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PRECISION MEDICINE IN ADVANCED GASTRIC CANCER: INTEGRATING NEW BIOMARKERS AND TARGETED STRATEGIES INTO CLINICAL PRACTICE

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CLINICAL TAKEAWAYS

Broader CLDN18.2 testing and lower expression thresholds may expand eligibility for future targeted therapies

- CLARITY-Gastric01 used a lower CLDN18.2 expression threshold (≥25%, any staining) than the threshold for zolbetuximab (≥75%, moderate to strong staining intensity), highlighting the importance of routine testing and collaboration with pathologists to identify eligible patients

CLDN18.2-directed ADCs may expand the treatment landscape into 2nd-line and beyond gastric/GEJ cancer

- Zolbetuximab plus chemotherapy improved both PFS and OS in SPOTLIGHT and GLOW. Meanwhile, in CLARITY-Gastric01, Sone-Ve doubled median OS in the 3rd-line-or-later population, with an OS benefit also observed in the 2nd-line-or-later population

Consider differences in treatment approach and tolerability

- Sone-Ve is a chemotherapy-free ADC, whereas zolbetuximab is combined with chemotherapy, with implications for treatment-related toxicity and management

Prepare for potential clinical implementation: optimise toxicity management & explore earlier lines of therapy

- Clinical implementation will require proactive toxicity management. Earlier treatment may benefit patients before they become too frail, while further studies clarify optimal sequencing and combinations

ADC, antibody-drug conjugate; CLDN18.2, claudin 18.2; OS, overall survival; PFS, progression-free survival

EDUCATIONAL OBJECTIVES

1. **Evaluate the clinical significance of CLDN18.2** as a therapeutic target and its impact on the evolving treatment algorithm for advanced gastric and GEJ cancers

2. **Apply best practices for CLDN18.2 biomarker testing**, including IHC scoring and its integration into the diagnostic workflow alongside HER2 and PD-L1

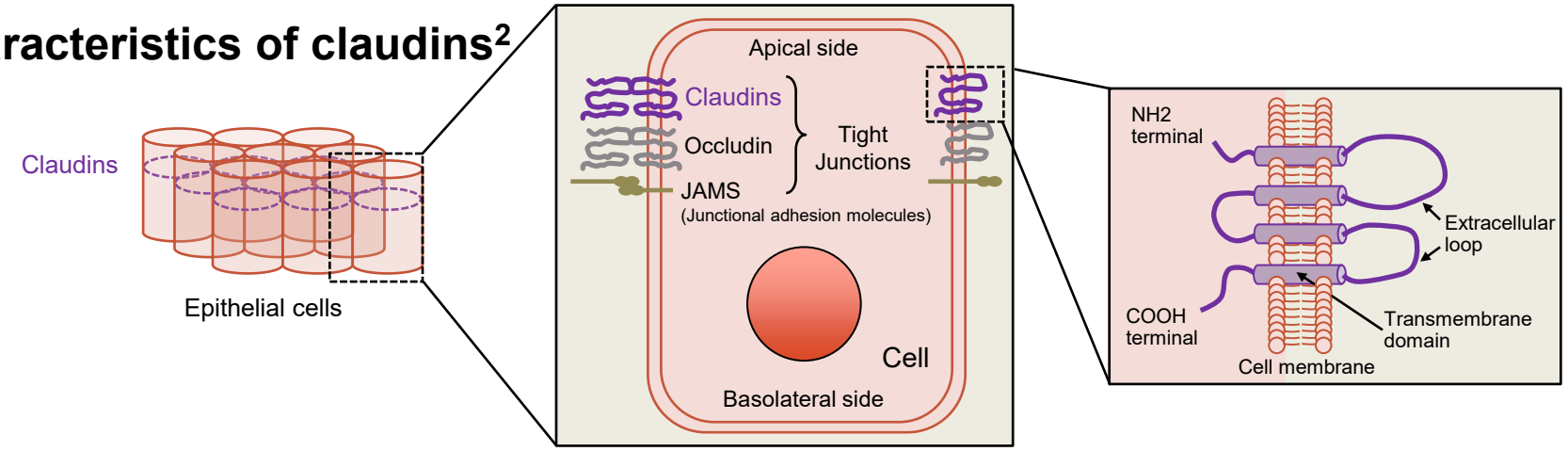
3. **Appraise the latest clinical evidence** regarding the efficacy and safety of CLDN18.2-targeted ADCs

ADC, antibody-drug conjugate; CLDN18.2, claudin 18.2; GEJ, gastroesophageal junction; IHC, immunohistochemistry

WHAT IS CLAUDIN (CLDN)18.2?

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in gastric cancer cells[1-3]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells,[1-4] making it a promising target[2,3,5]

Main characteristics of claudins[2]



What are claudins?
- Major membrane proteins which form the components of tight junctions
- 27 isoforms have been identified, whose expression is tissue-specific

Main function of claudins
- Seal intercellular space in epithelial sheets
- Regulate permeability, paracellular transport, and signal transduction in sealing intercellular spaces

Structure of claudins
- Size of 20–27-kDa
- Four transmembrane domains
- Two extracellular loops with the capacity to bind monoclonal antibodies

CLDN18.2, claudin 18.2; G/GEJ, gastric or gastroesophageal junction

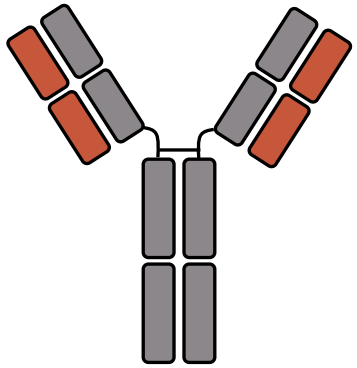
1. Moran D, et al. Ann Oncol. 2018;29 (Supplement 8):VIII32; 2. Kubota Y, Shitara K. Ther Adv Med Oncol. 2024;16:17588359231217967; 3. Waters R, et al. JCO Precis Oncol. 2024;8:e2300543; 4. Shitara K, et al. Gastric Cancer. 202;27:1058-1068; 5. Kubota K, et al. ESMO Open. 2023;8:100762

MAJOR CLAUDIN 18.2 STRATEGIES

FDA approved[1]

Engineered mAb

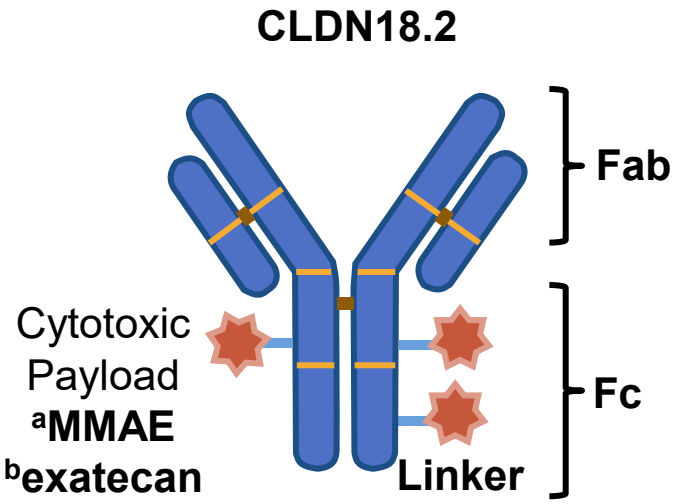
e.g. Zolbetuximab (Humanised IgG1)[2,3]



Emerging treatment strategies[3-5]

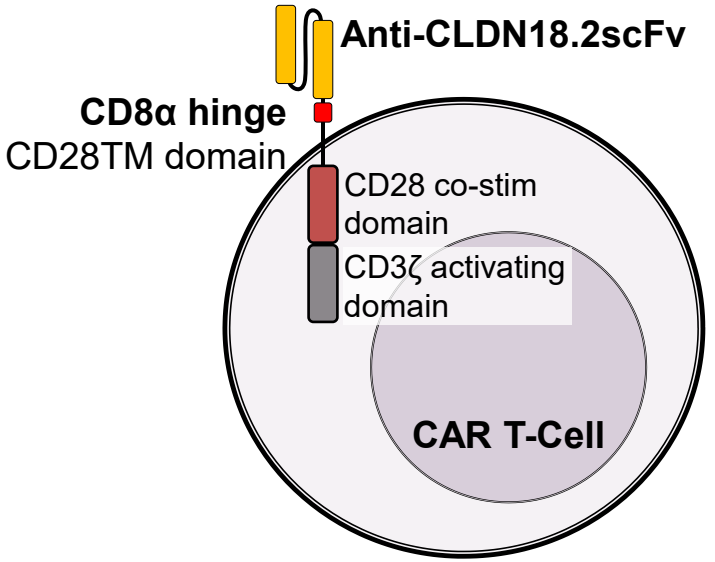
Antibody–Drug Conjugate[6]

e.g. Sonesitatug vedotin[a], Arcotatug tavatecan[b]



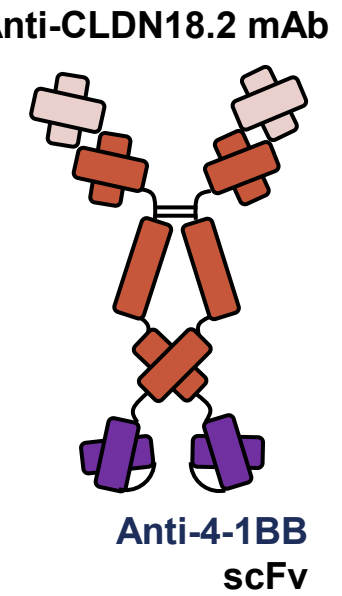
CAR T-Cell[7]

e.g. CT041



Bispecific Ab[8]

e.g. Givastomig



[a]Sonesitatug vedotin cytoxic payload is MMAE; [b]Arcotatug tavatecan cytoxic payload is exatecan

Ab, antibody; CAR-T, chimeric antigen receptor T cell; CLDN18.2, claudin 18.2; Fab, fragment antigen-binding; Fc, fragment crystallisable; FDA, Food and Drug Administration; mAb, monoclonal antibody; MMAE, monomethyl auristatin E

1. U.S. Food and Drug Administration. FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma. October 18, 2024. Available here (accessed Nov 17. 2026); 2. Kubota Y, Shitara K. Ther Adv Med Oncol. 2024;16:17588359231217967; 3. Cao W, et al. Biomark Res. 2022;10:38; 4. Zhou W, et al. Cancer Treat Rev. 2026;148:103176; 5. Sugiyama K and Chau I. Cancer Treat Rev. 2025;133:102888; 6. Cassier PA, et al. Br J Cancer. 2026;135:1365-1375; 7. Konno H, et al. Cancer Res. 2021;81(13_Supplement):1203; 8. Jiang W, et al. Cancer Res. 2020;80(16_Supplement):5644

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Gastric Cancer

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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred
- HER2-positive[b]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and trastuzumab[25]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)[c,f,26,27]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and zanidatamab-hrii[g,h,28]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, zanidatamab-hrii, and tislelizumab-jsgr[c,f,h,28]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and trastuzumab (category 1)[29]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)[c,f,26,27]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and zanidatamab-hrii (category 2B)[g,h,28]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, zanidatamab-hrii, and tislelizumab-jsgr[c,f,h,28]
- HER2-negative[b]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[c,f,30]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[c,f,31]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[c,f,32]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and zolbetuximab-clzb for CLDN18.2 positive[b] (category 1)[33,34]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[35-37]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[c,f,31]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[c,f,32]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[35,38-40]
- MSI-H/dMMR tumors (independent of PD-L1 status)[b]
  - Pembrolizumab[c,f,41-44]
  - Dostarlimab-gxly[c,f,45]
  - Nivolumab and ipilimumab[c,f,30]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[c,f,30]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[c,f,42,43]

Other Recommended
- Fluorouracil[a,i] and irinotecan[j,46]
- Paclitaxel with or without carboplatin or cisplatin[j,47-51]
- Docetaxel with or without cisplatin[j,52-55]
- Fluoropyrimidine[j,39,56,57] (fluorouracil[a] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a,j,58-60]

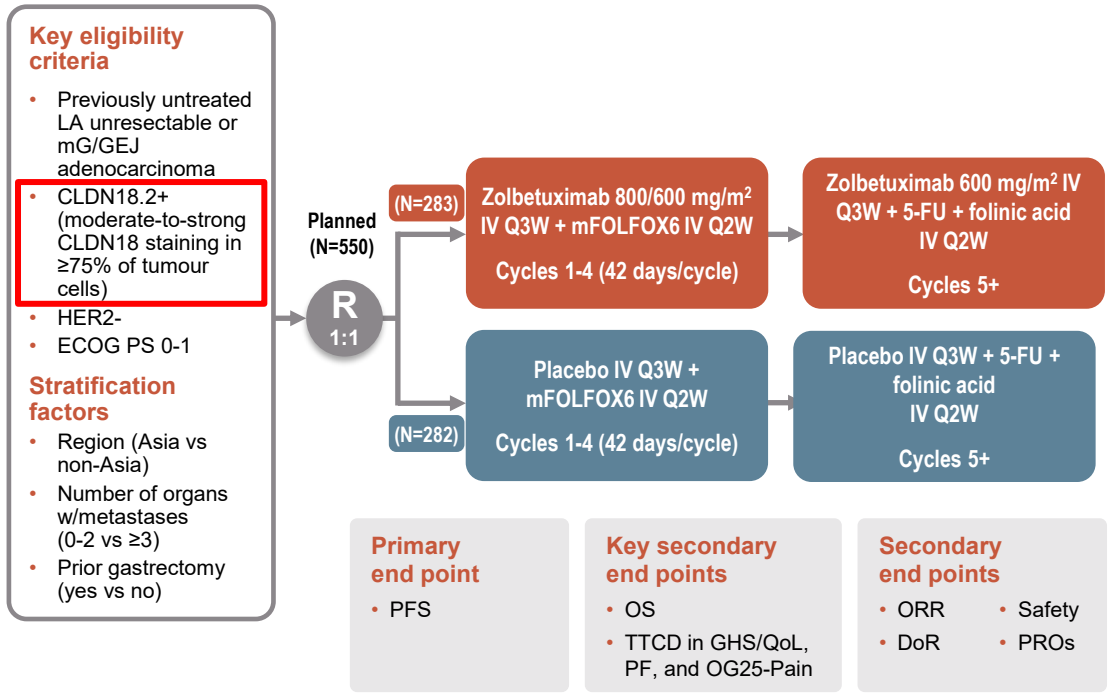
Zolbetuximab is FDA approved for use with chemotherapy for CLDN18.2-positive gastric cancer

CLDN18.2, claudin 18.2; CPS, combined positive score; FDA, Food and Drug Administration; PD-L1, programmed death-ligand 1

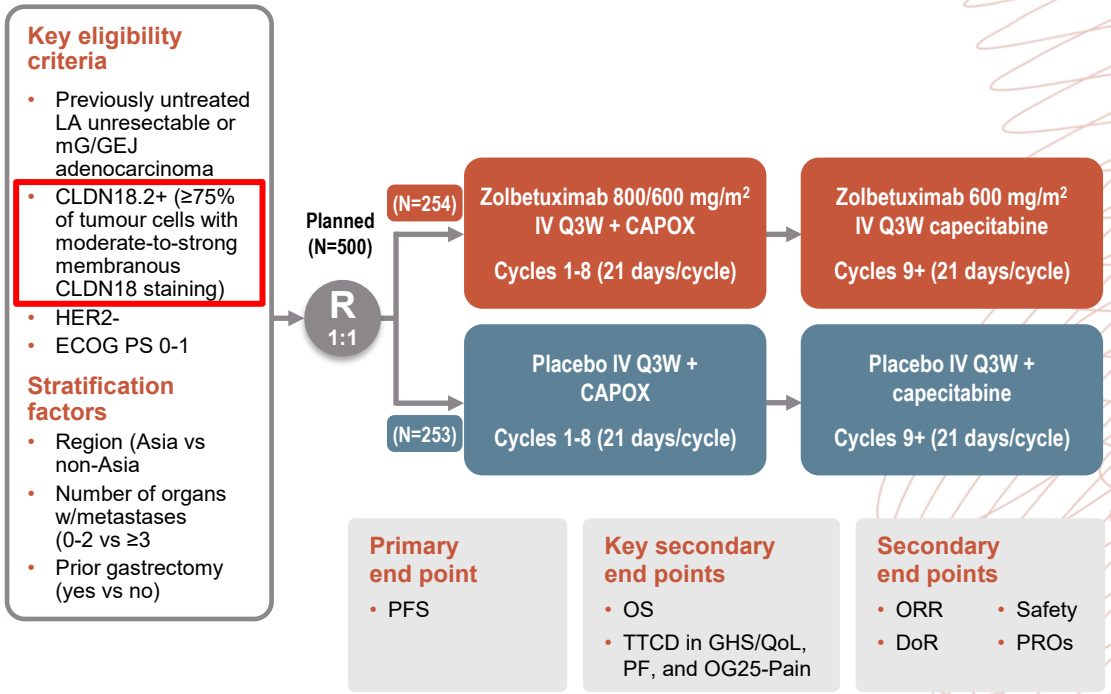
NCCN Guidelines®. Gastric Cancer. Version 4.2026. Available here (accessed Nov 16, 2026)

ZOLBETUXIMAB IN 1ST-LINE CLDN18.2-POSITIVE GASTRIC CANCER

SPOTLIGHT PHASE 3[1]



GLOW PHASE 3[2]

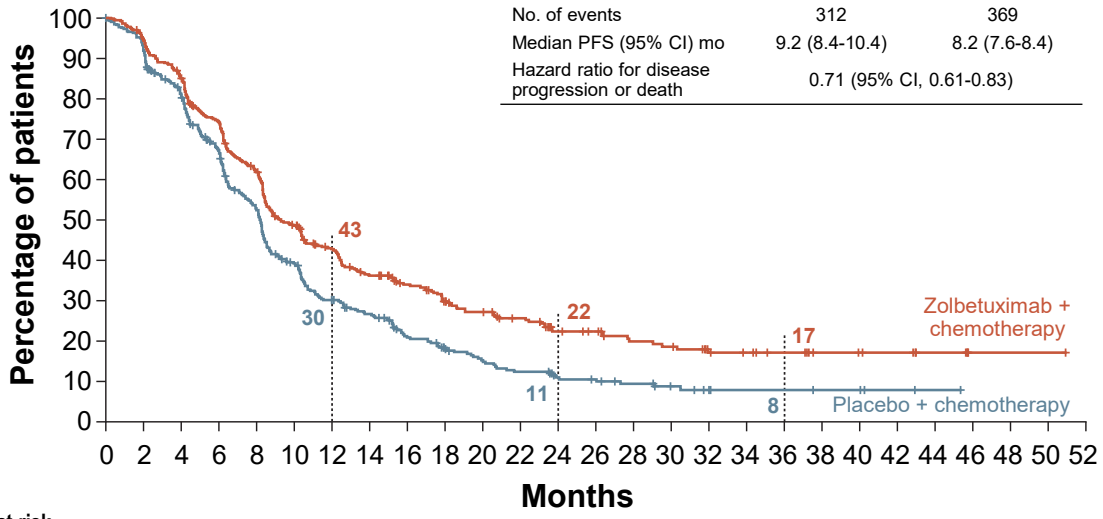


5-FU, 5-fluorouracil; CLDN18.2, claudin 18.2; CAPOX, capecitabine and oxaliplatin regimen; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GHS, global health status; IV, intravenous; LA, locally advanced; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin regimen; mG/GEJ, metastatic gastric/gastroesophageal; OG25-Pain, OesophagoGastric (OG25) Pain scale; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient reported outcome; QoL, quality of life; Q'X'W, every 'X' weeks; R, randomised; TTCD, time to confirmed deterioration

1. Shitara K, et al. Lancet, 2023;401:1655-1668; 2. Shah MA et al. Nat Med 2023;29(8):2133-2141

ZOLBETUXIMAB: COMBINED ANALYSIS OF SPOTLIGHT AND GLOW

PROGRESSION-FREE SURVIVAL

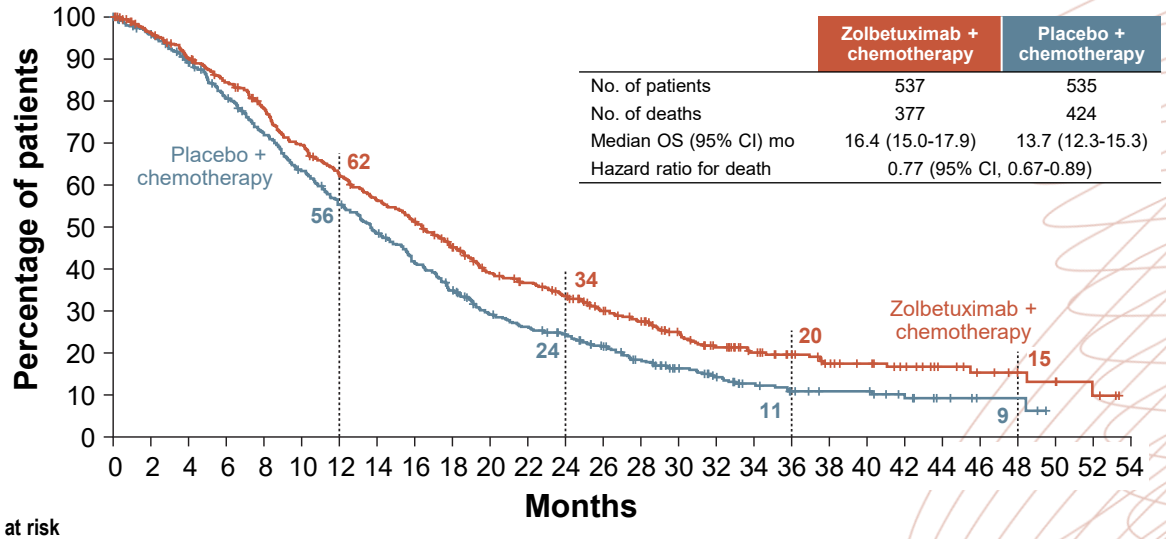


	Zolbetuximab + chemotherapy	Placebo + chemotherapy
No. of patients	537	535
No. of events	312	369
Median PFS (95% CI) mo	9.2 (8.4-10.4)	8.2 (7.6-8.4)
Hazard ratio for disease progression or death	0.71 (95% CI, 0.61-0.83)	

No. at risk

Zolbetuximab	537	459	397	321	249	183	145	120	100	82	72	58	42	39	31	28	21	19	16	11	10	8	5	1	1	1	0
Placebo	535	474	400	300	220	148	101	82	59	46	37	30	22	20	15	10	7	5	5	4	4	2	1	0	0	0	0

OVERALL SURVIVAL



	Zolbetuximab + chemotherapy	Placebo + chemotherapy
No. of patients	537	535
No. of deaths	377	424
Median OS (95% CI) mo	16.4 (15.0-17.9)	13.7 (12.3-15.3)
Hazard ratio for death	0.77 (95% CI, 0.67-0.89)	

No. at risk

Zolbetuximab	537	497	462	427	387	343	303	273	249	213	174	159	140	109	96	75	60	47	39	30	25	20	14	10	7	6	3	0
Placebo	535	506	463	409	362	317	278	239	204	169	135	119	102	85	65	50	38	28	21	17	17	11	6	3	3	0	0	0

	Zolbetuximab + chemotherapy (n=537)	Placebo + chemotherapy (n=535)
	ORR	
N	244	233
% (95% CI)	45.4 (41.2-49.8)	43.6 (39.3-47.9)

CI, confidence interval; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Shitara K, et al. N Engl J Med. 2024;391;12:1160-2

ZOLBETUXIMAB SAFETY: SPOTLIGHT AND GLOW

SPOTLIGHT[1]

Events, n (%)	Zolbetuximab + mFOLFOX6 (n=279)		Placebo + mFOLFOX6 (n=278)	
	All grade	Grade ≥3	All grade	Grade ≥3
All TEAEs	278 (>99%)	242 (87%)	277 (>99%)	216 (78%)
Treatment-emergent events				
Nausea	230 (82%)	45 (16%)	169 (61%)	18 (6%)
Vomiting	188 (67%)	45 (16%)	99 (36%)	16 (6%)

GLOW[2]

Events, n (%)	Zolbetuximab + CAPOX (n=254)		Placebo + CAPOX (n=249)	
	All grade	Grade ≥3	All grade	Grade ≥3
All TEAEs	251 (98.8)	185 (72.8)	244 (98.0)	174 (69.9)
Treatment-emergent events				
Nausea	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)

Nausea and vomiting (on target effect[3]) were more common in cycle 1 but decreased in later cycles
Approximately 20% of patients discontinued treatment due to TEAEs

AE, adverse event; CAPOX, capecitabine and oxaliplatin regimen; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin regimen; TEAE, treatment-emergent adverse event

1. Shitara K, et al. Lancet. 2023;401:1655-68; 2. Shah MA, et al. Nat Med. 2023;29(8):2133-41; 3. Yang J, et al. Clin Pharmacokinet. 2025;64:1465-1476

CURRENT CUT-OFF FOR CLDN18.2 EXPRESSION

BASED ON ZOLBETUXIMAB STUDIES

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Positivity of Claudin 18 Isoform 2 (CLDN18.2) in Gastric Cancer[10-12]

- **For patients with untreated inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom zolbetuximab therapy is being considered**

Table 4: IHC Criteria for Assessing CLDN18.2 Expression in Gastric Cancer

CLDN18.2 Assessment	Biopsy or Surgical Specimen Expression Pattern by IHC
Positive	≥75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining (2+ or 3+ intensity)
Negative	<75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining

CLDN18.2, claudin 18.2; IHC, immunohistochemistry

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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

STUDY POPULATION

N=594

2L+ GEC expressing CLDN18.2 (≥25% tumour cells with any intensity membranous staining

Stratified by
- Region
- Prior gastrectomy
- Treatment line

DOSE SELECTION

R 1:1:1[a]

- Sone-Ve 2.2 mg/kg Q3W (n=267)
- R 1:1
- Investigator's choice of therapy (n=265)
- **Sone-Ve 1.8 mg/kg Q3W (n=62):** *closed to enrolment*

MULTIPLE TESTING PROCEDURE

Dual-Primary

PFS in ITT 0.1% initial alpha → **OS in 3L+** 4.9% initial alpha

2-sided α recycling

→ **OS in ITT**

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+)[b]
- PFS by BICR (ITT [all 2L+])[c]

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+)

[a] 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 enrolment. Randomisation continued in a 1:1 ratio Sone-Ve 2.2 mg/kg Q3W or investigator's choice of therapy;
[b] All randomised patients who had received ≥2 prior lines of systemic therapy; [c] All randomised patients who had received ≥1 prior line of systemic therapy. PFS, ORR and DoR determined per RECIST v1.1.

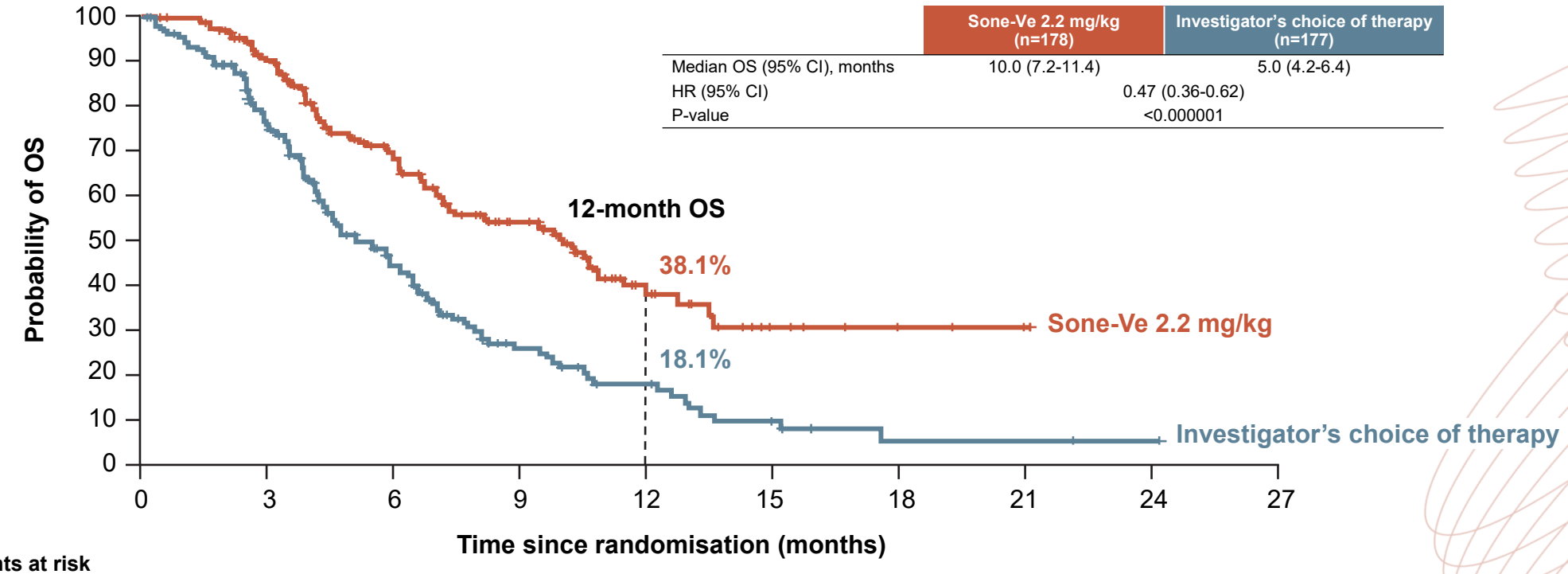
2L(+), 2nd (or later line); 3L+, 3rd or later line; BICR, blinded independent central review; CLDN18.2, claudin 18.2; DoR, duration of response; ITT, intention-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomised; RECIST v1.1., Response Evaluation Criteria in Solid Tumours v1.1; Sone-Ve, sonesitatug vedotin; TAS-102, tipiracil hydrochloride

Xu R-H, et al. Abstract LBA7, ESMO 2026 (oral presentation)

CLARITY-Gastric01: OVERALL SURVIVAL IN 3RD-LINE+

DUAL-PRIMARY ENDPOINT: OS IN 3RD LINE+

	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	



No. patients at risk										
Sone-Ve 2.2 mg/kg	178	146	95	59	19	7	3	1	0	0
Investigator's choice of therapy	177	117	58	24	14	6	2	2	1	0

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

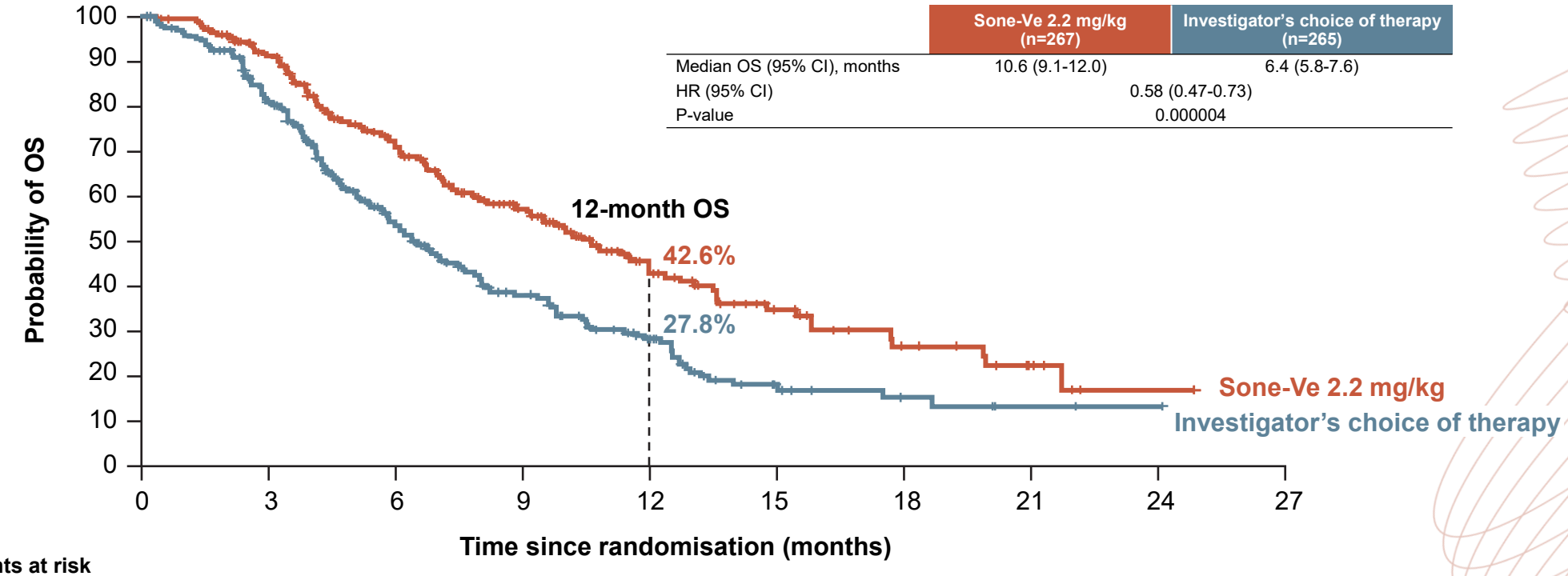
3L+, 3rd line or later; CI, confidence interval; HR, hazard ratio; OS, overall survival; Sone-Ve, sonesitatug vedotin

Xu R-H, et al. Abstract LBA7, ESMO 2026 (oral presentation)

CLARITY-Gastric01: OVERALL SURVIVAL IN ITT POPULATION

KEY SECONDARY ENDPOINT: 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	



No. patients at risk										
Sone-Ve 2.2 mg/kg	267	227	159	107	49	26	14	6	1	0
Investigator's choice of therapy	265	197	114	67	37	14	8	5	1	0

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

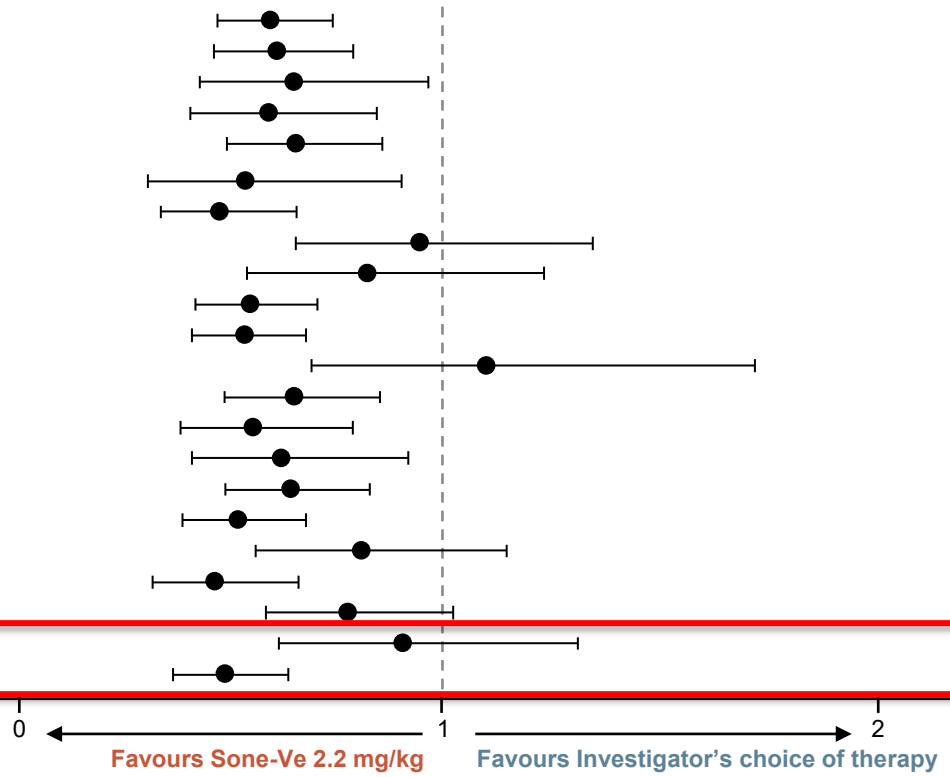
The HR and CI were estimated from a stratified Cox proportional-hazards model with ties = Efron. Stratification variables were geographical region, prior gastrectomy and line of therapy. The CI was calculated using a profile likelihood approach. A HR of less than 1 favours Sone-Ve. Tick marks indicate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

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; Sone-Ve, sonesitatug vedotin

Xu R-H, et al. Abstract LBA7, ESMO 2026 (oral presentation)

CLARITY-Gastric01: OS SUBGROUP ANALYSIS (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

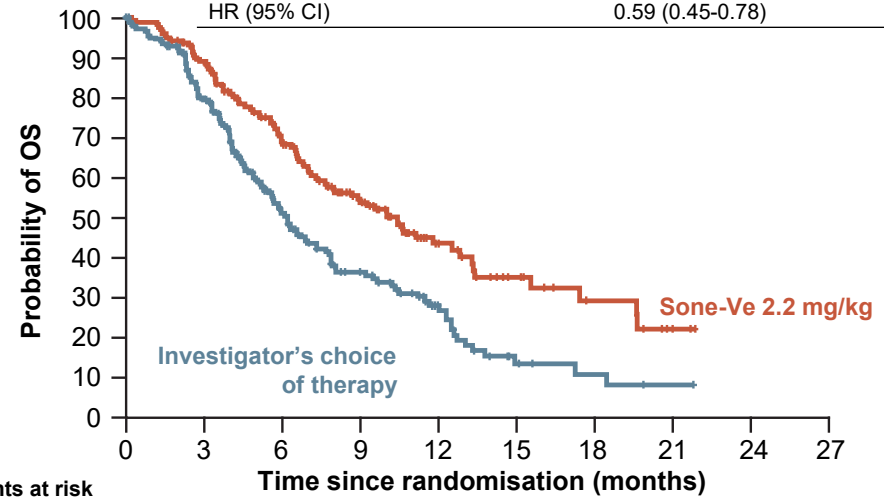
2L, 2nd line; 3L+, 3rd line or later; CI, confidence interval; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastroesophageal junction adenocarcinoma; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; RoW, rest of world; Sone-Ve, sonesitatug vedotin

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CLARITY-Gastric01: OS BY CLDN18.2 EXPRESSION (ITT)

CLDN18.2 ≥75% expression

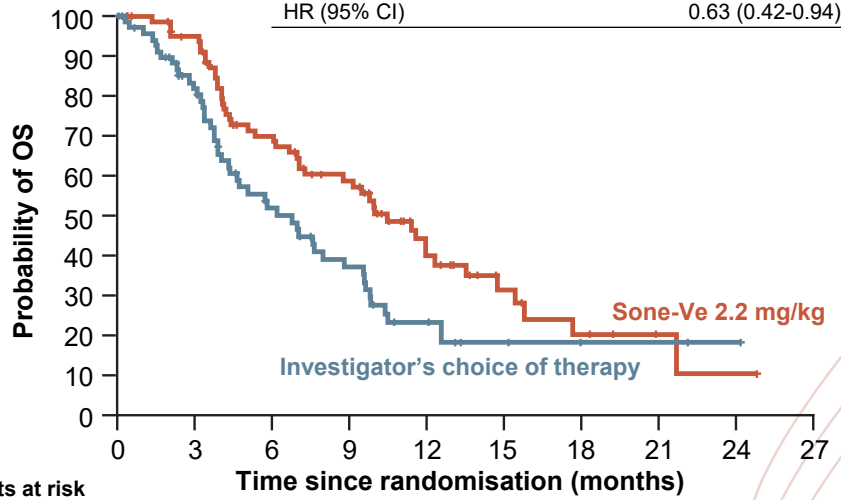
	Sone-Ve 2.2 mg/kg (n=183)	Investigator's choice of therapy (n=194)
Median OS (95% CI), months	10.6 (8.1-13.5)	6.4 (5.6-8.0)
HR (95% CI)	0.59 (0.45-0.78)	



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

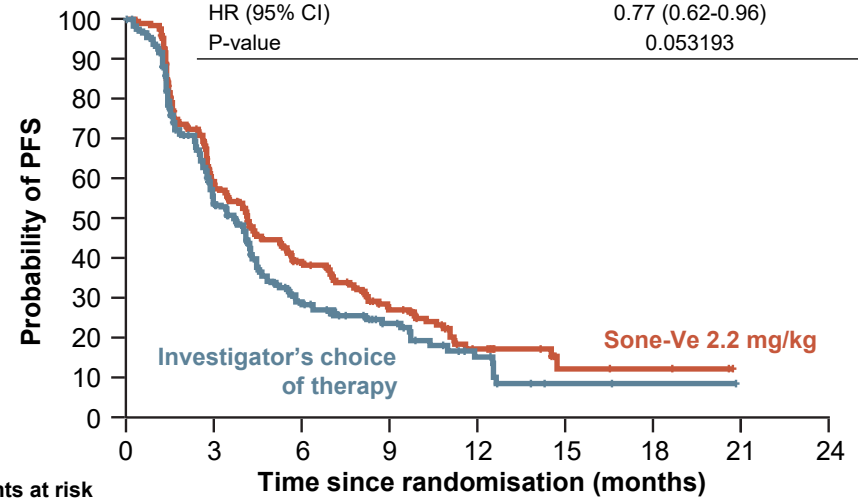
CI, confidence interval; CLDN18.2, claudin 18.2; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; Sone-Ve, sonesitatug vedotin

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CLARITY-Gastric01: PFS IN ITT AND 3RD-LINE+ (BICR)

Dual-primary endpoint: PFS by BICR in ITT

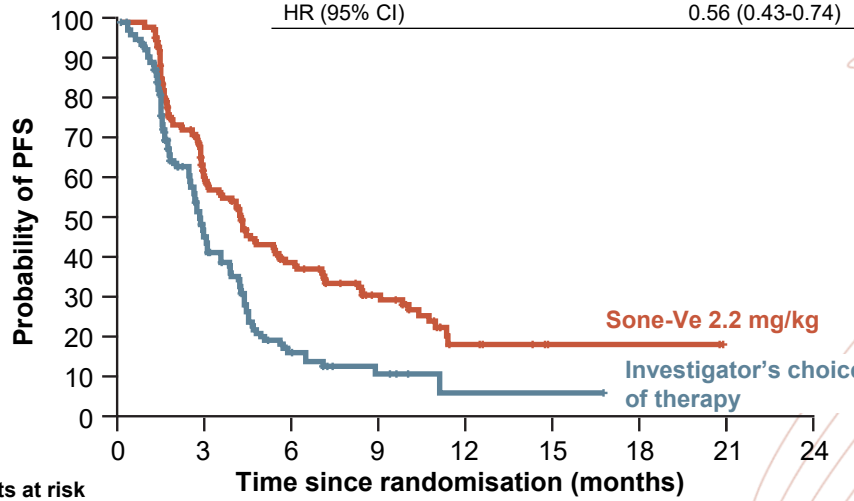
	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median PFS (95% CI), months	4.2 (3.5-5.3)	3.8 (3.0-4.2)
HR (95% CI)	0.77 (0.62-0.96)	
P-value	0.053193	



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 3rd-Line+

	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 3rd-Line+ population, Sone-Ve improved PFS by BICR versus investigator's choice of therapy[a]

[a] 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.

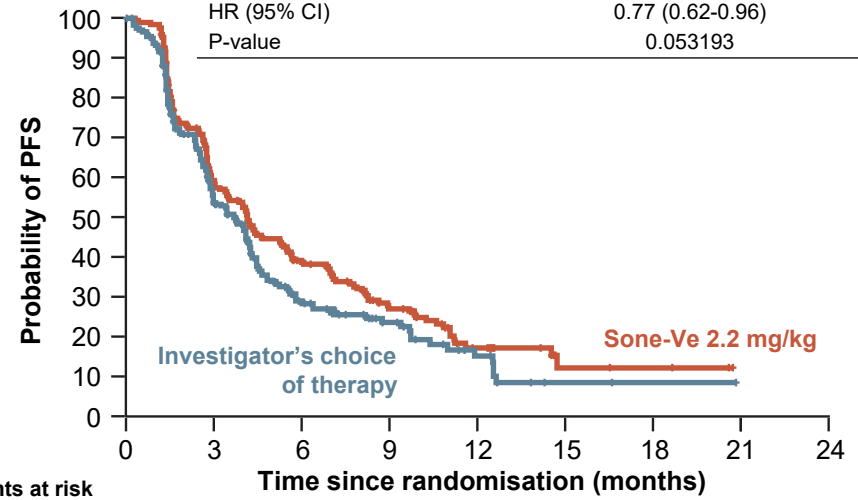
3rd-Line+, 3rd line or later; BICR, Blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival; Sone-Ve, sonesitatug vedotin

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CLARITY-Gastric01: PFS BY BICR AND BY INVESTIGATOR (ITT)

Dual-primary endpoint: PFS by BICR in ITT

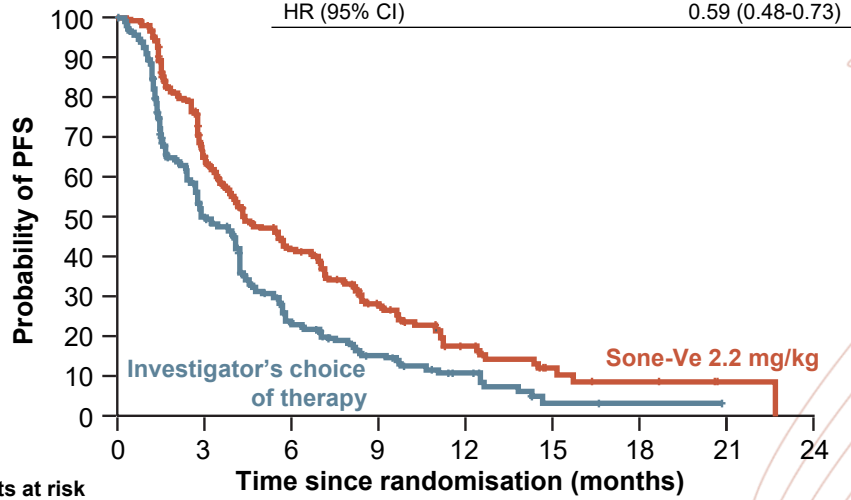
	Sone-Ve 2.2 mg/kg (n=267)	Investigator's choice of therapy (n=265)
Median PFS (95% CI), months	4.2 (3.5-5.3)	3.8 (3.0-4.2)
HR (95% CI)	0.77 (0.62-0.96)	
P-value	0.053193	



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

BICR, Blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; Sone-Ve, sonesitatug vedotin

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CLARITY-Gastric01: 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)
Adverse events, n (%)		
Any AE Possibly related to treatment[a]	254 (97.3) 224 (85.8)	237 (94.0) 205 (81.3)
Any AE of CTCAE Grade ≥3 Possibly related to treatment[a]	138 (52.9) 95 (36.4)	154 (61.1) 113 (44.8)
Any SAE	91 (34.9)	79 (31.3)
Any AE leading to discontinuation of study treatment Possibly related to treatment[a]	13.0 (5.0) 8 (3.1)	11 (4.4) 11 (4.4)
Any AE leading to interruption of study treatment or dose delay	95 (36.4)	102 (40.5)
Any AE leading to dose reduction	55 (21.1)	58 (23.0)
Any AE with outcome of death Possibly related to treatment[a,b]	11 (4.2) 3 (1.1)	6 (2.4) 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

[a] 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

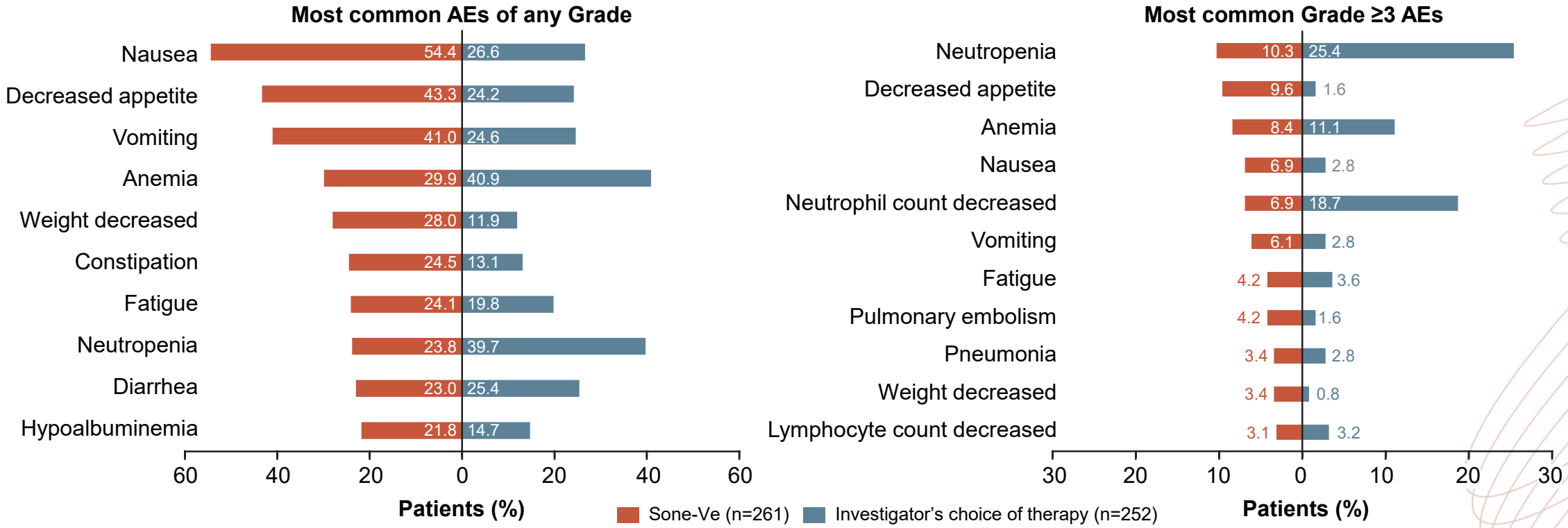
[b] Fatal AEs in Sone-Ve arm: pneumonia, jaundice cholestatic, cardiac failure; in investigator's choice of therapy arm: pulmonary embolism and abdominal infection

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; Sone-Ve, sonesitatug vedotin

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CLARITY-Gastric01: SAFETY

MOST COMMON ADVERSE EVENTS



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

Lower rates of hematologic 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 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

AE, adverse event; GI, gastrointestinal; Sone-Ve, sonesitatug vedotin

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SUMMARY

- **CLDN18.2 is an important emerging therapeutic biomarker** in advanced gastric and gastroesophageal junction (GEJ) cancer and should be **incorporated into routine biomarker assessment**
- Based on the SPOTLIGHT and GLOW trials, **zolbetuximab with chemotherapy is FDA approved as a 1st-line treatment** for adults with HER2 negative, CLDN18.2-positive-locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma
- **Sone-Ve represents a promising emerging treatment approach in the 2nd-line-or-later setting** for patients with advanced or metastatic CLDN18.2-positive gastroesophageal carcinoma based on data from CLARITY-Gastric01
- **Sone-Ve is an ADC administered as monotherapy, whereas zolbetuximab is a mAb given in combination with chemotherapy**, with implications for treatment-related toxicity and management
- Optimising treatment will require integrating CLDN18.2 expression, treatment setting, evolving clinical evidence and individual patient factors to inform treatment selection and sequencing

ADC, antibody-drug conjugate; CLDN18.2, claudin 18.2; FDA, Food and Drug Administration; mAb, monoclonal antibody; Sone-Ve, sonesitatug vedotin

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