XIX JORNADA DE ACTUALIZACIÓN ASCO GI 2025

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What's New in Esophagogastric Cancers?

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Clínic Barcelona IDIBAPS

Translational genomics and targeted therapies in solid tumors

DISCLOSURE INFORMATION

✅ Employment: Hospital Clinic de Barcelona.

✅ Consultant or Advisory Role: AMGEN, SANOFI, Pierre Fabre.

✅ Speaking: AstraZeneca, Brystol Meyers Squibb (BMS), Merck KGaA, SANOFI, Daiichi Sankyo, Merck Sharp & Domme (MSD)

✅ Other (Travel/acomodation): AstraZeneca, Brystol Meyers Squibb (BMS), Merck Sharp & Domme (MSD), Lilly, IPSEN, ROCHE, Merck KGaK and ADVANZ PHARMA SPAIN S.L.U.

OUTLINE

- ✅ **Introduction**
- ✅ **Advances in the Treatment of Esophageal Cancer**
  - Localized Esophageal Squamous Cell Carcinoma (ESCC)
- ✅ **Advances in the Treatment of Gastric cancer (GC) and Gastroesophageal Junction Cancer (GEJC)**
  - Perioperative Chemo in GC and GEJC - HER2+
  - Metastatic disease in GC and GEJC
- ✅ **Poster session**
- ✅ **Take-home messages**

INTRODUCTION

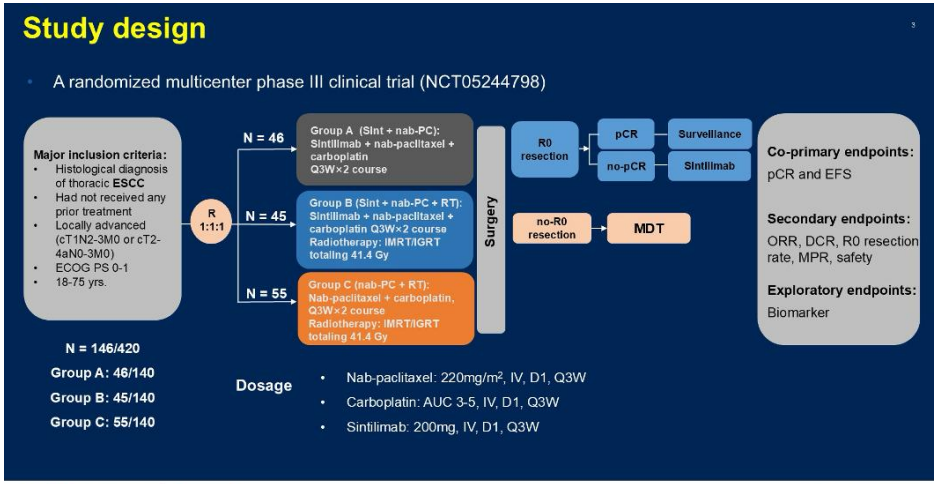
ASCO-GI 2025

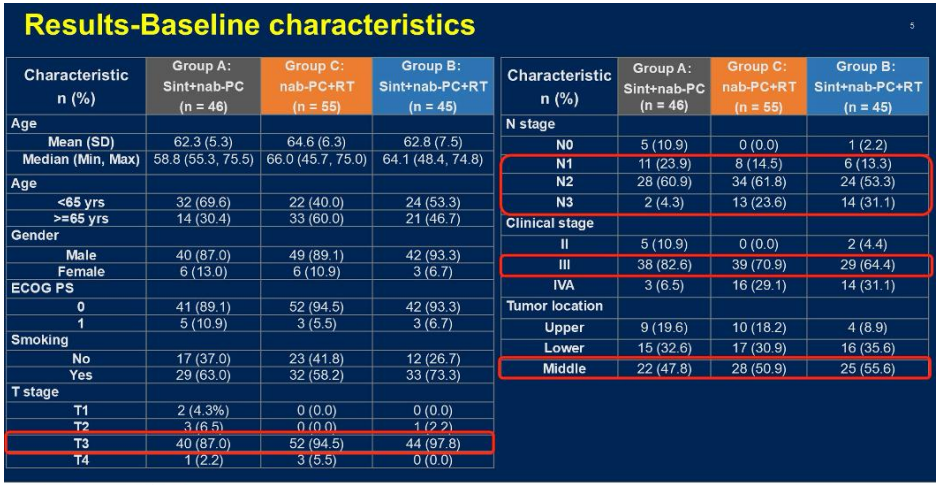
No Significant Changes in the Standard of Care for Esophagogastric Tumors

ASCO Gastrointestinal Cancers Symposium

No new studies with a significant impact on clinical practice.

TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)





Results-Baseline characteristics

Characteristic n (%)	Group A: Sint+nab-PC (n = 46)	Group C: nab-PC+RT (n = 55)	Group B: Sint+nab-PC+RT (n = 45)
Age			
Mean (SD)	62.3 (5.3)	64.6 (6.3)	62.8 (7.5)
Median (Min, Max)	58.8 (55.3, 75.5)	66.0 (45.7, 75.0)	64.1 (48.4, 74.8)
Age			
<65 yrs	32 (69.6)	22 (40.0)	24 (53.3)
>=65 yrs	14 (30.4)	33 (60.0)	21 (46.7)
Gender			
Male	40 (87.0)	49 (89.1)	42 (93.3)
Female	6 (13.0)	6 (10.9)	3 (6.7)
ECOG PS			
0	41 (89.1)	52 (94.5)	42 (93.3)
1	5 (10.9)	3 (5.5)	3 (6.7)
Smoking			
No	17 (37.0)	23 (41.8)	12 (26.7)
Yes	29 (63.0)	32 (58.2)	33 (73.3)
T stage			
T1	2 (4.3%)	0 (0.0)	0 (0.0)
T2	3 (6.5)	0 (0.0)	1 (2.2)
T3	40 (87.0)	52 (94.5)	44 (97.8)
T4	1 (2.2)	3 (5.5)	0 (0.0)

Characteristic n (%)	Group A: Sint+nab-PC (n = 46)	Group C: nab-PC+RT (n = 55)	Group B: Sint+nab-PC+RT (n = 45)
N stage			
N0	5 (10.9)	0 (0.0)	1 (2.2)
N1	11 (23.9)	8 (14.5)	6 (13.3)
N2	28 (60.9)	34 (61.8)	24 (53.3)
N3	2 (4.3)	13 (23.6)	14 (31.1)
Clinical stage			
II	5 (10.9)	0 (0.0)	2 (4.4)
III	38 (82.6)	39 (70.9)	29 (64.4)
IVA	3 (6.5)	16 (29.1)	14 (31.1)
Tumor location			
Upper	9 (19.6)	10 (18.2)	4 (8.9)
Lower	15 (32.6)	17 (30.9)	16 (35.6)
Middle	22 (47.8)	28 (50.9)	25 (55.6)

Data cut-off: september 2024

Patient Enrollment: November 2022 to June 2024

TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)

Results-Primary endpoints pCR

	Group A: Sint + nab-PC (n = 46)	Group C: nab-PC + RT (n = 55)	Group B: Sint + nab-PC + RT (n = 45)
pCR% (95% CI)	13 (4.9, 26.3)	47.3 (33.7, 61.2)	60 (44.3, 74.3)
Difference (95% CI), vs. Group A		34.2 (16.4, 49.1)	47 (27.8, 62.2)
OR (95% CI), vs. Group A		6 (2.3, 17.8)	10 (3.7, 30.8)
P value (vs. Group A)		0.0005	<0.0001

pCR rate: nab-PC + RT vs. Sint + nab-PC : 47.3% vs. 13%, (OR= 6, 95%CI, 2.3-17.8), *P*=0.0005

pCR rate: Sint + nab-PC + RT vs. Sint + nab-PC : 60% vs. 13%, (OR=10, 95% CI, 3.7-30.8), *P* <0.0001

Results- Tumor regression grade

Tumor regression grade n (%)	Group A: Sint + nab-PC (n = 46)	Group C: nab-PC + RT (n = 55)	Group B: Sint + nab-PC + RT (n = 45)
0	6 (13.0)	26 (47.3)	27 (60.0)
1	6 (13.0)	14 (25.5)	11 (24.4)
2	24 (52.2)	12 (21.8)	7 (15.6)
3	10 (21.7)	3 (5.5)	0 (0.0)

TRG: In 45 patients, all patients in Group B demonstrated a treatment response to the Sint + nab-PC + RT regimen

TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)

Results-Surgical complications

	Group A: Sint + nab-PC (n = 46)	Group C: nab-PC + RT (n = 55)	Group B: Sint + nab-PC + RT (n = 45)
Any events, n(%)			
No	13 (28.3)	28 (50.9)	24 (53.3)
Yes	33 (71.7)	27 (49.1)	21 (46.7)
Anastomotic leak, n (%)			
No	46 (100.0)	52 (94.5)	44 (97.8)
Yes	0 (0.0)	3 (5.5)	1 (2.2)
Postoperative hemorrhage, n (%)			
No	41 (89.1)	54 (98.2)	45 (100.0)
Yes	5 (10.9)	1 (1.8)	0 (0.0)
Pulmonary infection, n(%)			
No	15 (32.6%)	29 (52.7)	25 (55.6)
Yes	31 (67.4)	26 (47.3)	20 (44.4)

Results-TEAEs (≥5%)

Adverse Events (%)	Group A: Sint + nab-PC (n = 46)	Group C: nab-PC + RT (n = 55)	Group B: Sint + nab-PC + RT (n = 45)
White blood cell count decreased	4 (8.7)	31 (56.4)	34 (75.6)
Neutrophil count decreased	2 (4.3)	15 (27.3)	25 (55.6)
Hypoalbuminemia	9 (19.6)	28 (50.9)	6 (13.3)
Lymphocyte count decreased	1 (2.2)	23 (41.8)	11 (24.4)
Platelet count decreased	2 (4.3)	19 (34.5)	16 (35.6)
Anemia	1 (2.2)	17 (30.9)	10 (22.2)
Alanine aminotransferase increased	0	0	4 (8.9)
Aspartate aminotransferase increased	0	0	3 (6.7)
Esophageal anastomotic leak	0	3 (5.5%)	0

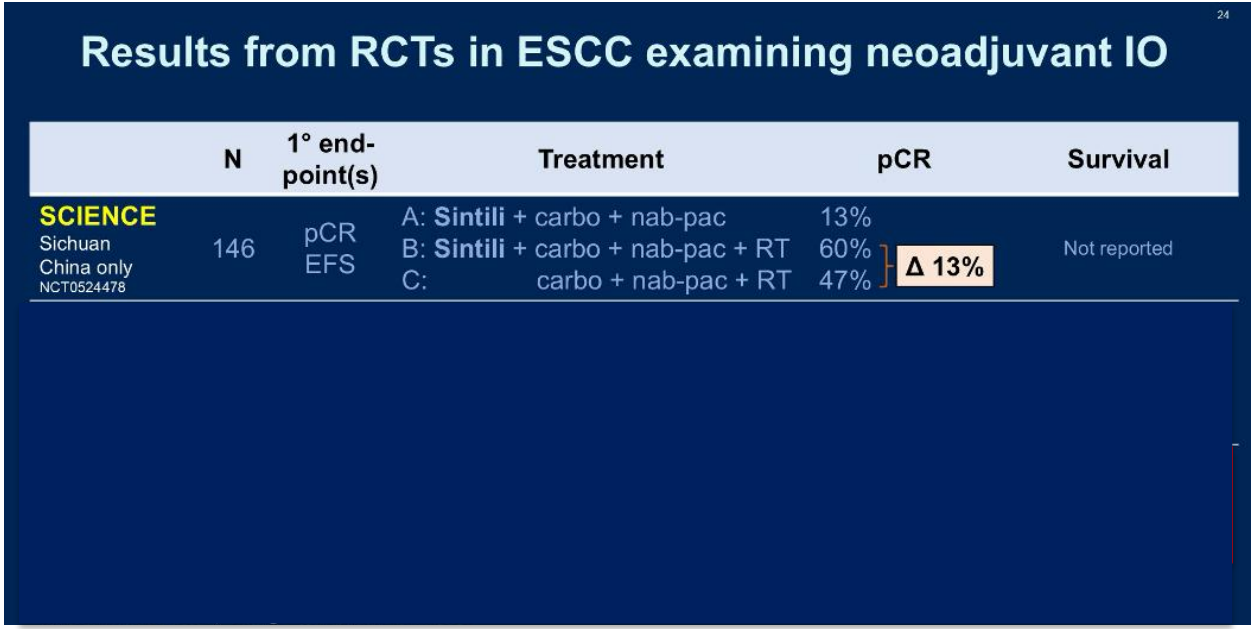
TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)

Results-TEAEs of Grade ≥ 3

11

Adverse Events (%)	Group A: Sint + nab-PC (n = 46)	Group C: nab-PC + RT (n = 55)	Group B: Sint + nab-PC + RT (n = 45)
Lymphopenia	0	17 (30.9)	5 (11.1)
Leukopenia	2 (4.3)	16 (29.1)	11 (24.4)
Neutropenia	1 (2.2)	9 (16.4)	4 (8.9)
Thrombocytopenia	1 (2.2)	1 (1.8)	2 (4.4)
Anemia	0	1 (1.8)	0
Hyperglycemia	0	1 (1.8)	0
Hypernatremia	0	1 (1.8)	0

TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)

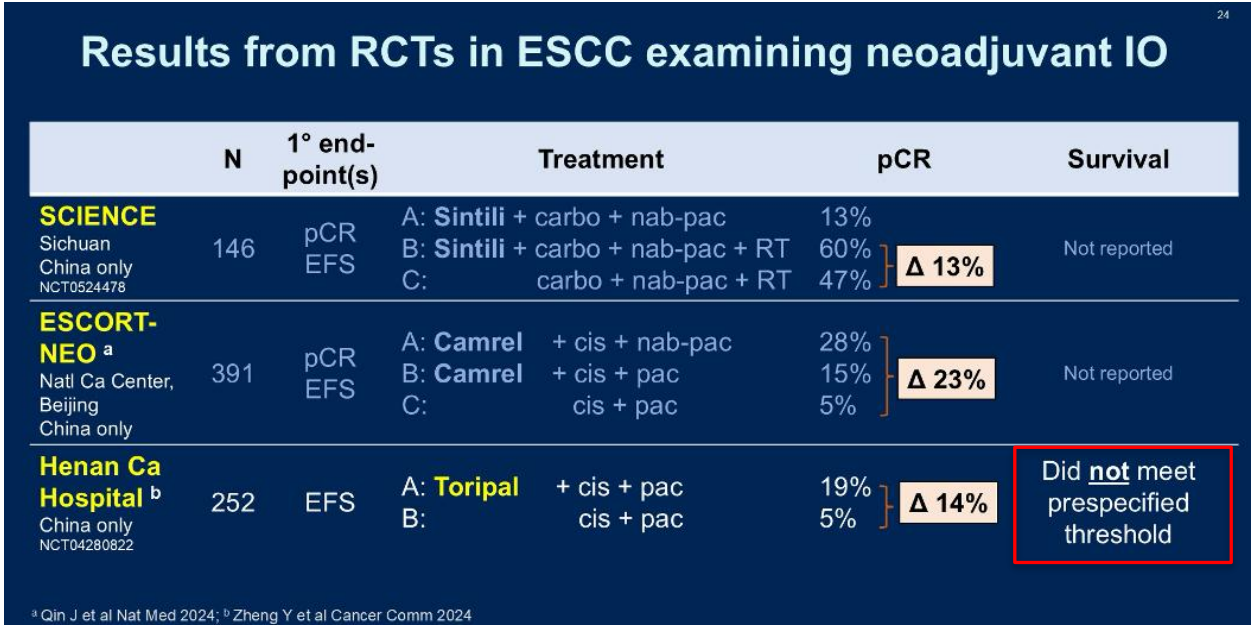


TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)

Results from RCTs in ESCC examining neoadjuvant IO

	N	1° end-point(s)	Treatment	pCR		Survival
SCIENCE Sichuan China only NCT0524478	146	pCR EFS	A: **Sintili** + carbo + nab-pac B: **Sintili** + carbo + nab-pac + RT C: carbo + nab-pac + RT	13% 60% 47%	Δ 13%	Not reported
ESCORT-NEO [a] Natl Ca Center, Beijing China only	391	pCR EFS	A: **Camrel** + cis + nab-pac B: **Camrel** + cis + pac C: cis + pac	28% 15% 5%	Δ 23%	Not reported

TREATMENT OF ESOPHAGEAL SCC (SCIENCE STUDY)



SCIENCE STUDY

✅ Promising pCR rate without increasead surgical risks and toxicity.

❌ In western countries: Chemo + RT → surgery → Nivolumab (if non-pCR) (SOC).

❌ In some parts of the world: Chemo → surgery (SOC).

❌ No chemotherapy-only arm included.

❌ **EFS (co-primary endpoint) not reported.**

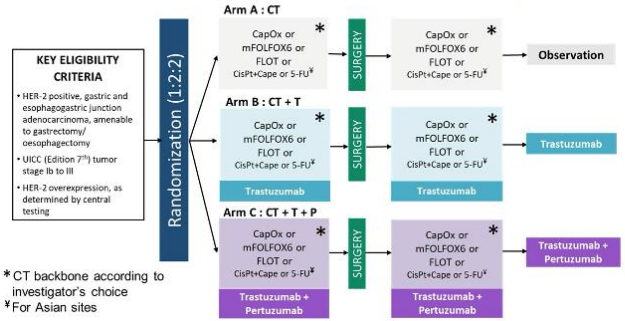
❌ pCR has limitations as a marker of efficacy comparing Chemo vs. Chemo + RT.

🤔 Awaiting EFS and OS data.

Advances in the Treatment of (GC) and (GEJC) – Localized disease.

Methods

- Randomized, open-label phase II, NCT 02205047
- Started in 2015, with Cisplatin/Fluoropyrimidine as chemotherapy backbone.
- After the publication of FLOT-4[1] in 2019, the chemotherapy backbone was changed to FLOT in European si



Objective & endpoints

Objective: To increase the major pathological response rate (< 10% vital tumor cells) to neoadjuvant treatment by integrating either trastuzumab or both trastuzumab and pertuzumab into perioperative chemotherapy for HER-2 positive, resectable gastric cancer.

Primary endpoint : Major pathological response rate (mpRR): less than 10% viable tumor cells[1] after neoadjuvant therapy as determined by central review

➢ *first reported at ASCO 2023 and WCGIC 2023*

Secondary endpoints :

- R0 resection
- Pathological complete response
- Toxicity

➢ *first reported at ASCO 2023 and WCGIC 2023*

- Locoregional failure
- Distant failure
- Recurrence-free survival (RFS)
- Progression-free survival (PFS) according to RECIST v1.1
- Overall survival (OS)

➢ *now reported after a median follow-up of 4.5 years*

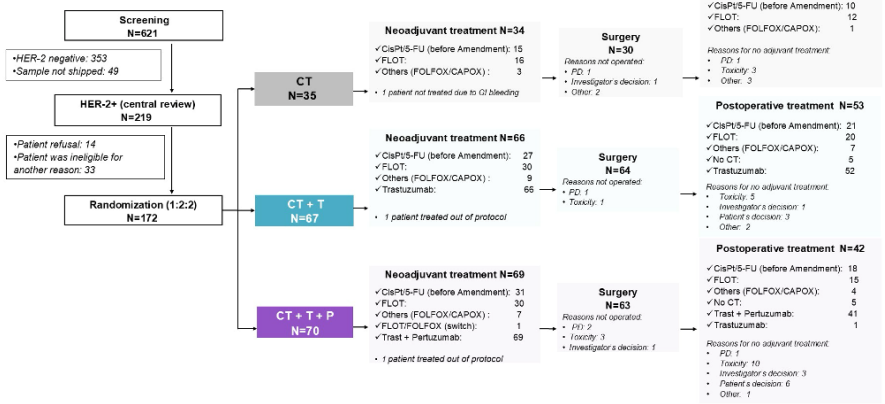
PFS: *time from randomisation to disease progression or death.*

- ✓ *Patients with a R2 resection or distant metastases discovered at surgery will be considered failures at the time of surgery.*
- ✓ *For patients who are operated and disease-free, the first event is a recurrence after surgery.*

PFS and OS are analyzed in the per-protocol population

Advances in the Treatment of (GC) and (GEJC) – Localized disease.

Patient Disposition



35.26% of patients were HER2 positive.

Patient Characteristics & Treatment Exposure

	Treatment arm (Per protocol population)		
	CT (N=33)	CT + T (N=64)	CT + T + P (N=64)
Age (years), Median (Range)	63 (32- 79)	63 (36-84)	64 (42-78)
Sex, N (%)			
Male	31 (93.9)	43 (67.2)	57 (89.1)
Female	2 (6.1)	21 (32.8)	7 (10.9)
Tumor localization, N (%)			
Stomach	12 (36.4)	26 (40.6)	23 (35.9)
Esophagogastric junction	21 (63.6)	38 (59.4)	41 (64.1)
Histological subtype, N (%)			
Intestinal	25 (75.8)	45 (70.3)	46 (71.9)
Non-intestinal	8 (24.2)	19 (29.7)	18 (28.1)
Region, N (%)			
Asia	4 (12.1)	7 (10.9)	5 (7.8)
Europe	29 (87.9)	57 (89.1)	59 (92.2)
HER-2 status, N (%)			
IHC2+/FISH+	4 (12.1)	16 (25.0)	16 (25.0)
HER-2 IHC 3+	29 (87.9)	48 (75.0)	48 (75.0)

Neoadjuvant treatment	Safety population		
	CT (N=19)	CT + T (N=39)	CT + T + P (N=38)
Number of cycles – Antibody, N (%)		N=39	N=38
≥ 3*		36 (92.3)	34 (89.5)
Number of cycles – CAPOX, N (%)	N=1	N=2	N=1
3	1 (100.0)	2 (100.0)	1 (100.0)
Number of cycles – FLOT, N (%)	**N=16**	**N=30**	**N=31**
4	**15 (93.8)**	**28 (93.3)**	**25 (80.6)**
Number of cycles – FOLFOX, N (%)	N=2	N=7	N=6
4	1 (50.0)	6 (85.7)	6 (100.0)

FLOT Relative Dose intensity** (%) Median	CT (N=16)	CT + T (N=30)	CT + T + P (N=31)
Oxaliplatin	99.0	93.9	87.9
Docetaxel	98.1	94.0	85.5
Folinic acid	99.1	94.6	93.2
5-FU	99.5	94.1	82.0
Trastuzumab		98.7	100.0
Pertuzumab			100.0

2 patients in CT+T received 4 cycles of antibody
**calculated based on the number of cycles actually started by the patient*

Advances in the Treatment of (GC) and (GEJC) – Localized disease.

Related grade 3 & 4 adverse events with frequency ≥5%

System Organ Class + Preferred term	CT (N=34)		CT+T (N=66)		CT+T+P (N=69)	
	Grade 3 N (%)	Grade 4 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 3 N (%)	Grade 4 N (%)
PATIENTS' WORST GRADE	**15 (44.1)**	**4 (11.8)**	**29 (43.9)**	**15 (22.7)**	**45 (65.2)**	**9 (13.0)**
GASTROINTESTINAL DISORDERS						
Diarrhea	**2 (5.9)**		**2 (3)**		**18 (26.1)**	
Mucositis Oral	1 (2.9)		1 (1.5)		7 (10.1)	
Nausea	5 (14.7)		3 (4.5)		7 (10.1)	
Other AE	4 (11.8)		2 (3)		1 (1.4)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue	1 (2.9)		5 (7.6)		2 (2.9)	
Other AE			4 (6.1)		2 (2.9)	
INVESTIGATIONS						
Neutrophil Count Decreased	**11 (32.4)**	**1 (2.9)**	**14 (21.2)**	**7 (10.6)**	**15 (21.7)**	**4 (5.8)**
Weight Loss	2 (5.9)				3 (4.3)	
METABOLISM AND NUTRITION DISORDERS						
Hypokalemia	1 (2.9)		2 (3)		5 (7.2)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Pleural Effusion	2 (5.9)		2 (3)		3 (4.3)	1 (1.4)

Results Primary Endpoint mpRR*

*mpRR: major pathological Response Rate

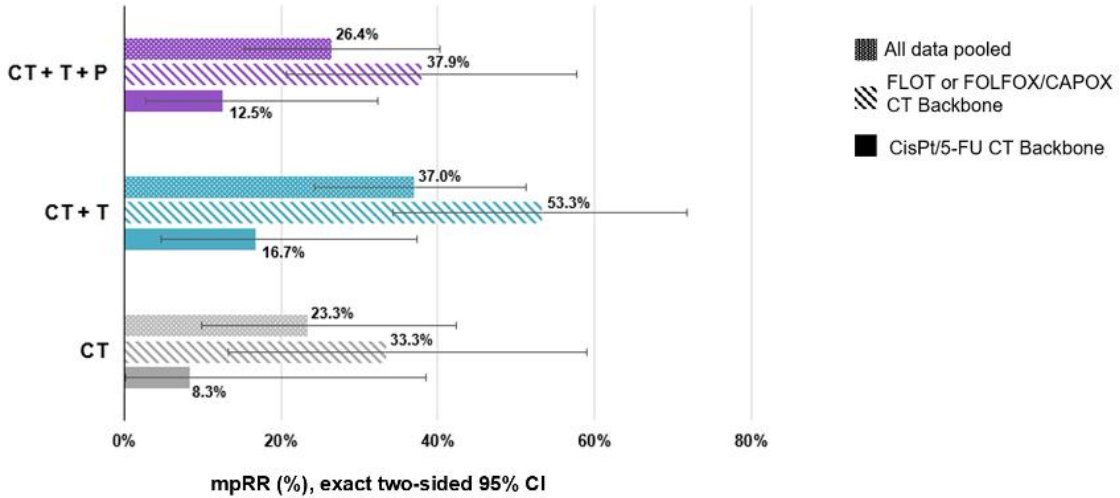
	Per protocol population – Treatment arm		
	CT (N=33)	CT + T (N=64)	CT + T + P (N=64)
Major pathological response, N (%)	N=30	N=54	N=53
Yes	**7 (23.3)**	**20 (37.0)**	**14 (26.4)**
Final Becker tumor regression grade, N (%)	N=26	N=53	N=48
0	1 (3.8)	8 (15.1)	3 (6.3)
1	6 (23.1)	12 (22.6)	11 (22.9)
2	9 (34.6)	8 (15.1)	14 (29.2)
3	10 (38.5)	25 (47.2)	20 (41.7)
Surgery performed, N (%)			
Yes	28 (84.8)	63 (98.4)	59 (92.2)

	CT + T	CT + T + P
Difference in mpRR between each experimental arm and CT arm [asymptotic two-sided 80% CI]	**13.7% [0.7%, 26.7%]**	**3.1% [-9.5%, 15.7%]**

Patients not operated were considered as failures for mpRR (per protocol population):
C: 4/33; C+T: 1/64; C+T+P: 5/64

Advances in the Treatment of (GC) and (GEJC) – Localized disease.

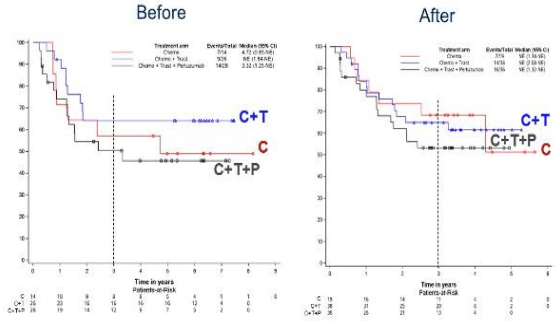
Results Primary Endpoint mpRR



Advances in the Treatment of (GC) and (GEJC) – Localized disease.

3 years PFS - Results Before & After Amendment

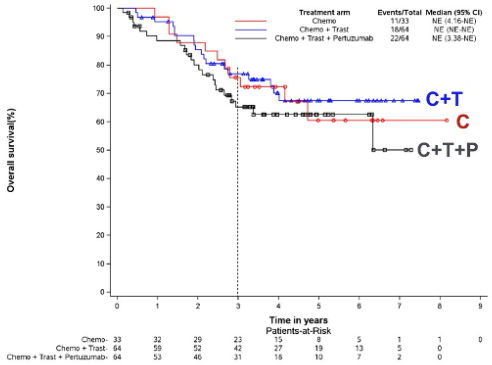
Arm (N)	PFS (%) at 3 Years (95% CI)	Hazard Ratio (95% CI)
Before amendment		
CT (N=14)	57.1 (28.4, 78.0)	1.0
CT+T (N=26)	64.2 (42.5, 79.5)	0.64 (0.24, 1.72)
CT+T+P (N=28)	50.4 (30.1, 67.6)	1.18 (0.48, 2.93)
After amendment		
CT (N=19)	68.4 (42.8, 84.4)	1.00
CT+T (N=38)	65.0 (47.5, 78.0)	1.04 (0.42, 2.57)
CT+T+P (N=36)	53.3 (35.4, 68.3)	1.45 (0.60, 3.53)



OS – Results in the Overall Population

Arm (N)	Observed Events	Median (95% CI) (Years)	% at 3 Year(s) (95% CI)	Hazard Ratio (95% CI)
CT (N=33)	11	Not reached	75.6 (57.1, 87.0)	1.00
CT+T (N=64)	18	Not reached	76.9 (64.1, 85.6)	0.89 (0.42, 1.88)
CT+T+P (N=64)	22	Not reached	65.2 (51.3, 76.1)	1.29 (0.62, 2.66)

Cause of death	CT (N=11)	CT+T (N=18)	CT+T+P (N=22)	Total (N=51)
Progression of disease (PD)	8 (72.7)	13 (72.2)	17 (77.3)	38 (74.5)
Toxicity	0 (0.0)	2 (11.1)	2 (9.1)	4 (7.8)
Cardiovascular disease (not due to tox. or PD)	1 (9.1)	0 (0.0)	0 (0.0)	1 (2.0)
Other	1 (9.1)	3 (16.7)	2 (9.1)	6 (11.8)
Missing	1 (9.1)	0 (0.0)	1 (4.5)	2 (3.9)



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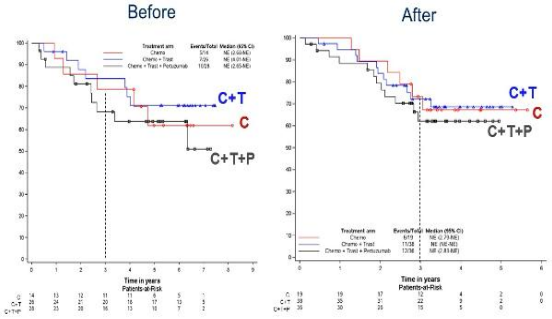
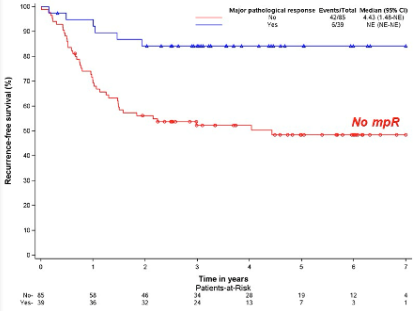
Advances in the Treatment of (GC) and (GEJC) – Localized disease.

3 years OS Results – Before & After Amendment

Arm (N)	OS (%) at 3 Years (95% CI)	Hazard Ratio (95% CI)
Before amendment		
CT (N=14)	78.6 (47.3, 92.5)	1.00
CT+T (N=26)	83.6 (62.0, 93.5)	0.77 (0.25, 2.44)
CT+T+P (N=28)	88.3 (46.3, 82.8)	1.28 (0.44, 3.75)
After amendment		
CT (N=19)	73.3 (47.2, 87.9)	1.00
CT+T (N=38)	72.2 (54.3, 84.0)	0.99 (0.37, 2.69)
CT+T+P (N=36)	62.2 (42.6, 76.8)	1.30 (0.49, 3.48)

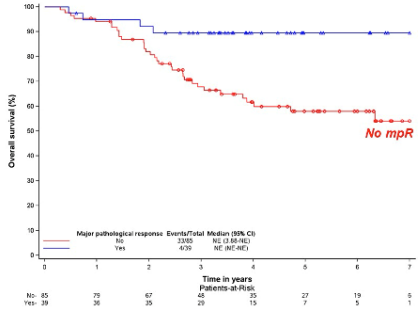


RFS Results by mpR



HR (95% CI): 0.26 (0.13-0.53)
P-value: 0.0008

OS Results by mpR

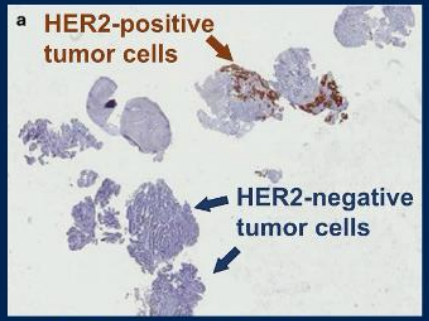


HR (95% CI): 0.25 (0.10-0.59)
P-value: 0.0041

Advances in the Treatment of (GC) and (GEJC) – Localized disease.

Still worth studying HER2 targets in resectable GEA

Source of Resistance	Potential Approaches
HER2 inter/intratumor heterogeneity	Further enrich HER2 population
	Therapies with "bystander" effect (eg, ADC)
Lack of HER2 internalization	Novel HER2 agents (eg, ZW25, HLX22)
Immunosuppression	HER2/immune engagers, other immune modulators [a]
Many others …	… in crowded space



Ruschoff et al, 2012, Mod Pathol

[a] Shitara et al. ASCO GI 2025, Rapid Oral, ASPEN-06 study of CD47 checkpoint inhibitor

STUDY INNOVATION

❌ The INNOVATION study did not meet its primary endpoint.

❌ CT + T + P was associated with higher toxicity and no advantage.

❌ PFS and OS showed numerical improvement with the addition of T to CT doublet, but not after the amendment when patients received FLOT.

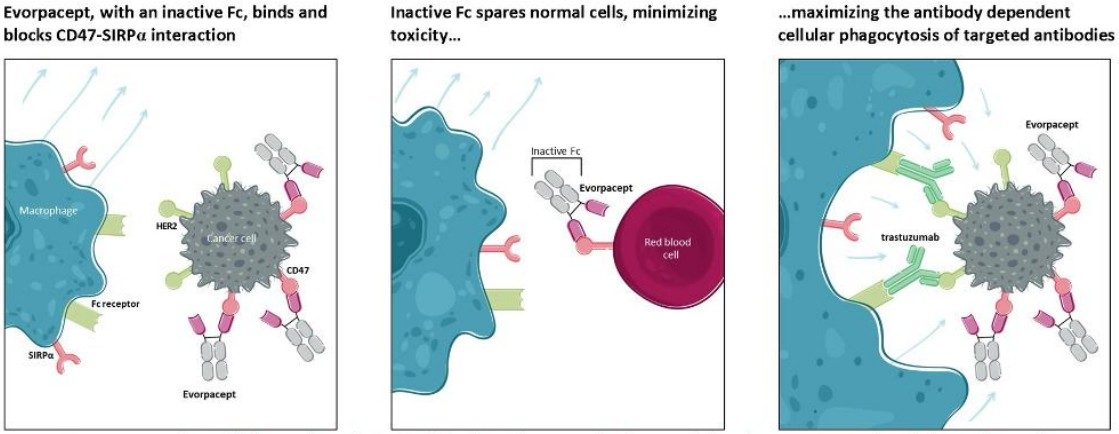
❌ Survival results are immature. Median OS has not been reached, and the majority of patients remain censored for OS.

❌ pCR in gastroesophageal adenocarcinoma is not good surrogate for survival.

✅ **Based on its very high mpRR, the addition of T to CT may be considered, especially when tumor downsizing is needed to achieve a curative resection.**

Advances in the Treatment in HER2+ disease.

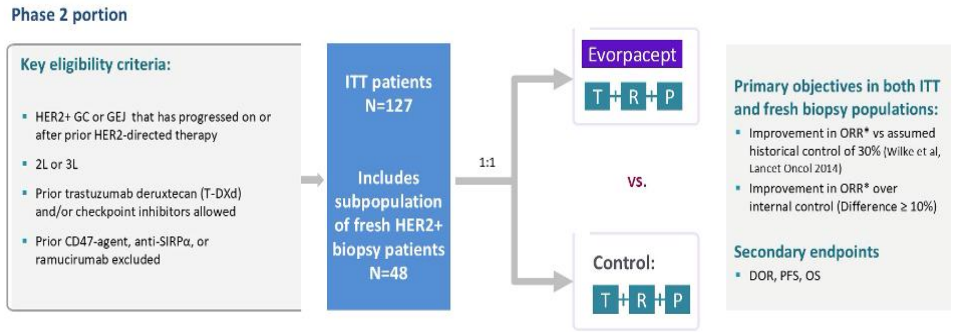
ASPEN-06: Final analysis of the randomized phase 2 part of the ASPEN-06 study: A phase 2/3 study of Evorpacept (ALX148) , a CD47 myeloid checkpoint inhibitor, in patients with HER2-overexpressing gastric/gastroesophageal cancer (GC)



Evorpacept is a differentiated CD47 blocker that works in combination to spare healthy cells and deliver cancer cells for macrophage destruction

Evorpacept increases antibody dependent cellular phagocytosis (ADCP) in combination with trastuzumab without Fc-driven toxicity.

Advances in the Treatment in HER2+ disease.



All patients enrolled received a prior HER2-targeted therapy (eg, trastuzumab) and were enrolled with either a HER2+ fresh or archival biopsy

Dosing: Evorpacept 30 mg/kg IV Q2W, trastuzumab 6 mg/kg › 4 mg/kg Q2W, ramucirumab 8 mg/kg Q2W, paclitaxel 80 mg/m² on day 1, 8, 15 of 28-day cycle

GC- gastric cancer, GEJ- gastroesophageal junction, TRP- trastuzumab, ramucirumab, paclitaxel

Minimization factors: Primary tumor place (i.e., Gastric vs GEJ); Time of biopsy (i.e., fresh vs archival); Region (Asia vs other); Treatment line (i.e., 2nd vs 3rd line); HER2 status (3+ vs 2+/ISH+); Prior T-DXd

*Based on investigator assessment

Study population:

		Evo + T + R + P N=63	T + R + P N=64
Median age, years (range)		64 (34-81)	63 (31-86)
Sex, n%	Male	55 (87.3%)	48 (75.0%)
	Female	8 (12.7%)	16 (25.0%)
Race, n%	Asian	31 (49.2%)	31 (48.4%)
	White	19 (30.2%)	19 (29.7%)
	Other	1 (1.6%)	0 (0%)
	Unknown	12 (19.0%)	13 (20.3%)
ECOG PS, n%	0	30 (47.6%)	27 (42.2%)
	1	33 (52.4%)	37 (57.8%)
Cancer Type, n%	Gastric	48 (76.2%)	44 (68.8%)
	GEJ	15 (23.8%)	20 (31.3%)
Treatment Line, n%	2nd line	49 (77.8%)	44 (68.8%)
	3rd line	14 (22.2%)	20 (31.3%)
HER2 status, n%	IHC 3+	52 (82.5%)	53 (82.8%)
	IHC2+/ISH+	11 (17.5%)	11 (17.2%)
Fresh, n%	Yes	22 (34.9%)	26 (40.6%)
ctDNA HER2+	Yes	43 (68.3%)	43 (67.2%)
Prior T-DXd, n%	Yes	8 (12.7%)	10 (15.6%)
Prior anti-PD1, n%	Yes	11 (17.5%)	16 (25.0%)
Asia Region, n%	Yes	31 (49.2%)	30 (46.9%)

Data Cutoff as of 02 Dec 2024

- Patients with a fresh HER2+ biopsy underwent a biopsy at a median of 1.1 months before dosing (vs. 14.1 months for patients with an archival biopsy)
- As an exploratory endpoint, ctDNA extracted from plasma samples collected on Cycle 1 Day 1 prior to dosing was assessed for HER2 amplification utilizing Guardant360 comprehensive genome profiling (Guardant Health®)*

*HER2 plasma gene amplification reportable range ≥2.18 copies

ALX ONCOLOGY

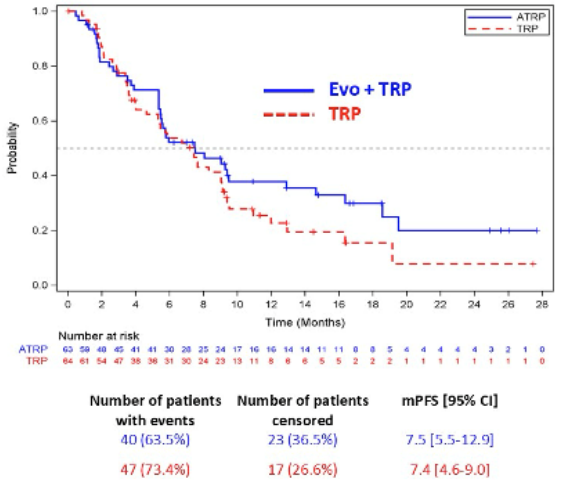
Clínic Barcelona IDIBAPS

Translational genomics and targeted therapies in solid tumors

Advances in the Treatment in HER2+ disease.

	Evo +T+R+P	T+R+P
N evaluable	63	64
Confirmed ORR, n (%) [95% CI]	**26 (41.3%) [29.0%; 54.4%]**	**17 (26.6%) [16.3%; 39.1%]**
CR (Complete Response)	1 (1.6%)	1 (1.6%)
PR (Partial Response)	25 (39.7%)	16 (25.0%)
SD (Stable Disease)	21 (33.3%)	35 (54.7%)
PD (Progressive Disease)	9 (14.3%)	7 (10.9%)
NE (Not Evaluable)	2 (3.2%)	1 (1.6%)
No Post baseline assessment	5 (7.9%)	4 (6.3%)
Median DOR (months) [95% CI]	**15.7 [7.7; NR]**	**9.1 [5.3; NR]**
Number of events	12 (46.2%)	9 (52.9%)

ITT population.



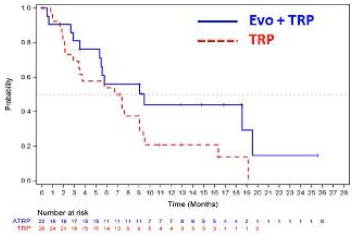
PFS Hazard Ratio: 0.77 [0.49; 1.20]

Advances in the Treatment in HER2+ disease.

	HER2+ confirmed with Fresh Biopsy		HER2+ confirmed with Fresh Biopsy OR ctDNA+	
	Evo +T+R+P	T+R+P	Evo +T+R+P	T+R+P
N evaluable	22	26	47	49
Confirmed ORR, n (%) [95% CI]	**13 (59.1%) [36.4%; 79.3%]**	**6 (23.1%) [9.0%; 43.6%]**	**23 (48.9%) [34.1%; 63.9%]**	**12 (24.5%) [13.3%; 38.9%]**
CR (Complete Response)	0	0	1 (2.1%)	1 (2.0%)
PR (Partial Response)	13 (59.1%)	6 (23.1%)	22 (46.8%)	11 (22.4%)
SD (Stable Disease)	6 (27.3%)	13 (50.0%)	15 (31.9%)	27 (55.1%)
PD (Progressive Disease)	0	5 (19.2%)	4 (8.5%)	6 (12.2%)
NE (Not Evaluable)	0	1 (3.8%)	2 (4.3%)	1 (2.0%)
No Post baseline assessment	3 (13.6%)	1 (3.8%)	3 (6.4%)	3 (6.1%)
Median DOR (months) [95% CI]	**15.7 [4.0; NR]**	**14.5 [7.4; NR]**	**15.7 [7.7; NR]**	**9.1 [3.5; NR]**
Number of events	6 (46.2%)	3 (50.0%)	11 (47.8%)	7 (58.3%)

Progression-free survival (PFS) based on investigator assessment

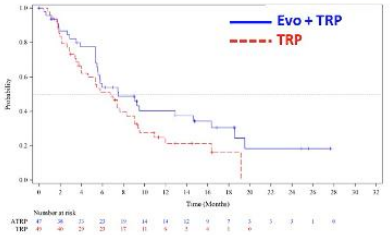
HER2+ fresh biopsy (n=48)



	Number of patients with events	Number of patients censored	mPFS [95% CI]
Evo + TRP	13 (59.1%)	9 (40.9%)	9.5 [5.4-19.5]
TRP	22 (84.6%)	4 (15.4%)	7.1 [2.9-9.1]

Hazard Ratio: 0.62 [0.28; 1.36]

HER2+ (fresh biopsy OR ctDNA+) (n=96)



	Number of patients with events	Number of patients censored	mPFS [95% CI]
Evo + TRP	30 (63.8%)	17 (36.2%)	7.5 [5.5-14.7]
TRP	37 (75.5%)	12 (24.5%)	6.7 (4.0-9.0)

Hazard Ratio: 0.64 [0.39; 1.07]

Advances in the Treatment in HER2+ disease.

Summary of treatment-emergent adverse events grades 3-5
(with frequency >5% on either arm)

	Evo + T + R + P N=63			T + R + P N=63		
Grade	3	4	5	3	4	5
Neutrophil count decreased	12 (19.0%)	7 (11.1%)	-	12 (19.0%)	4 (6.3%)	-
Anemia	14 (22.2%)	-	-	11 (17.5%)	-	-
Neutropenia	11 (17.5%)	4 (6.3%)	-	7 (11.1%)	2 (3.2%)	-
White blood cell count decreased	7 (11.1%)	-	-	6 (9.5%)	-	-
Hypertension	6 (9.5%)			4 (6.3%)		
Sepsis	2 (3.2%)	-	2 (3.2%)	2 (3.2%)	-	1 (1.6%)
Asthenia	2 (3.2%)	-	-	4 (6.3%)	-	-
Febrile neutropenia	1 (1.6%)	-	-	3 (4.8%)	2 (3.2%)	-

All G5 TEAEs: ETRP (N=4): Sepsis N=2, Esophageal perforation N=1, Respiratory failure N=1; TRP (N=7) : Sepsis N=1, Pneumonia/pneumopathy/respiratory infection N=1 each, Sudden death N=1, death from unknown cause N=1, esophageal hemorrhage N=1

- The incidence of adverse events due to any cause was comparable by arm
- There were 11 Grade 5 treatment emergent adverse events, 2 of which were deemed to be treatment related: esophageal perforation (ETRP) and pneumopathy (TRP)

Evorpacept's safety profile was consistent with its prior experience in over 700 patients treated to date

ASPEN-06 STUDY (final analysis of the phase 2)

✅ **Positive study**: In the ITT population, **E + TRP** demonstrated an **ORR of 41.3%** and a **DOR of 15.7** months, compared to the **TRP** control with an **ORR of 26.6%** and a **DOR of 9.1 months**.

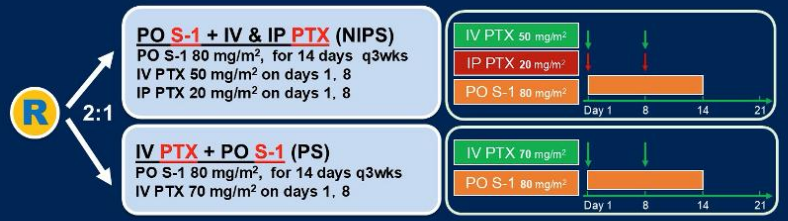
✅ **Patients with confirmed HER2 expression**, either through fresh biopsy or ctDNA, **showed the greatest benefit** in ORR, DOR, and PFS, indicating that **HER2+ expression** is a key biomarker and validating evorpacept's MOA.

✅ Evorpacept has a **favorable safety profile**.

❌ HER2 status determination is not mandatory before patient inclusion in the study.

DRAGON-01 trial (results of the phase 3)

Methods: Study Design



- **Research Objects**: Gastric cancer with peritoneal metastasis
- **Primary Endpoint**: Overall survival in mITT population
- **Secondary Endpoints**: Conversion surgery rate, pathological response, adverse events, etc.

Methods: Study Design

Key Eligibility Criteria	Key Exclusion Criteria
1. Histologically confirmed gastric cancer	1. Confirmed evidence of distant metastasis other than peritoneal metastasis (ovarian metastasis is permitted)
2. Peritoneal metastasis confirmed by laparoscopy	2. Gastric outflow tract obstruction or intestinal obstruction
3. Age between 18 and 75 years	3. Any prior anti-cancer therapy
4. ECOG-PS of 0 or 1	4. Synchronous or metachronous (within 5 years) malignancies
5. Expected survival of at least 3 months	5. Clinically severe heart disease, pulmonary disease, mental disease, etc.
6. Adequate organ function	6. Severe uncontrolled infections or other concomitant disease
	7. Anaphylaxis to paclitaxel or any research drug ingredient

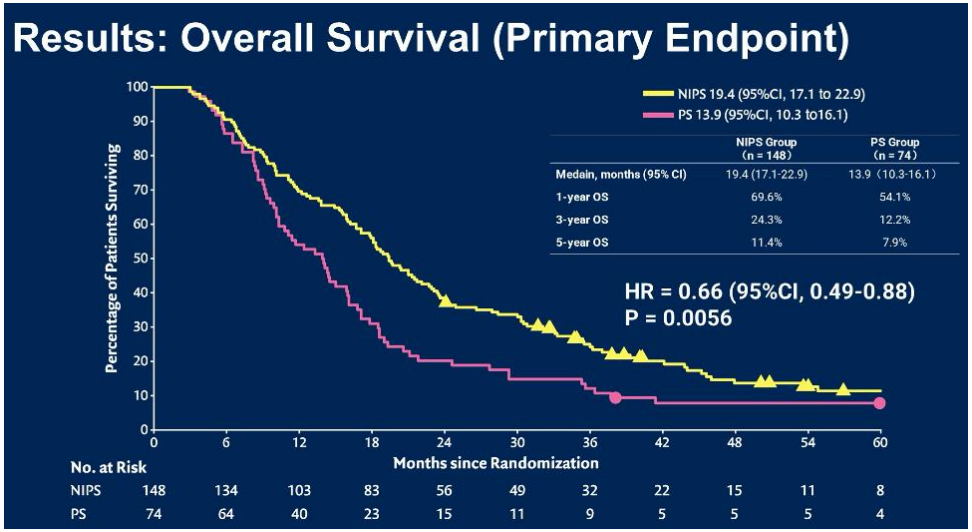
DRAGON-01 trial (results of the phase 3)

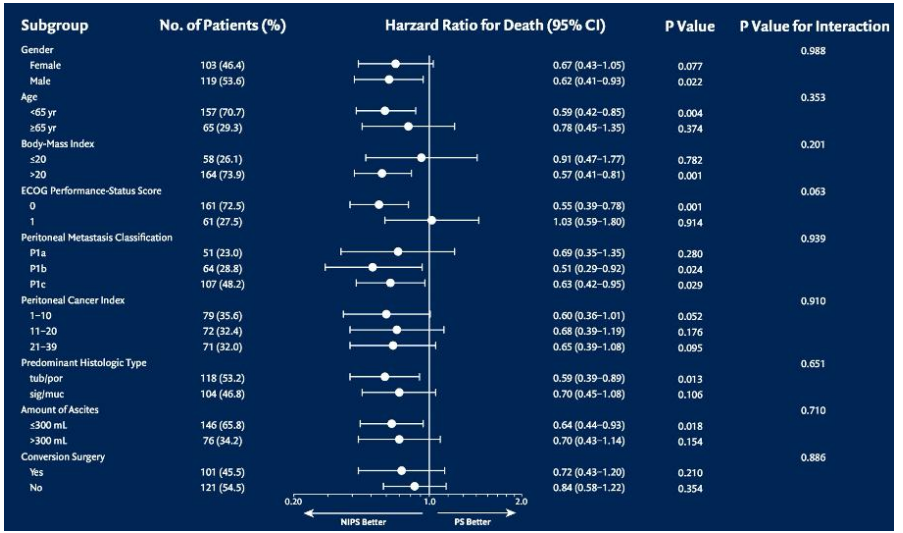
Results: Baseline Characteristics

Characteristic	NIPS (N = 148)	PS (N = 74)
Median age (range) — yr	60 (24-70)	56 (23-74)
Sex — no. (%)		
Female	68 (45.9)	36 (48.6)
Male	80 (54.1)	38 (51.4)
Body Weight — kg	59.3±10.6	62.4±11.0
Body-Mass Index		
Mean Value — kg/m²	21.7±3.1	23.0±3.2
Distribution — no. (%)		
> 20	102 (68.9)	62 (83.8)
≤ 20	46 (31.1)	12 (16.2)
ECOG-PS — no. (%)		
0	108 (73.0)	53 (71.6)
1	40 (27.0)	21 (28.4)
Predominant Histologic Type — no. (%)		
Tubular/Poorly Differentiated Adenocarcinoma	84 (56.8)	34 (45.9)
Signet Ring Cell Carcinoma	58 (39.2)	37 (50.0)
Mucinous Adenocarcinoma	6 (4.1)	3 (4.1)

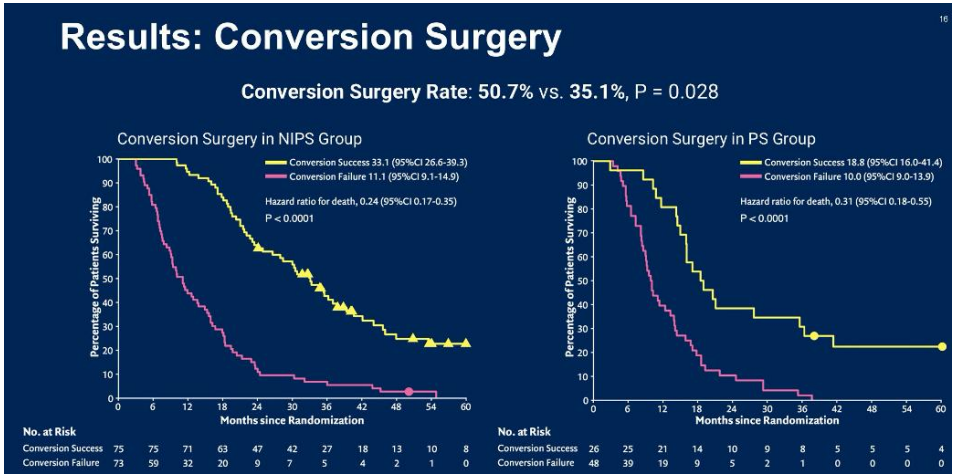
Characteristic	NIPS (N = 148)	PS (N = 74)
PM Japanese Classification — no. (%)		
P1a	32 (21.6)	19 (25.7)
P1b	45 (30.4)	19 (25.7)
P1c	71 (48.0)	36 (48.6)
Peritoneal Cancer Index — no. (%)		
1 to 10	48 (32.4)	31 (41.9)
11 to 20	54 (36.5)	18 (24.3)
21 to 39	46 (31.1)	25 (33.8)
Median Value (IQR)	15.0 (9.0-23.0)	14.0 (8.0-22.8)
Peritoneal Cytology — no. (%)		
Positive	73 (49.3)	38 (51.4)
Negative	75 (50.7)	36 (48.6)
Amount of Ascites Evaluated by Laparoscopy — mL		
≤ 300	98 (66.2)	48 (64.9)
> 300	50 (33.8)	26 (35.1)
Median Follow-up Time (IQR) since diagnosis of PM — mo	56.9 (40.3-68.1)	64.3 (59.9-70.2)

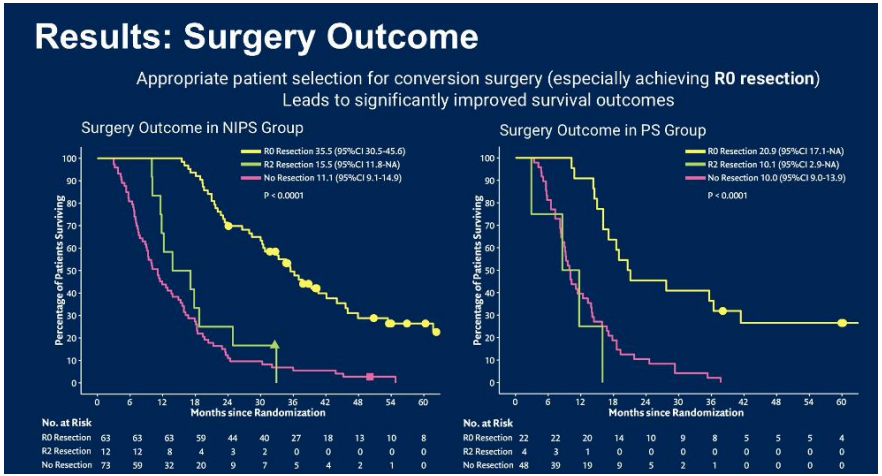
DRAGON-01 trial (results of the phase 3)





DRAGON-01 trial (results of the phase 3)





DRAGON-01 trial (results of the phase 3)

Results: Adverse Events

Adverse Events Grade 3-4: **38.4%** vs **42.5%** P = 0.562	NIPS Group (N=148)			PS Group (N=74)		
	Grade 1-2 (**87.0%**)	Grade 3 (**37.0%**)	Grade 4 (**12.3%**)	Grade 1-2 (**83.6%**)	Grade 3 (**39.7%**)	Grade 4 (**9.6%**)
Leukopenia	77 (49.4)	28 (17.9)	6 (3.8)	40 (51.9)	17 (22.1)	2 (2.6)
Neutropenia	63 (40.4)	25 (16.0)	6 (3.9)	33 (42.9)	14 (18.2)	4 (5.2)
Anemia	63 (42.6)	16 (10.3)	2 (1.3)	30 (39.0)	10 (12.9)	2 (2.6)
Thrombocytopenia	26 (16.7)	7 (4.5)	1 (0.6)	12 (15.6)	5 (6.5)	1 (1.3)
ALT Increased	40 (25.6)	6 (3.8)	0 (0.0)	20 (25.9)	4 (5.2)	0 (0.0)
AST Increased	43 (27.5)	5 (3.2)	0 (0.0)	19 (24.7)	3 (3.9)	0 (0.0)
Creatinine Increased	10 (6.4)	1 (0.6)	0 (0.0)	6 (7.8)	1 (1.3)	0 (0.0)
Fatigue	81 (51.9)	12 (7.7)	0 (0.0)	43 (55.8)	7 (9.1)	0 (0.0)
Nausea	49 (31.4)	3 (1.9)	0 (0.0)	28 (36.3)	3 (3.9)	1 (1.3)
Vomiting	26 (16.7)	2 (1.3)	0 (0.0)	16 (20.8)	1 (1.3)	0 (0.0)
Diarrhea	29 (18.6)	7 (4.5)	0 (0.0)	15 (19.5)	5 (6.5)	0 (0.0)
Anorexia	79 (50.6)	8 (5.1)	0 (0.0)	41 (53.2)	6 (7.8)	0 (0.0)
Peripheral Neuropathy	37 (23.7)	3 (1.9)	0 (0.0)	19 (24.6)	2 (2.6)	0 (0.0)
Mucositis oral	30 (19.2)	4 (2.6)	1 (0.6)	17 (22.1)	3 (3.9)	0 (0.0)
Alopecia	99 (63.4)	12 (7.7)	0 (0.0)	51 (66.2)	6 (9.1)	0 (0.0)
Fever	37 (23.7)	2 (1.3)	0 (0.0)	20 (25.9)	1 (1.3)	0 (0.0)

DRAGON-01 trial (results of the phase 3)

❌ The study was conducted exclusively in Asian Population.

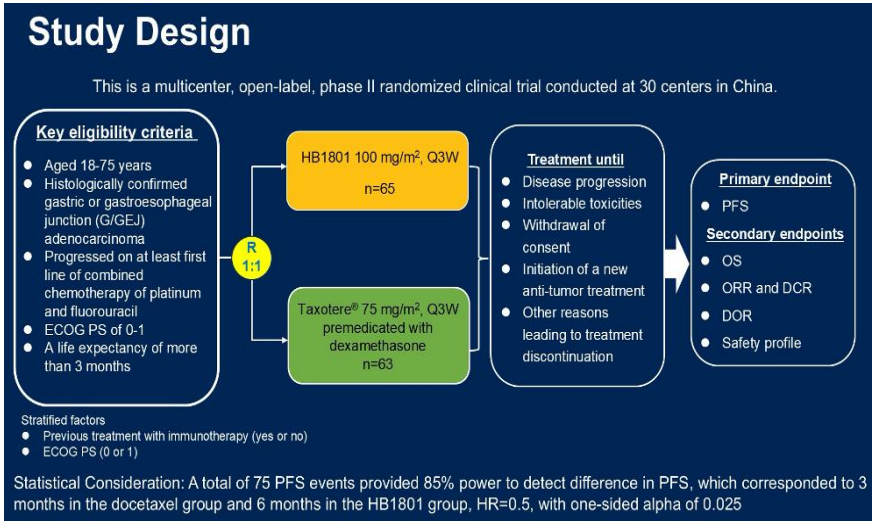
❌ Systemic Chemo of both groups.

✅ Significant impact of drug administration route for GCPM patients.

✅ Practice-Changing Results. 🤔

✅ Remarkable survival outcomes with conversion surgery.

Albumin-bound docetaxel HB1801 (Multicenter, randomized, phase 2)

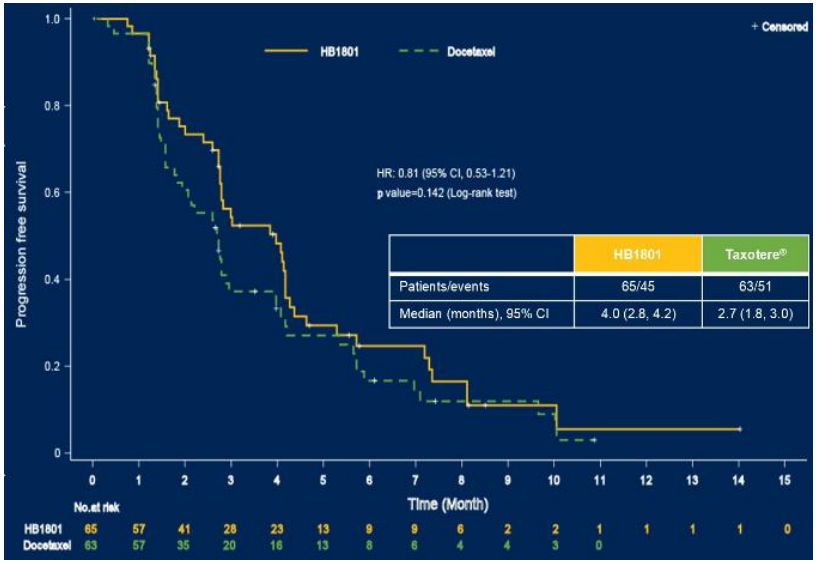


Baseline characteristics (ITT)

	HB1801 (n=65)	Taxotere® (n=63)
Median age, range (years)	58.0 (27, 75)	59.0 (30, 74)
Sex, n (%)		
Male	50 (76.9)	42 (66.7)
Female	15 (23.1)	21 (33.3)
BMI, mean±SD (kg/m²)	20.5±3.0	21.2±3.0
ECOG PS, n (%)		
0	11 (16.9)	11 (17.5)
1	54 (83.1)	52 (82.5)
No. of metastatic organs, n (%)		
0	4 (6.2)	1 (1.6)
1	22 (33.8)	25 (39.7)
≥2	39 (60.0)	37 (58.7)
Peritoneal metastasis, n (%)		
Yes	22 (33.8)	18 (28.6)
No	43 (66.2)	45 (71.4)
No. of previous lines of therapy, n (%)		
1	53 (81.5)	54 (85.7)
2	10 (15.4)	8 (12.7)
Others	2 (3.1)	1 (1.6)
Previous treatment with immunotherapy, n (%)	38 (58.5)	38 (60.3)

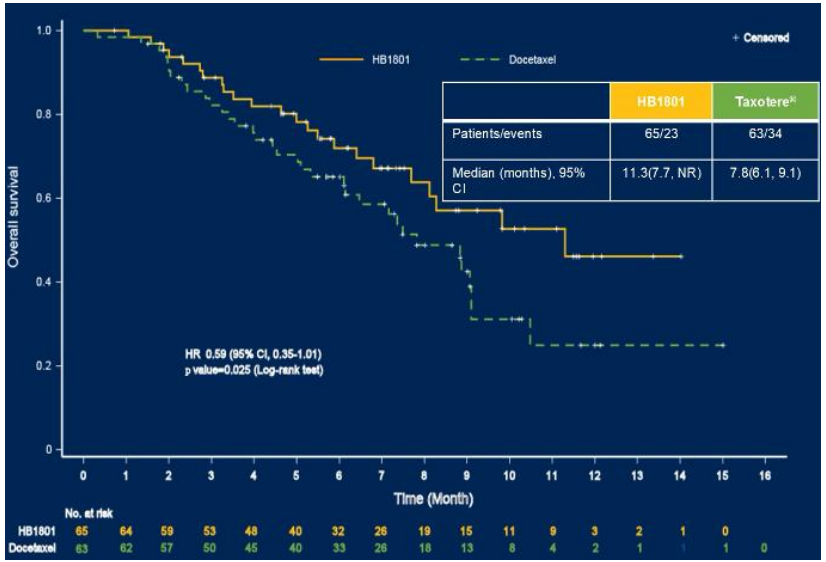
Albumin-bound docetaxel HB1801 (Multicenter, randomized, phase 2)

PFS (ITT population.)



	HB1801	Taxotere®
Patients/events	65/45	63/51
Median (months), 95% CI	4.0 (2.8, 4.2)	2.7 (1.8, 3.0)

OS (ITT population.)



	HB1801	Taxotere®
Patients/events	65/23	63/34
Median (months), 95% CI	11.3(7.7, NR)	7.8(6.1, 9.1)

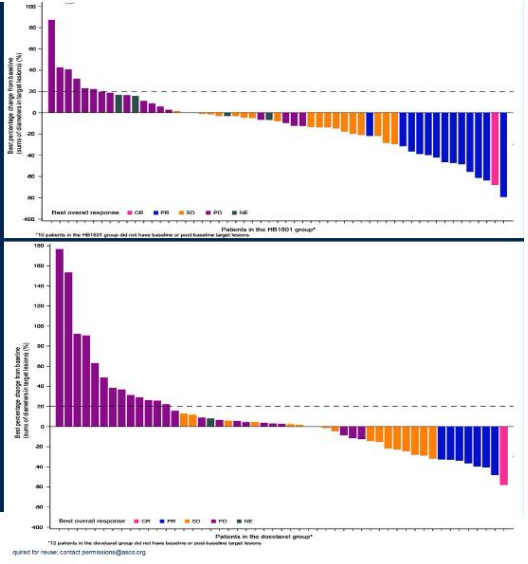
Albumin-bound docetaxel HB1801 (Multicenter, randomized, phase 2)

Efficacy: ORR (ITT)

Cutoff date: June 25, 2024
Median duration of follow-up: 4.6 months

	HB1801 (n=65)	Taxotere® (n=63)
Best Response		
CR	1(1.5)	1(1.6)
PR	13(20.0)	8(12.7)
SD	20(30.8)	17(27.0)
Non CR/Non PD	3(4.6)	1(1.6)
PD	17(26.2)	27(42.9)
NE	11(16.9)	9(14.3)
ORR, 95%CI	21.5 (12.3, 33.5)	14.3 (6.8, 25.4)
DCR, 95%CI	56.9 (44.0, 69.2)	42.9 (30.5, 56.0)

CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; SD, stable disease.



Safety: Summary of AEs (SS)

Cutoff date: June 25, 2024
Median duration of follow-up: 4.6 months

	HB1801 (n=65)	Taxotere® (n=63)
TEAEs	64 (98.5)	61 (96.8)
≥Grade 3 TEAEs	26 (40.0)	24 (38.1)
SAEs	15 (23.1)	16 (25.4)
TEAES leading to death	0	3 (4.8)
TEAES leading to treatment discontinuation	6 (9.2)	5 (7.9)
TEAES leading to treatment interruption	23 (35.4)	11 (17.5)
TEAEs leading to dose reduction	12 (18.5)	9 (14.3)
TRAEs	61 (93.8)	59 (93.7)
≥Grade 3 TRAEs	20 (30.8)	19 (30.2)
Treatment related SAEs	10 (15.4)	10 (15.9)
TRAES leading to death	0	1 (1.6)
TRAES leading to treatment discontinuation	6 (9.2)	2 (3.2)
TRAES leading to treatment interruption	17 (26.2)	7 (11.1)
TRAEs leading to dose reduction	11 (16.9)	9 (14.3)

AEs, adverse events; SAEs, serious adverse events; SS, safety analysis set; TEAEs, treatment emergent adverse events; TRAEs, treatment related adverse events.

Albumin-bound docetaxel HB1801 (Multicenter, randomized, phase 2)

❌ This is a negative study that fails to achieve its primary endpoint.

❌ The study was conducted exclusively in Asian Population.

✅ Despite being a phase II study, it is a randomized, multicenter study.

✅ HB-1801 had a manageable safety profile.

📋 A phase III study (NCT06296706) in now ongoing to compare HB1801 vs docetaxel in locally advanced or metastatic G/GEJ adenocarcinoma with previous first-line treatment failure.

POSTER SESSION

Molecular profiling of a gastroesophageal adenocarcinoma (GEA) multicohort using next-generation sequencing (NGS)

ASCO Gastrointestinal Cancers Symposium

494P

Poster Board: H9

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BACKGROUND

- The **mutational landscape of GEA** is rapidly evolving with the identification of **promising molecular targets**[1].
- Targeted therapies addressing *HER2* amplifications[2], *FGFR2* overexpression[3] and claudin-18.2 overexpression[4] have demonstrated significant improved outcomes in phase 2 and 3 clinical studies.
- However, the use of **NGS is not standardized in gastric cancer** and **histological subtypes are insufficient to capture the molecular heterogeneity**[5] in these patients (pts).

OBJECTIVES

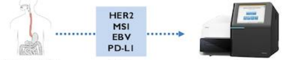
1. To describe the **clinicopathological features** and their association with **molecular findings** obtained through immunohistochemistry (IHC) and tissue-based NGS in a GEA cohort.

- **SECONDARY:**

1. To evaluate the ability of NGS to **guide clinical and therapeutic decisions** in patients with metastatic GEA.
2. To analyze **oncological outcomes** and their prognostic stratification according to the molecular alterations identified via IHC and tissue-based NGS.

METHODS

- Retrospective and descriptive study on GEA from 2019 to 2024 (n=115).
- **IHC** was used to evaluate <u>*HER2* expression, microsatellite instability (MSI), Epstein-Barr virus (EBV) and PD-L1 status</u>.
- **In-house and commercial NGS platforms** were used to detect molecular alterations from tumor samples.



- Cox regression model was used to analyze **overall survival (OS)** based on the **clinicopathological and molecular subgroups**.

RESULTS

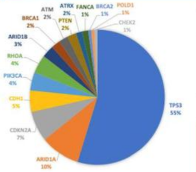


Figure 1. Distribution of the most frequent and clinically significant PV detected in tissue samples from pts with metastatic GEA.

- We analyzed **115 pts** diagnosed with metastatic GEA.
- NGS techniques identified **253 pathogenic variants (PV) and 310 copy number alterations (CNA) in 107 and 71 pts, respectively.** Figure 1 presents the 15 most frequently observed alterations, highlighting those with potential clinical and therapeutic significance.

PV and CNA detected through NGS

PV with <u>potential clinical therapeutic implications</u> in 20 pts (17.4%): *PIK3CA* (5.2%), *BRCA1/2* (3.5%), *ATM* (2.6%), *FANCA* (1.7%), *PTEN* (2.6%), *CHEK2* (0.9%) and *POLD1* (0.9%).

Along with <u>molecularly accionable</u> **CNA** in 33 pts (28.7%): *ERBB2* (10.4%), *EGFR* (8.7%), *MET* (5.2%) and *FGFR2* (4.3%) genes, among others.

Oncological outcomes

We observed a **significantly worse OS** in pts with <u>diffuse vs intestinal tumors</u> (Figure 2; A) (15.7m vs 19.1m; HR = 1.61 [1.01-2.58]; p=0.04) and a trend toward shorter survival in pts with *CDKN2A* mutations (11.97m vs 17.83m; HR=1.33 [0.67-2.67]; p=0.41); (Figure 2; B) .

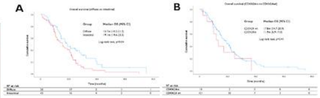


Figure 2. Oncological outcomes in terms of OS regarding histological patterns (A) and molecular profile (B).

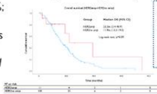
		N=115 (%)
Age Median years [range]		54 [18-83]
Sex	Male	69 (60.0)
Tumor site	Gastric	72 (62.6)
	Gastroesophageal junction	37 (32.2)
	Esophagus	6 (5.2)
Histological subtype	Diffuse or pooly cohesive	51 (44.3)
	Intestinal or tubular	46 (40.0)
	Others	18 (15.7)
Stage at diagnosis	Advanced	74 (66.9)
	Localized	41 (33.1)
Metastatic site	Peritoneum	53 (46.1)
	Liver	34 (29.6)
Molecular profile (IHC)	HER2 (+)	20 (17.4)
	MSI	5 (4.3)
	EBV (+)	2 (1.8)
	PDL1 (CPS) ≥1	35 (30.4)

Table 1. Clinicopathological characteristics of the 115 pts with metastatic GEA included in our study.

Clinicopathological features and molecular distribution

- <u>Early (<50y) vs late-onset (≥50y)</u> → ↑ rate of PV in *CDH1* (10.42% vs 4.48%; p=0.22) and *PIK3CA* (8.33% vs 2.99%; p=0.20) genes.
- <u>Diffuse vs intestinal</u> → ↑ frequency of PV in *ARID1A* (17.6% vs 2.2%; p=0.01) and *CDH1* (11.8% vs 0%; p=0.02) genes.
- <u>Peritoneal vs liver disease</u> → ↑ prevalence of PV in *CDH1* (12% vs 0%; p=0.04) and RHOA (10% vs 0%; p=0.06) genes.

Although not significantly, CNA in *ERBB2* were associated with a better prognosis (22.2m vs 16.2m; HR=0.47 [0.19-1.18]; p=0.09).



<u>Discrepancies in HER2+ tumors:</u>
- **IHC (2+/ISH+ // 3+) (n=20)** → ERBB2 CNA gain (n=10)
- **ERBB2 CNA gain (n=12)** → IHC (2+/ISH+ // 3+) (n=10)

CONCLUSIONS

- Our results support the **utility of NGS platforms** in detecting novel molecular targets with prognostic and clinical impact, beyond *ERBB2*.
- Additionally, we observed **poorer prognosis in diffuse subtype tumors**, which exhibited a higher frequency of mutations in *ARID1A* and *CDH1* genes.

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Translational genomics and targeted therapies in solid tumors

TAKE-HOME MESSAGES

✅ No Significant Changes in the Standard of Care for Esophagogastric Tumors.

✅ Promising pCR rate without increased surgical risks or toxicity in ESCC with chemo + RT and sintilimab.

✅ Although the INNOVATION study did not meet its primary endpoint, the addition of trastuzumab to perioperative chemotherapy improved the mpRR.

✅ ASPEN-06: Positive study: In the ITT population, E + TRP demonstrated an ORR of 41.3% and a DOR of 15.7 months, compared to the TRP control with an ORR of 26.6% and a DOR of 9.1 months.

✅ DRAGON-01: Remarkable survival outcomes with conversion surgery, although the study was conducted exclusively in an Asian population.

✅ Support for the use of NGS platforms to identify new molecular targets with prognostic and clinical impact beyond ERBB2.


The future depends on what we do in the present.
— Mahatma Gandhi —

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