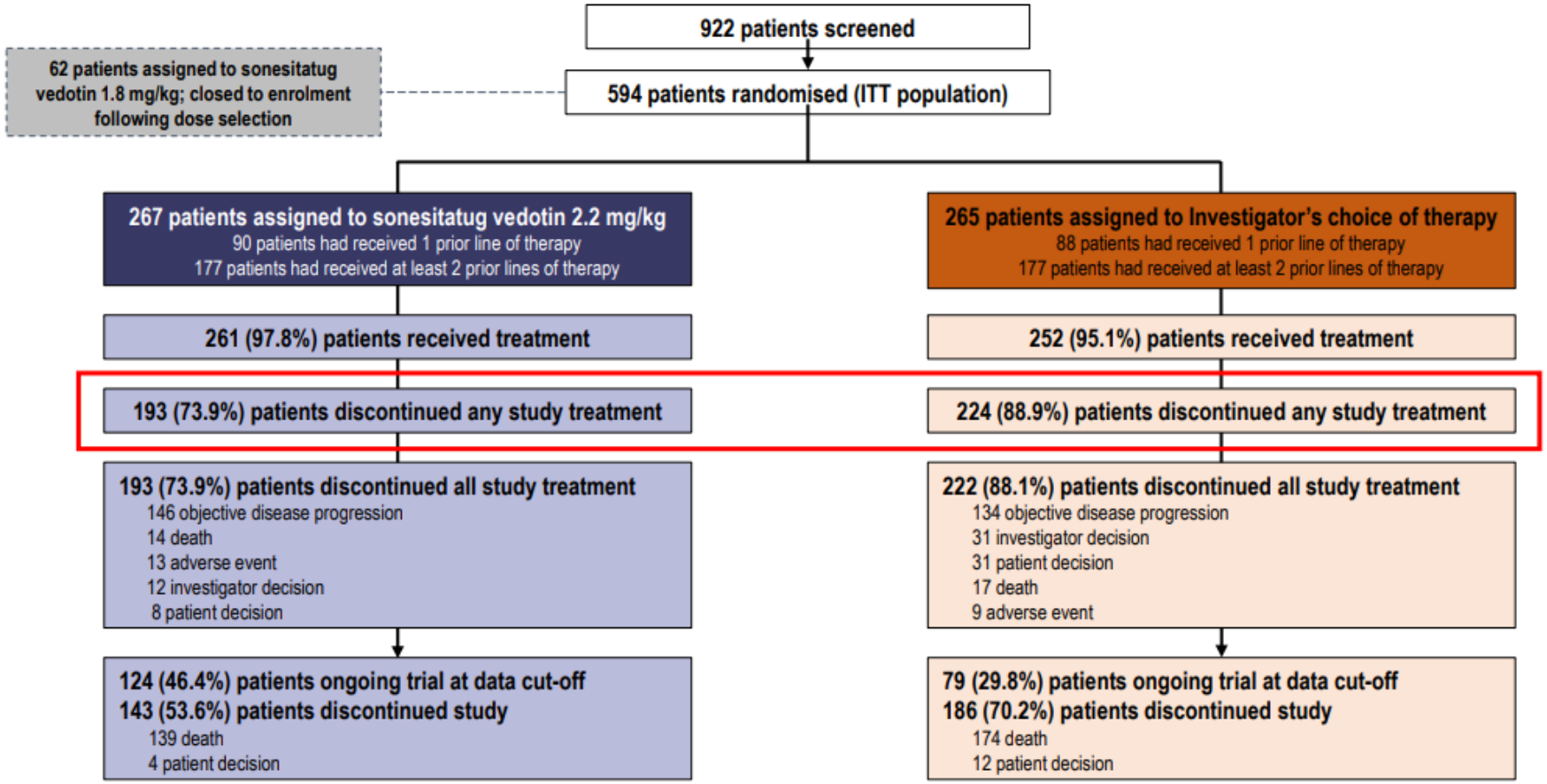
DUAL PRIMARY
- OS (3L+)†
- PFS by BICR (ITT [all 2L+])‡

KEY SECONDARY
- OS (ITT)

ADDITIONAL SECONDARY / EXPLORATORY
- PFS by BICR (3L+)
- ORR and DoR by BICR (ITT, 3L+)
- Safety
- OS by CLDN18.2 expression (ITT)
- PFS, ORR and DoR by Investigator (ITT, 3L+)
- OS in prespecified subgroups (ITT, 3L+)

*Patients were randomised 1:1:1 to Sone-Ve 2.2 mg/kg Q3W, Sone-Ve 1.8 mg/kg Q3W, or investigator's choice of therapy. As of January 2025, the optimal Sone-Ve monotherapy dose was determined to be 2.2 mg/kg IV Q3W and the 1.8 mg/kg arm was closed to enrollment. Randomisation continued in a 1:1 ratio Sone-Ve 2.2 mg/kg Q3w or investigator's choice of therapy. †All randomised patients who had received ≥2 prior lines of systemic therapy; ‡All randomised patients who had received ≥1 prior line of systemic therapy. PFS, ORR and DoR determined per RECIST v1.1. BICR, blinded independent central review; CLDN18.2, Claudin 18 isoform 2; DoR, duration of response; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomised; RECIST v1.1., Response Evaluation Criteria in Solid Tumours v1.1; Sone-Ve, sonesitatug vedotin; TAS-102, tipracil hydrochloride.

Patient disposition



Rates of discontinuation of any study treatment were higher in the investigator's choice of therapy versus the Sone-Ve arm

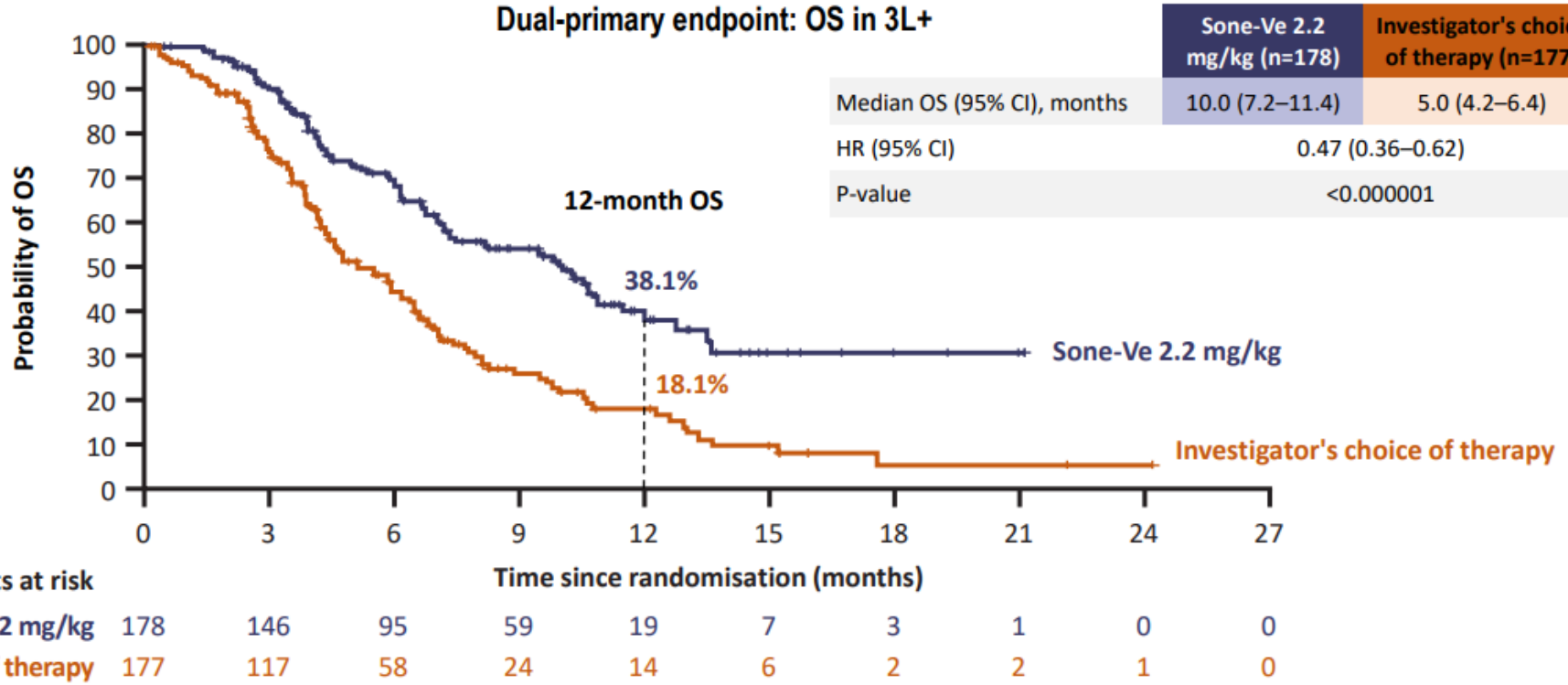
Baseline characteristics

Characteristic	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median age (range), years	57 (24 to 82)	57 (24 to 82)
Male sex, n (%)	150 (56.2)	159 (60.0)
Region, n (%)		
Japan or South Korea	55 (20.6)	54 (20.4)
Other Asia	107 (40.1)	106 (40.0)
Rest of world	105 (39.3)	105 (39.6)
Primary tumour location, n (%)		
Stomach	213 (79.8)	194 (73.2)
Gastroesophageal junction/Esophagus	54 (20.2)	71 (26.8)
Peritoneal metastasis, Yes, n (%)	163 (61.0)	148 (55.8)
CLDN18.2 expression,* n (%)		
<25%	1 (0.4)‡	0
≥25–<75%	83 (31.1)	71 (26.8)
≥75%	183 (68.5)	194 (73.2)
Prior gastrectomy, Yes, n (%)	98 (36.7)	93 (35.1)
Line of therapy,† n (%)		
2L	90 (33.7)	88 (33.2)
3L+	177 (66.3)	177 (66.8)
Prior anti-CLDN18.2 mAb, n (%)		
Zolbetuximab	10 (3.7)	7 (2.6)
Other	8 (3.0)	1 (0.4)

Demographics and baseline disease characteristics were generally balanced across treatment arms in the ITT population

*Expression in tumour cells with membranous staining at any intensity; †Line of therapy data are from the clinical reporting form and the number of patients in the sonesitatug vedotin arm differs from the equivalent data in the IRT due to mis-stratification in the clinical reporting form (IRT: 2L, n=89) ; ‡One patient had negative CLDN18.2 result but was randomised. IRT, interactive reporting technology software; mAb, monoclonal antibody.

OS in 3L+



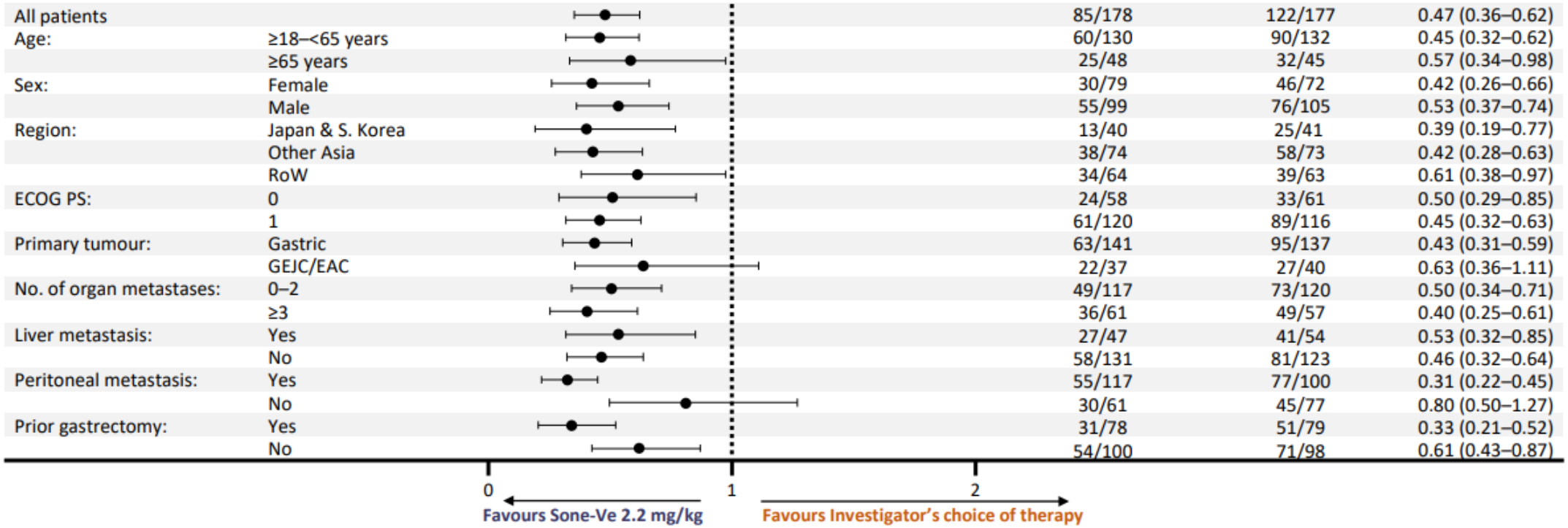
	Sone-Ve 2.2 mg/kg (n=178)	Investigator's choice of therapy (n=177)
Median OS (95% CI), months	10.0 (7.2–11.4)	5.0 (4.2–6.4)
HR (95% CI)	0.47 (0.36–0.62)	
P-value	<0.000001	

Sone-Ve significantly improved OS versus investigator's choice of therapy in the 3L+ population

The HR and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate censored observations. CI, confidence interval; HR, hazard ratio.

OS subgroup analysis in 3L+

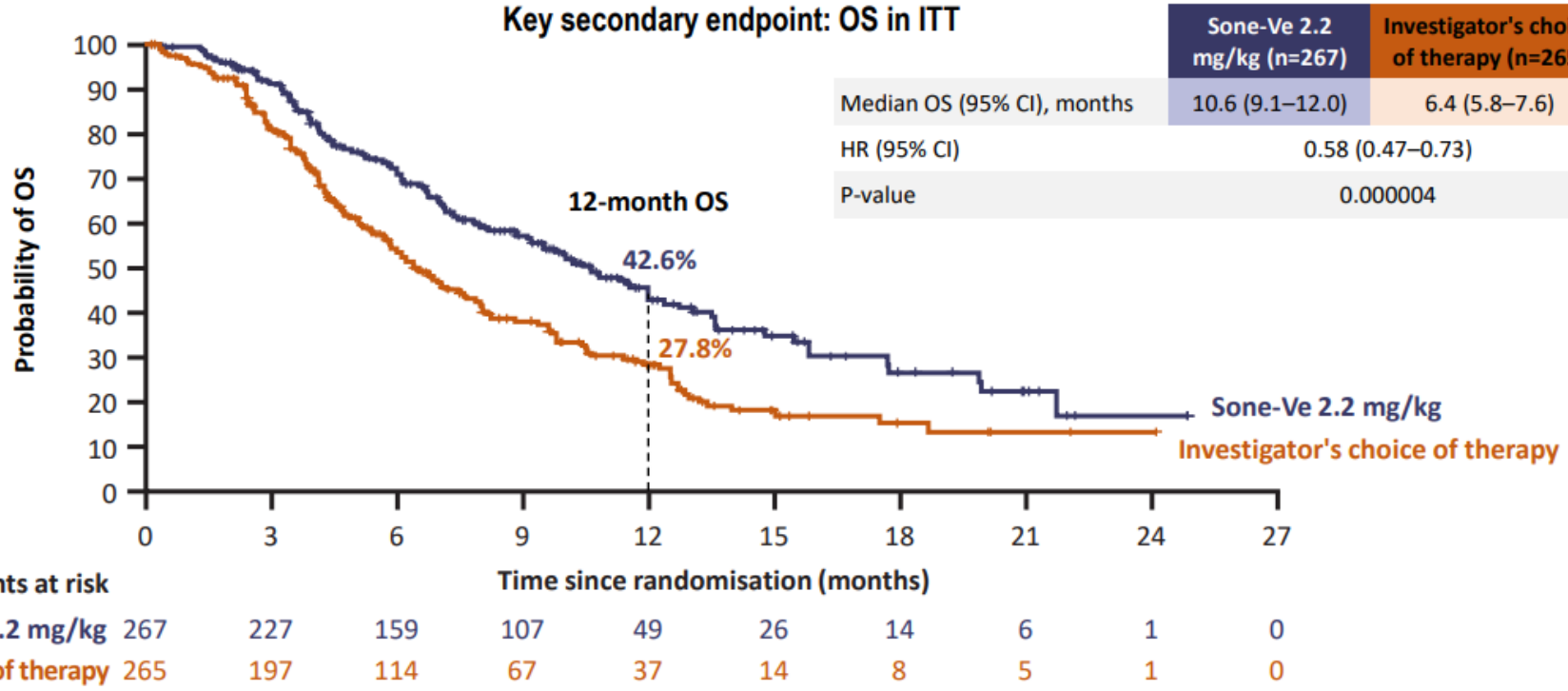
Subgroup		Sone-Ve 2.2 mg/kg	Investigator's choice of therapy	Hazard ratio (95% CI)
		No. of events/total no. of patients		
All patients		85/178	122/177	0.47 (0.36–0.62)
Age:	≥18–<65 years	60/130	90/132	0.45 (0.32–0.62)
	≥65 years	25/48	32/45	0.57 (0.34–0.98)
Sex:	Female	30/79	46/72	0.42 (0.26–0.66)
	Male	55/99	76/105	0.53 (0.37–0.74)
Region:	Japan & S. Korea	13/40	25/41	0.39 (0.19–0.77)
	Other Asia	38/74	58/73	0.42 (0.28–0.63)
	RoW	34/64	39/63	0.61 (0.38–0.97)
ECOG PS:	0	24/58	33/61	0.50 (0.29–0.85)
	1	61/120	89/116	0.45 (0.32–0.63)
Primary tumour:	Gastric	63/141	95/137	0.43 (0.31–0.59)
	GEJC/EAC	22/37	27/40	0.63 (0.36–1.11)
No. of organ metastases:	0–2	49/117	73/120	0.50 (0.34–0.71)
	≥3	36/61	49/57	0.40 (0.25–0.61)
Liver metastasis:	Yes	27/47	41/54	0.53 (0.32–0.85)
	No	58/131	81/123	0.46 (0.32–0.64)
Peritoneal metastasis:	Yes	55/117	77/100	0.31 (0.22–0.45)
	No	30/61	45/77	0.80 (0.50–1.27)
Prior gastrectomy:	Yes	31/78	51/79	0.33 (0.21–0.52)
	No	54/100	71/98	0.61 (0.43–0.87)



OS HR point estimates favoured Sone-Ve versus investigator's choice of therapy across all clinically relevant subgroups in the 3L+ population

All subgroups were prespecified in the protocol. The analysis was based on the Kaplan-Meier technique and was performed using an unstratified Cox proportional hazards model. The overall HR was calculated using a stratified Cox proportional hazards model, adjusting for Interactive Response Technology strata, including prior gastrectomy, region and line of therapy and using an implemented pooling strategy per the statistical analysis plan with treatment as the only covariate. Ties were handled by the Efron approach. CIs were calculated using a profile likelihood approach. A HR below 1 favours Sone-Ve. Because PFS and OS were the only endpoints that were part of the multiple testing procedure, the widths of the CIs for subgroups have not been adjusted for multiplicity and may not be used in place of hypothesis testing. EAC, oesophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastroesophageal junction adenocarcinoma; RoW, rest of world.

OS in ITT



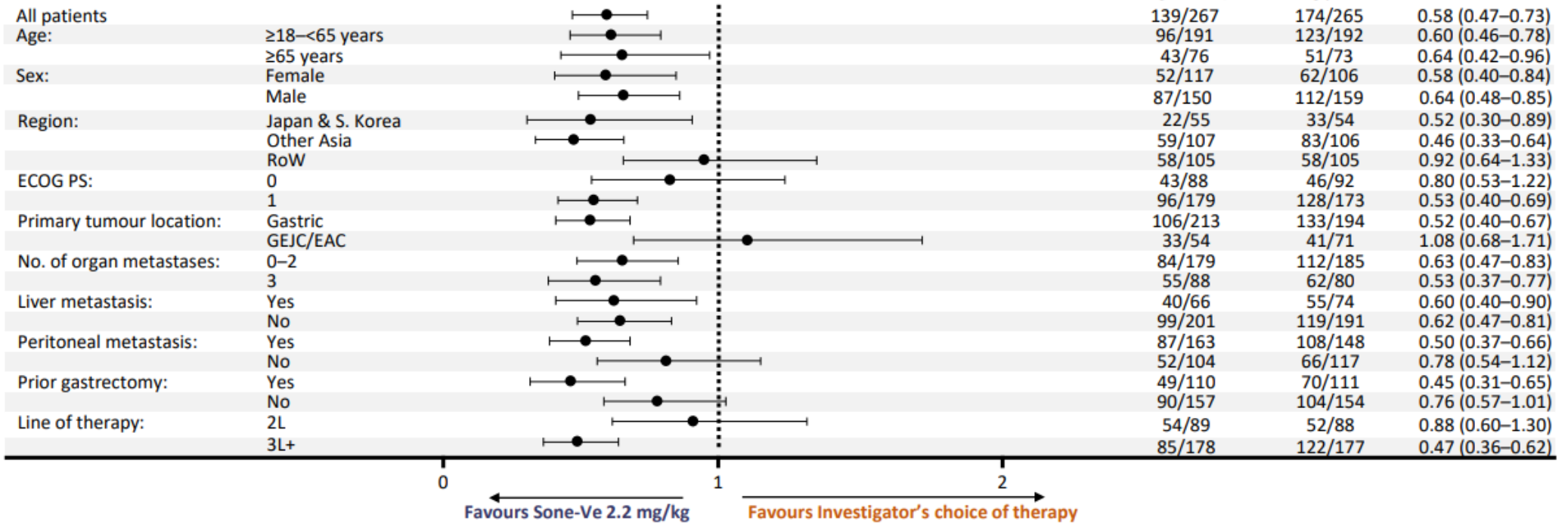
	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median OS (95% CI), months	10.6 (9.1–12.0)	6.4 (5.8–7.6)
HR (95% CI)	0.58 (0.47–0.73)	
P-value	0.000004	

Sone-Ve significantly improved OS versus investigator's choice of therapy in the ITT population

The HR and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate censored observations.

OS subgroup analysis in ITT

Subgroup		Sone-Ve 2.2 mg/kg	Investigator's choice of therapy	Hazard ratio (95% CI)
		No. of events/total no. of patients		
All patients		139/267	174/265	0.58 (0.47–0.73)
Age:	≥18–<65 years	96/191	123/192	0.60 (0.46–0.78)
	≥65 years	43/76	51/73	0.64 (0.42–0.96)
Sex:	Female	52/117	62/106	0.58 (0.40–0.84)
	Male	87/150	112/159	0.64 (0.48–0.85)
Region:	Japan & S. Korea	22/55	33/54	0.52 (0.30–0.89)
	Other Asia	59/107	83/106	0.46 (0.33–0.64)
	RoW	58/105	58/105	0.92 (0.64–1.33)
ECOG PS:	0	43/88	46/92	0.80 (0.53–1.22)
	1	96/179	128/173	0.53 (0.40–0.69)
Primary tumour location:	Gastric	106/213	133/194	0.52 (0.40–0.67)
	GEJC/EAC	33/54	41/71	1.08 (0.68–1.71)
No. of organ metastases:	0–2	84/179	112/185	0.63 (0.47–0.83)
	3	55/88	62/80	0.53 (0.37–0.77)
Liver metastasis:	Yes	40/66	55/74	0.60 (0.40–0.90)
	No	99/201	119/191	0.62 (0.47–0.81)
Peritoneal metastasis:	Yes	87/163	108/148	0.50 (0.37–0.66)
	No	52/104	66/117	0.78 (0.54–1.12)
Prior gastrectomy:	Yes	49/110	70/111	0.45 (0.31–0.65)
	No	90/157	104/154	0.76 (0.57–1.01)
Line of therapy:	2L	54/89	52/88	0.88 (0.60–1.30)
	3L+	85/178	122/177	0.47 (0.36–0.62)



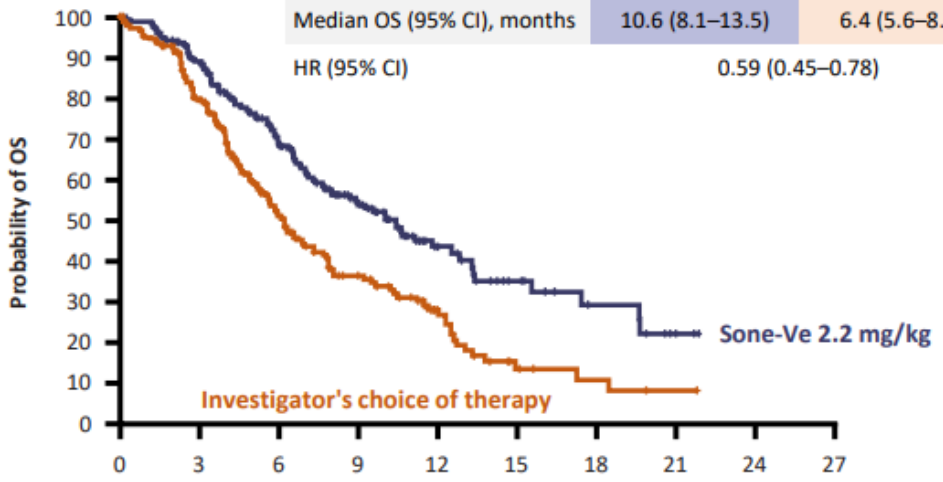
OS HR point estimates favoured Sone-Ve versus investigator's choice of therapy across most clinically relevant subgroups in the ITT population

All subgroups were prespecified in the protocol. The analysis was based on the Kaplan-Meier technique and was performed using an unstratified Cox proportional hazards model. The overall HR was calculated using a stratified Cox proportional hazards model, adjusting for Interactive Response Technology strata, including prior gastrectomy, region and line of therapy and using an implemented pooling strategy per the statistical analysis plan with treatment as the only covariate. Ties were handled by the Efron approach. CIs were calculated using a profile likelihood approach. A HR below 1 favours Sone-Ve. Because PFS and OS were the only endpoints that were part of the multiple testing procedure, the widths of the CIs for subgroups have not been adjusted for multiplicity and may not be used in place of hypothesis testing. EAC, oesophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastroesophageal junction adenocarcinoma; RoW, rest of world.

OS by CLDN18.2 expression levels in ITT

CLDN18.2 ≥75% expression

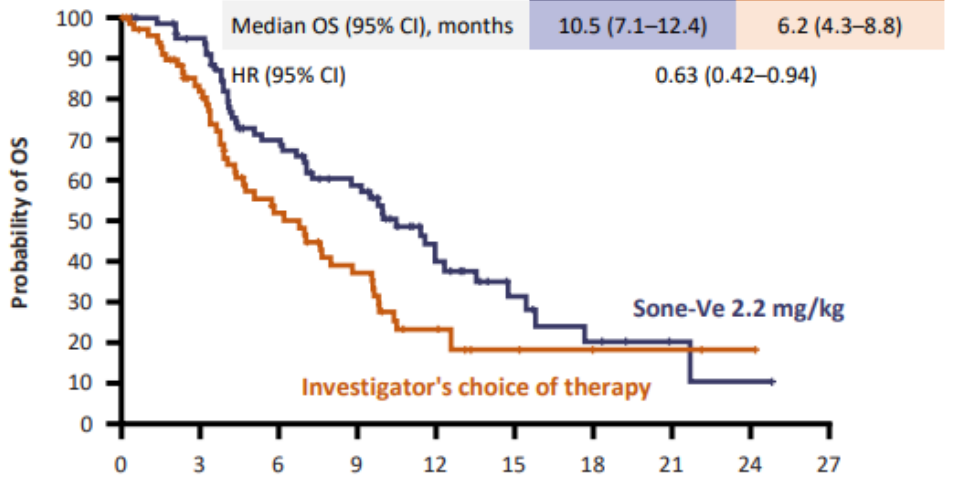
	Sone-Ve 2.2 mg/kg (n=183)	Investigator's choice of therapy (n=194)
Median OS (95% CI), months	10.6 (8.1–13.5)	6.4 (5.6–8.0)
HR (95% CI)	0.59 (0.45–0.78)	



No. of patients at risk										
Sone-Ve 2.2 mg/kg	183	152	107	70	31	17	9	4	0	0
Investigator's choice of therapy	194	146	85	48	27	9	5	2	0	0

CLDN18.2 ≥25% to <75% expression

	Sone-Ve 2.2 mg/kg (n=83)	Investigator's choice of therapy (n=71)
Median OS (95% CI), months	10.5 (7.1–12.4)	6.2 (4.3–8.8)
HR (95% CI)	0.63 (0.42–0.94)	



No. of patients at risk										
Sone-Ve 2.2 mg/kg	83	74	51	37	18	9	5	2	1	0
Investigator's choice of therapy	71	51	29	19	10	5	3	3	1	0

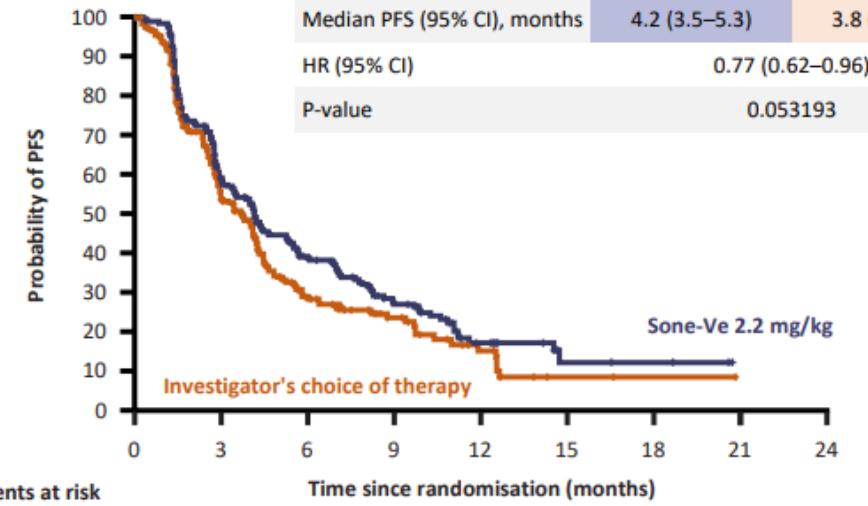
OS benefit with Sone-Ve vs investigator's choice of therapy was consistent across CLDN18.2 expression levels

The HR and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate censored observations.

PFS by BICR in ITT and in 3L+

Dual-primary endpoint: PFS by BICR in ITT

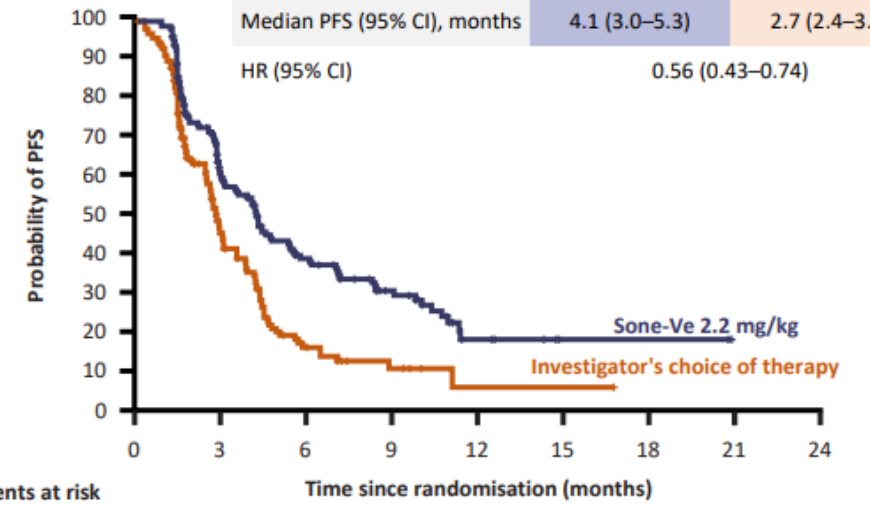
	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median PFS (95% CI), months	4.2 (3.5–5.3)	3.8 (3.0–4.2)
HR (95% CI)	0.77 (0.62–0.96)	
P-value	0.053193	



No. of patients at risk									
Sone-Ve 2.2 mg/kg	267	133	76	39	15	4	3	0	0
Investigator's choice of therapy	265	114	45	23	10	2	1	0	0

Secondary endpoint: PFS by BICR in 3L+

	Sone-Ve 2.2 mg/kg (n=178)	Investigator's choice of therapy (n=177)
Median PFS (95% CI), months	4.1 (3.0–5.3)	2.7 (2.4–3.0)
HR (95% CI)	0.56 (0.43–0.74)	



No. of patients at risk									
Sone-Ve 2.2 mg/kg	178	82	46	24	7	2	2	0	0
Investigator's choice of therapy	177	53	13	5	1	1	0	0	0

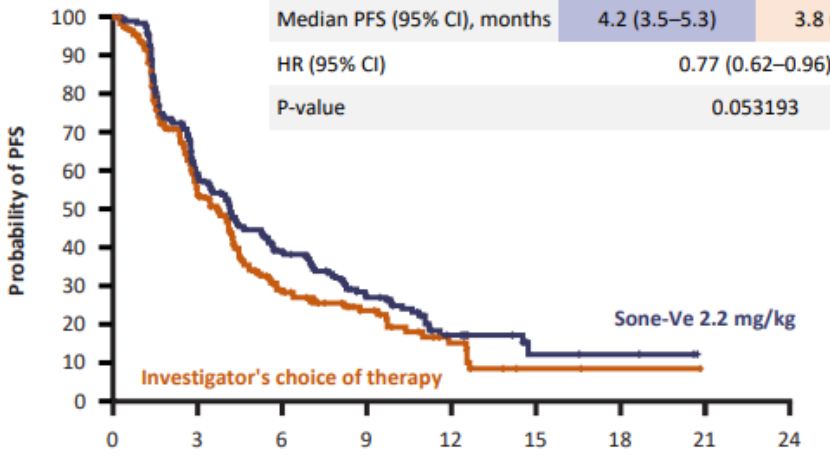
In the ITT population, Sone-Ve showed a positive trend for PFS by BICR, but did not meet the threshold for statistical significance
In the 3L+ population, Sone-Ve improved PFS by BICR versus investigator's choice of therapy*

*Not formally tested. The HR for event or death and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate censored observations. BICR, blinded independent central review.

PFS by BICR and PFS by investigator in ITT

Dual-primary endpoint: PFS by BICR in ITT

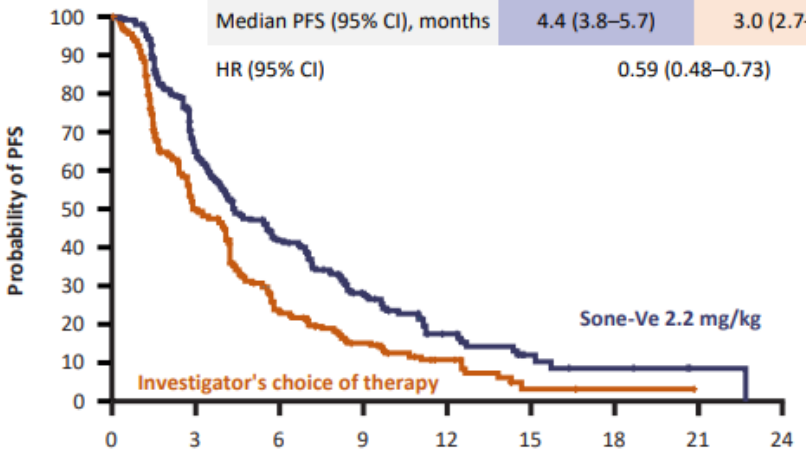
	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median PFS (95% CI), months	4.2 (3.5–5.3)	3.8 (3.0–4.2)
HR (95% CI)	0.77 (0.62–0.96)	
P-value	0.053193	



No. of patients at risk									
Sone-Ve 2.2 mg/kg	267	133	76	39	15	4	3	0	0
Investigator's choice of therapy	265	114	45	23	10	2	1	0	0

Exploratory endpoint: PFS by investigator in ITT

	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median PFS (95% CI), months	4.4 (3.8–5.7)	3.0 (2.7–4.1)
HR (95% CI)	0.59 (0.48–0.73)	

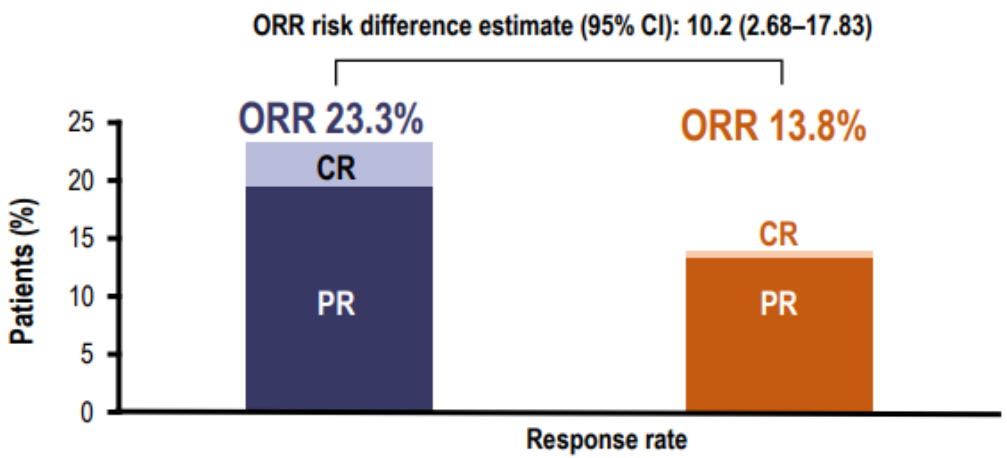


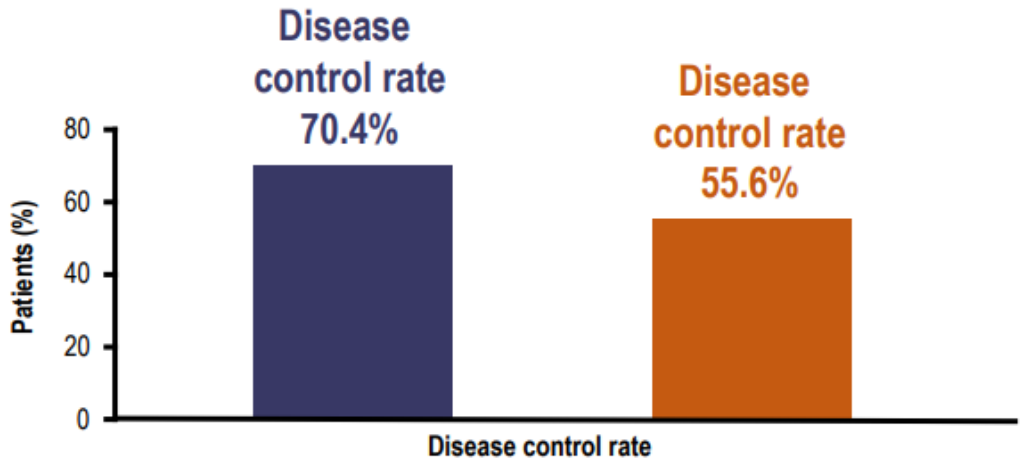
No. of patients at risk									
Sone-Ve 2.2 mg/kg	267	151	91	48	20	7	4	1	0
Investigator's choice of therapy	265	111	44	23	12	2	1	0	0

PFS assessment by investigator showed a more pronounced treatment effect (HR 0.59) than BICR, consistent with the observed OS benefit

The HR for event or death and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate censored observations.

Response and disease control in ITT





	Sone-Ve 2.2 mg/kg	Investigator's choice of therapy
Patients with measurable disease at baseline	189	189
Confirmed ORR, n (%)	44 (23.3)	26 (13.8)
Complete response, n (%)	7 (3.7)	1 (0.5)
Disease control rate, n (%)	133 (70.4)	105 (55.6)
Median duration of response, months (95% CI)*	8.5 (5.8–NC)	6.8 (2.9–NC)

Sone-Ve demonstrated higher response and disease control rates, and longer duration of response versus investigator's choice of therapy
More participants achieved complete response with Sone-Ve versus investigator's choice of therapy

*Duration of response by BICR is calculated in all randomised patients in each arm (Sone-Ve n=267; Investigator's choice of therapy, n=265). BICR, blinded independent central review; CR, complete response; NC, not calculated; ORR, objective response rate; PR, partial response.

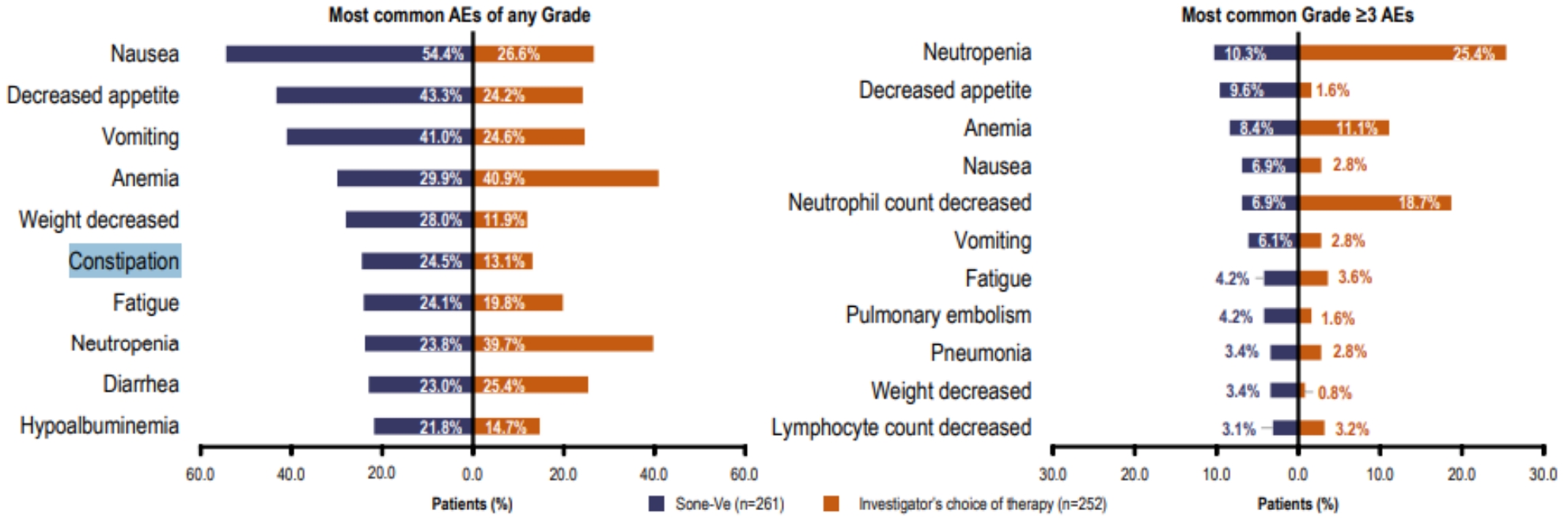
Safety

	Sone-Ve 2.2 mg/kg (n=261)	Investigator's choice of therapy (n=252)
Median (range) duration of exposure, months	3.9 (0.2–24.7)	2.1 (0.2–22.0)
Any AE, n (%)	254 (97.3)	237 (94.0)
Possibly related to treatment, n (%)*	224 (85.8)	205 (81.3)
Any AE of CTCAE Grade ≥3, n (%)	138 (52.9)	154 (61.1)
Possibly related to treatment, n (%)*	95 (36.4)	113 (44.8)
Any SAE, n (%)	91 (34.9)	79 (31.3)
Any AE leading to discontinuation of study treatment, n (%)	13 (5.0)	11 (4.4)
Possibly related to study treatment, n (%)*	8 (3.1)	11 (4.4)
Any AE leading to interruption of study treatment or dose delay, n (%)	95 (36.4)	102 (40.5)
Any AE leading to dose reductions, n (%)	55 (21.1)	58 (23.0)
Any AE with outcome of death, n (%)	11 (4.2)	6 (2.4)
Possibly related to treatment,† n (%)*	3 (1.1)	2 (0.8)

Sone-Ve was associated with a manageable safety profile with a lower incidence of Grade ≥3 AEs than investigator's choice of therapy

Safety was assessed in the Safety Analysis Set, defined as all patients who received ≥1 dose of treatment. Included are AEs with an onset date or that worsen on or after the date of first dose and up to and including 97 days following the date of last dose of study treatment, or, up to the day prior to start of subsequent cancer therapy, whichever comes first. Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences. *Possibly related to treatment is defined as reasonable possibility that the adverse event was caused by study treatment, as assessed by investigator. Missing responses are counted as possibly related. †Fatal AEs in Sone-Ve arm: pneumonia, jaundice cholestatic, cardiac failure; in investigator's choice of therapy arm: pulmonary embolism and abdominal infection. CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

Most common adverse events



Higher rates of GI-related AEs were observed with Sone-Ve versus investigator's choice of therapy
Lower rates of haematologic toxicity were observed with Sone-Ve versus investigator's choice of therapy

Safety was assessed in the Safety Analysis Set, defined as all patients who received ≥1 dose of treatment. Included are adverse events with an onset date or that worsen on or after the date of first dose and up to and including 97 days following the date of last dose of study treatment, or, up to the day prior to start of subsequent cancer therapy, whichever comes first. Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences. The top 10 most common treatment-emergent AEs of any Grade and Grade ≥3 AEs are shown. Neutropenia includes decreased neutrophil count, neutropenia, and febrile neutropenia.. Any Grade peripheral neuropathy occurred in 56 (21.5%) patients in the Sone-Ve arm and 36 (14.3%) patients in the investigator's choice of therapy arm; Grade ≥3 peripheral neuropathy occurred in 2 (0.8%) patients in the Sone-Ve arm and 1 (0.4%) patients in the investigator's choice of therapy arm. Any Grade alopecia occurred in 13 (5.0%) of patients in the Sone-Ve arm and 36 (14.3%) in investigator's choice of therapy arm.

Conclusions

CLARITY-Gastric01 is the first global, Phase 3 trial to demonstrate a statistically significant OS benefit and a manageable safety profile with a CLDN18.2 targeting antibody-drug conjugate in patients with previously treated advanced or metastatic CLDN18.2-positive GEC (defined as ≥25% tumour cells with membraneous staining at any intensity)

Sone-Ve showed a statistically significant and clinically meaningful improvement in OS versus investigator's choice of therapy

- Median OS was doubled to 10 months in the 3L+ population and improved by over 4 months to 10.6 months in the ITT (2L+) population
- OS benefit was maintained across CLDN18.2 expression subgroups

PFS by BICR in ITT (HR 0.77) did not reach the threshold for statistical significance

- PFS by BICR in 3L+ was improved with Sone-Ve versus investigator's choice of therapy (HR 0.56)
- Assessment of PFS by investigator in ITT showed a more pronounced treatment effect (HR 0.59) than by BICR

Sone-Ve demonstrated a differentiated and manageable safety profile versus investigator's choice of therapy

Sone-Ve is a potential new standard of care in the 2L+ setting for patients with advanced or metastatic CLDN18.2-positive gastroesophageal carcinoma