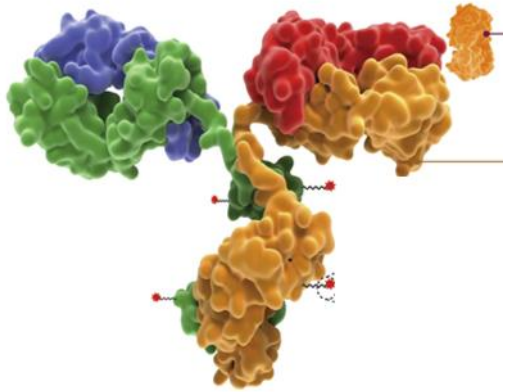
II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

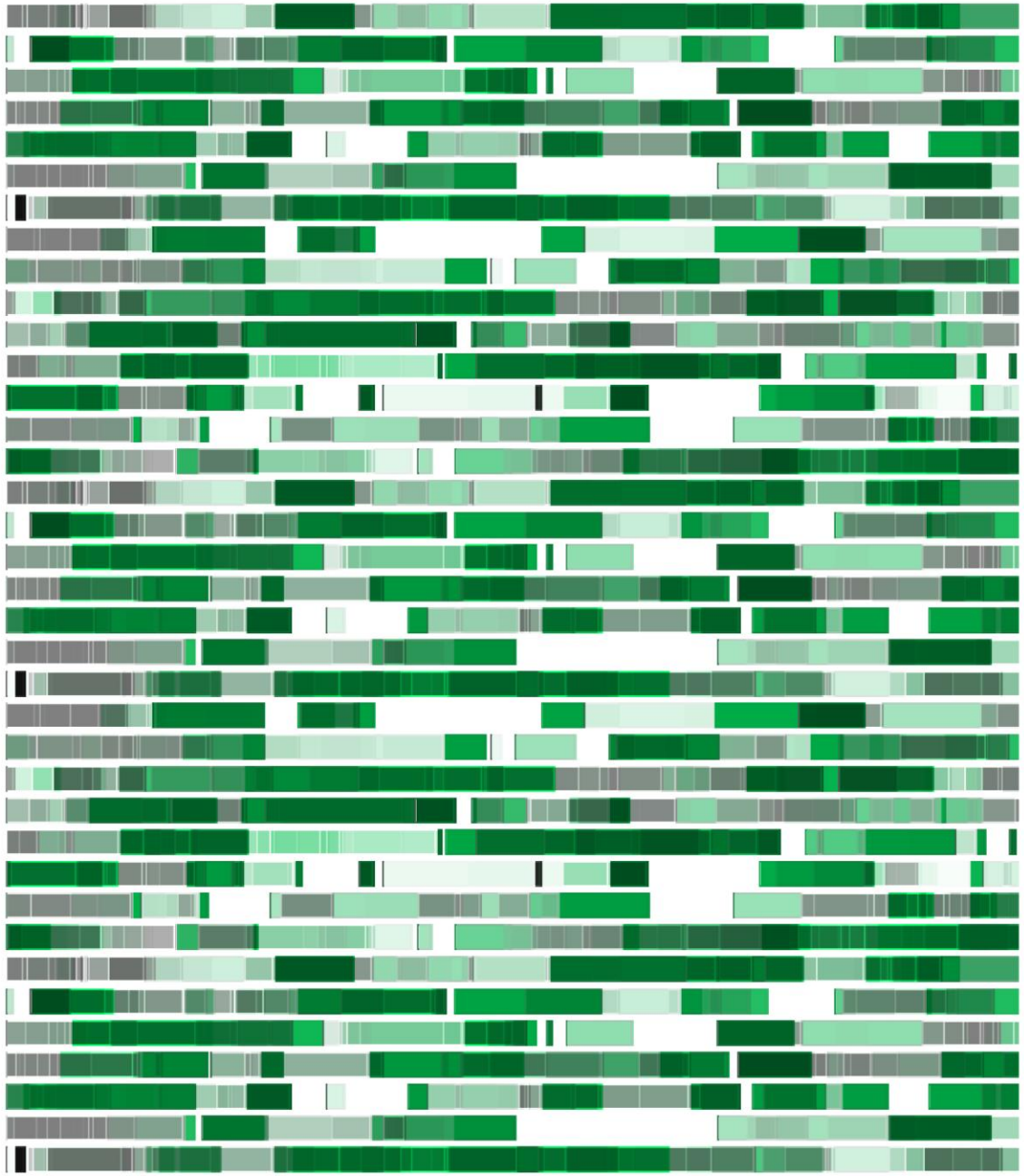
SEVILLA, 6 Y 7 DE FEBRERO DE 2025

ADC EN TUMORES DIGESTIVOS

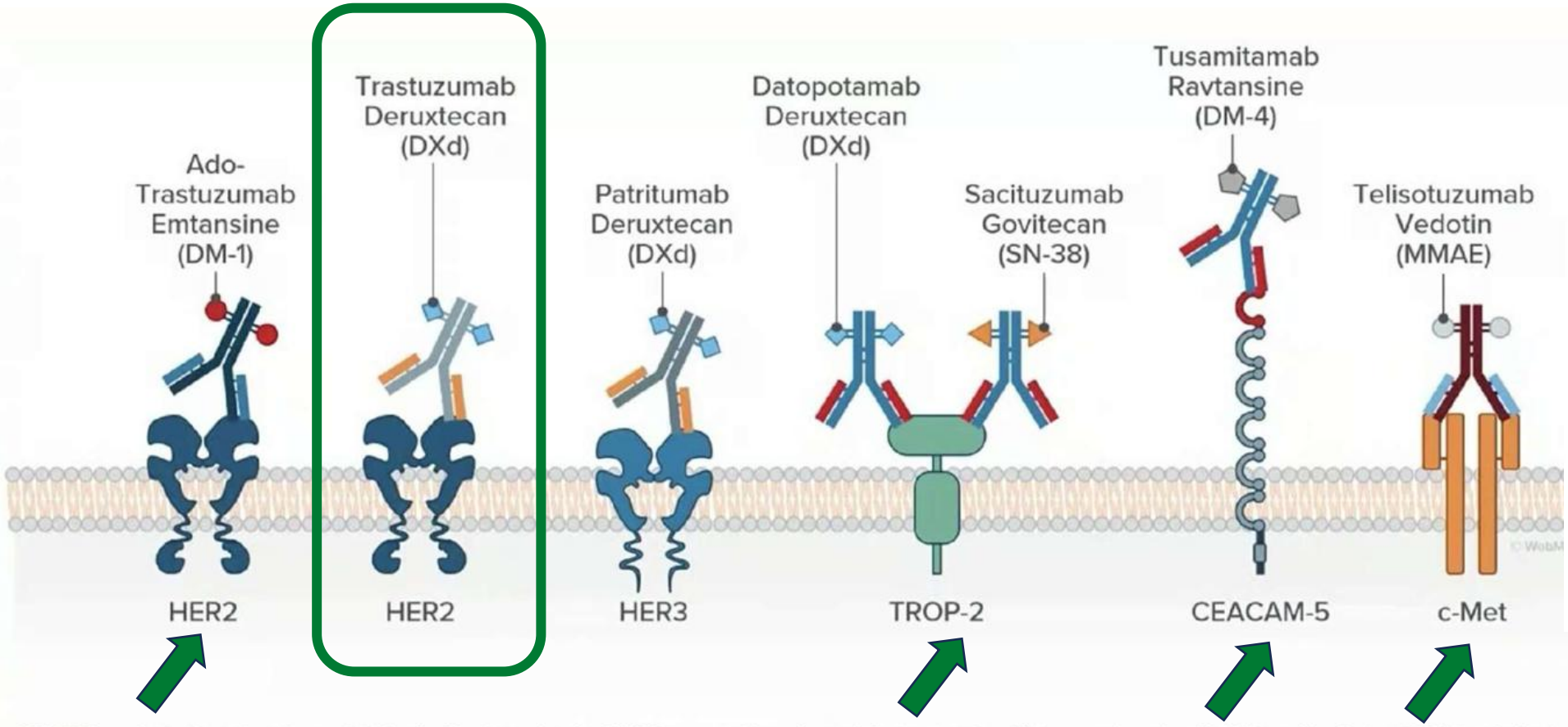


Mª A. Gómez-España

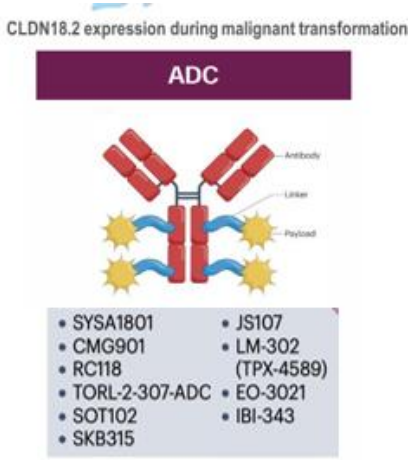
H.U. Reina Sofía, IMIBIC, UCO, Córdoba. CIBERONC.

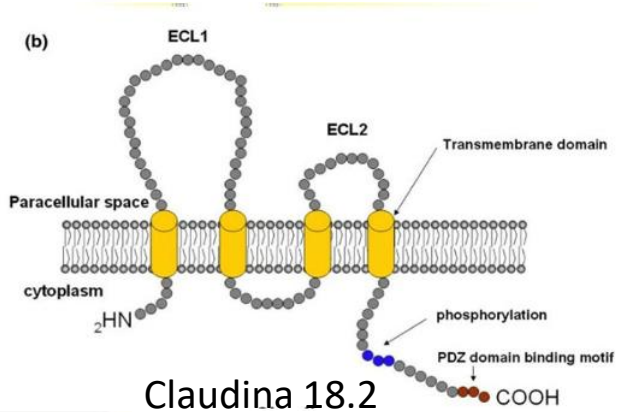


ADCs (ANTIBODY-DRUG CONJUGATES) TARGET



CEACAM, carcinoembryonic antigen-related cell adhesion molecules; HER, human epidermal growth factor receptor; Met, mesenchymal epithelial transition factor; TROP, trophoblast cell surface antigen.
Desai A, et al. Lung Cancer. 2022;163:96-106.



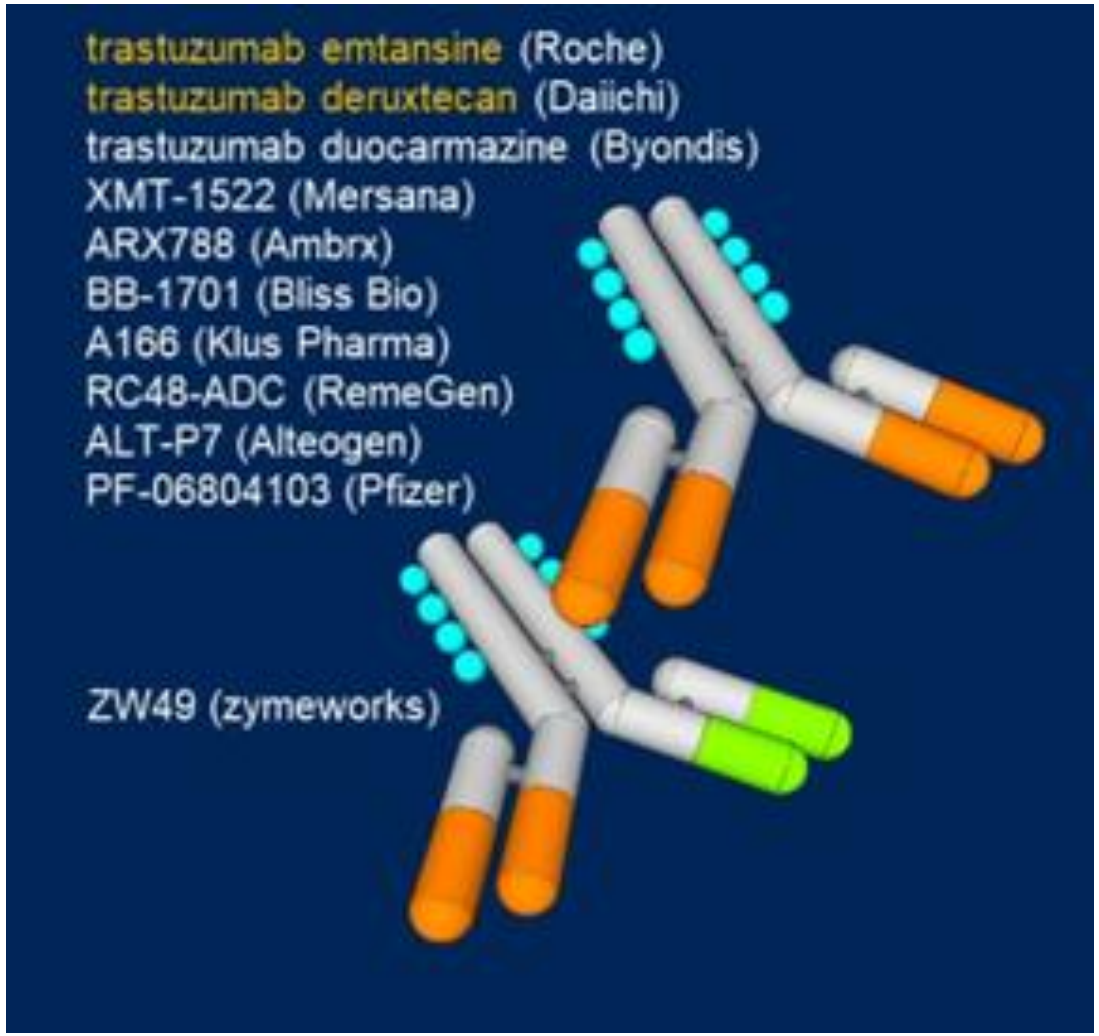


Claudina 18.2

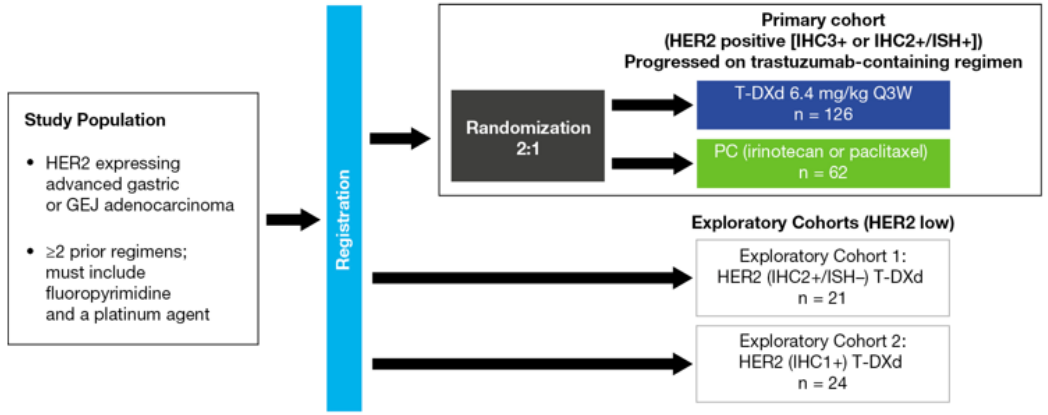
HER2 ADCs

HER2 ADCs (ANTIBODY-DRUG CONJUGATES)

- 3-5% CRC
  - Prognostic?, > brain M1, resistence anti-EGFR. Male, left localization
- 15-25% GC/GEJ
  - Poor prognostic, > M1, > GEJ and intestinal subtype
- 5-20% BTC: poor prognostic, agresive phenotype
  - 19-31% GB
  - 17-18% eCC
  - 3-5% iCC
- 1-7% Pancreatic
- IHC/FISH. Heterogeneity
- Rebiopsy/LB

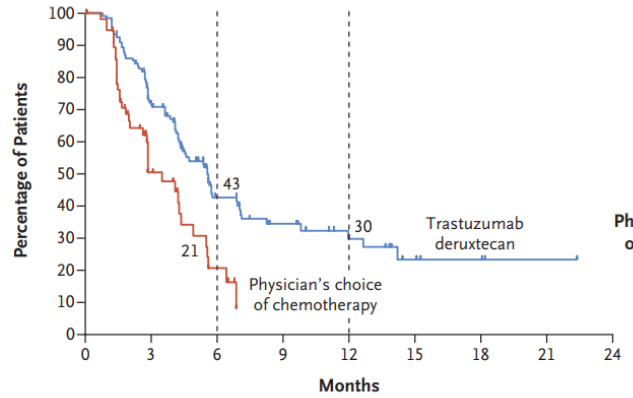


GC/GEJ A HER-2 ANTIBODY-DRUG CONJUGATE: TRASTUZUMAB DERUXTECAN (DESTINY GASTRIC 01)



Endpoint/Outcome	T-Dxd (n=119)	PC Overall (n=56)
ORR (CR + PR) by ICR, n(%)	51,3% (n=61) 95% CI, 41.9-60.5; p<.0001)	14.3% (n=8) 95% CI, 6.4-26.2
Confirmed ORR	42.9% (n=51) 95% CI, 33.8-52.3	12.5% (n=7) 95% CI, 5.2-24.1)
Confirmed DCR (CR + PR + SD), n(%)	85.7% (n=102) 95% CI, 78.1-91.5	62.5% (n=35) 95% CI, 48.5-75.1
Confirmed DOR, median, mo	11.3 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, mo	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

B Progression-free Survival

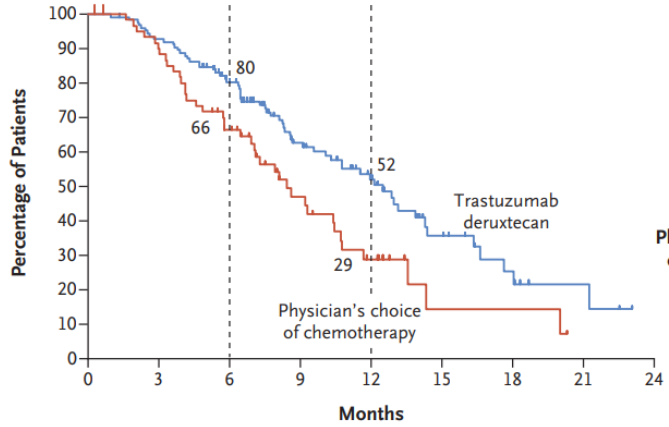


	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI) mo
Trastuzumab Deruxtecan	73/125	5.6 (4.3–6.9)
Physician's Choice of Chemotherapy	36/62	3.5 (2.0–4.3)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.31–0.71)

No. at Risk									
Trastuzumab deruxtecan	125	82	35	20	12	5	3	1	0
Physician's choice of chemotherapy	62	19	5	0	0	0	0	0	0

A Overall Survival



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Trastuzumab Deruxtecan	62/125	12.5 (9.6–14.3)
Physician's Choice of Chemotherapy	39/62	8.4 (6.9–10.7)

Hazard ratio for death, 0.59 (95% CI, 0.39–0.88) P=0.01

No. at Risk									
Trastuzumab deruxtecan	125	115	88	54	33	14	7	3	0
Physician's choice of chemotherapy	62	54	37	19	10	2	2	0	0

Shitara K, et al. N. Engl J Med 2020 Yamaguchi K et al. Presented at: ASCO Virtual Congress 2021; June 4-8, 2021.

GC/GEJ A HER-2 ANTIBODY-DRUG CONJUGATE:
TRASTUZUMAB DERUXTECAN (DESTINY GASTRIC 02)

Objective: To determine the efficacy and safety of T-DXd monotherapy as a second-line treatment in Western patients with HER2-positive (IHC 3+, IHC 2+/ISH+), unresectable or metastatic gastric or GEJ cancer who progressed on or after a trastuzumab-containing regimen

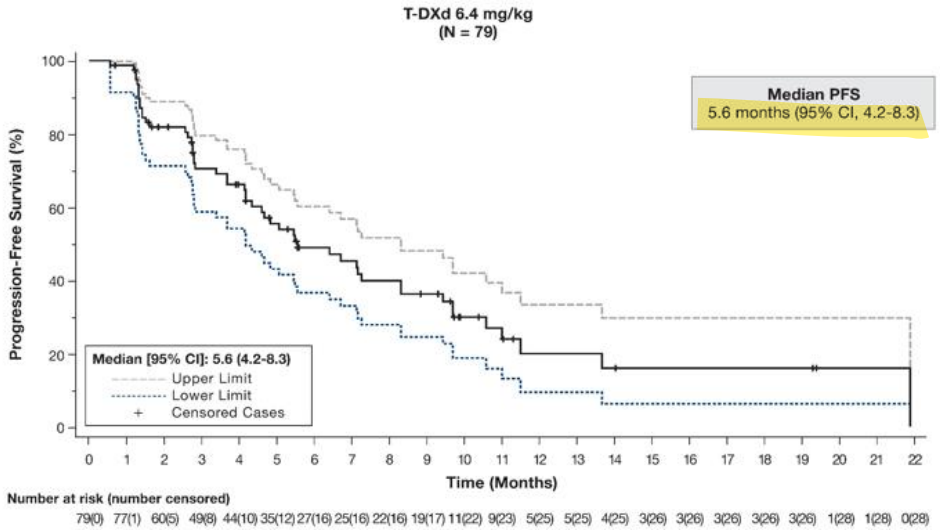
Key eligibility criteria
- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Progressive disease on or after first-line therapy with a trastuzumab-containing regimen
- Centrally confirmed HER2-positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

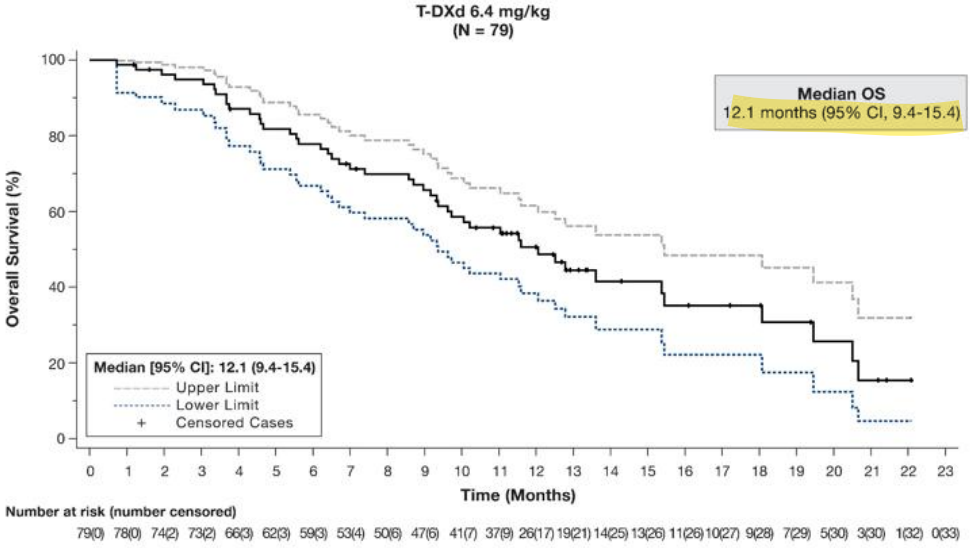
→ T-DXd 6.4 mg/kg Q3W N = 79[a] →

Primary endpoint
- Confirmed ORR by ICR

Secondary endpoints[b]
- PFS by ICR
- OS
- DoR by ICR
- Safety
- Patient-reported outcomes

Response Assessment by ICR	April 9, 2021 Data Cutoff[a] Patients (N = 79)	November 8, 2021 Data Cutoff[b] Patients (N = 79)
Confirmed ORR,[c] % (n)	38.0 (30) (95% CI, 27.3-49.6)	41.8 (33) (95% CI, 30.8-53.4)
Confirmed best overall response, % (n)		
CR	3.8 (3)	5.1 (4)
PR	34.2 (27)	36.7 (29)
SD	43.0 (34)	39.2 (31)
PD	16.5 (13)	16.5 (13)
Not evaluable	2.5 (2)	2.5 (2)
Confirmed DCR,[d] % (n)	81.0 (64) (95% CI, 70.6-89.0)	81.0 (64) (95% CI, 70.6-89.0)
Median DoR, months	8.1 (95% CI, 4.1-NE)	8.1 (95% CI, 5.9-NE)[e]
Median TTR, months	1.4 (95% CI, 1.4-2.6)	1.4 (95% CI, 1.4-2.7)



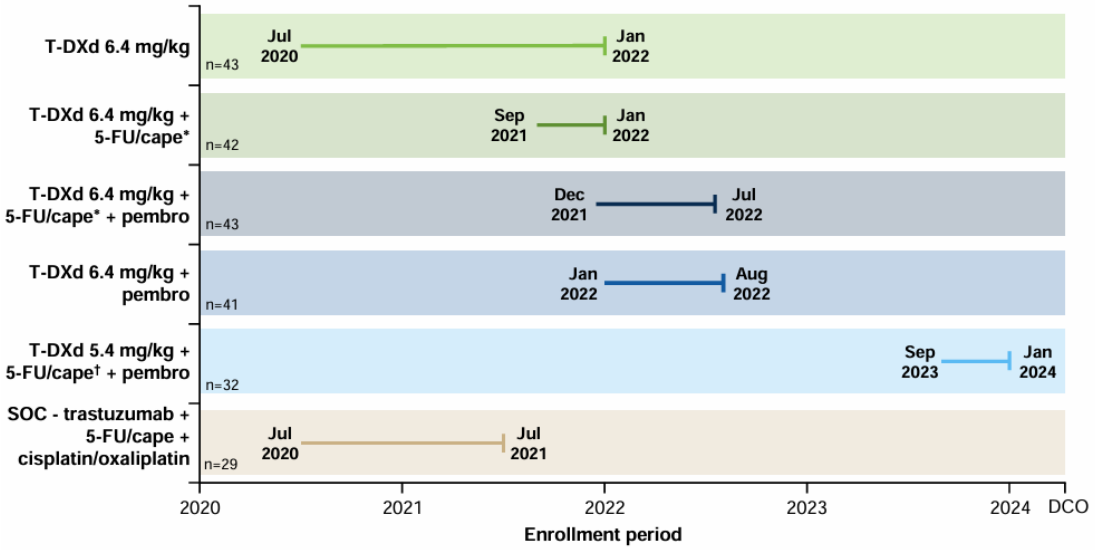


Van Cutsem E, et al. Lancet 2023

GC/GEJ A HER-2 ANTIBODY-DRUG CONJUGATE:
TRASTUZUMAB DERUXTECAN (DESTINY GASTRIC 03)

Janjigian Y, et al. ESMO 2024

Part 2 of DESTINY-Gastric03, a Phase 1b/2 trial (NCT04379596), with **non-contemporaneous and non-randomized arms**



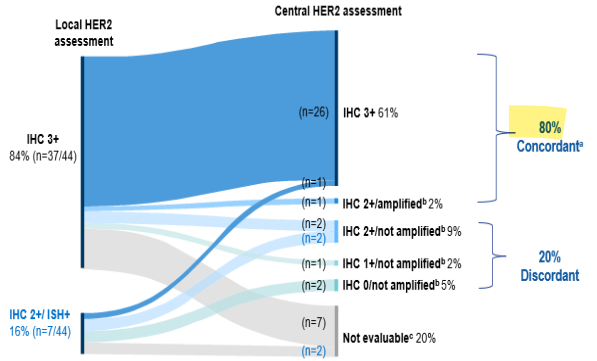
Patient population

- Adults ≥18 years
- Unresectable, locally advanced or metastatic esophageal adenocarcinoma/GC/GEJA
- HER2+ (IHC 3+ or IHC 2+/ISH+ per local assessment)
- Treatment naïve for metastatic disease
- ECOG PS of 0 or 1

Part 2 endpoints

Primary	Secondary	Exploratory
Confirmed ORR by investigator assessment	• ORR, DOR, and PFS by investigator assessment, and OS • Safety and tolerability	Antitumor activity by PD-L1 status

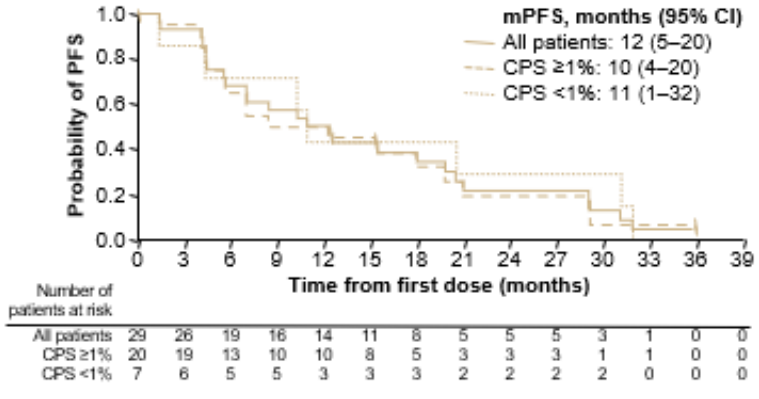
Results: HER2 Status per Local and Central Assessment



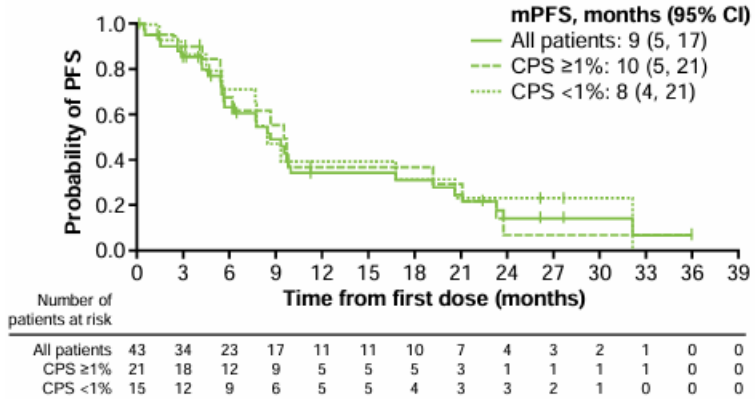
Excluding non-evaluable samples, 80% (28/35) of samples were concordant and 20% (7/35 samples) were discordant

	A Trastuzumab + platinum + FP (SOC; n = 29)	B T-DXd 6.4 mg/kg (n = 43)*	C T-DXd 6.4 mg/kg + FP (n = 41)	D T-DXd 6.4 mg/kg + FP + pembro (n = 43)	E T-DXd 6.4 mg/kg + pembro (n = 41)	F T-DXd 5.4 mg/kg + FP + pembro (n = 32)
Median follow up, months	18.4	16.7	22.0	16.2	14.6	7,8 m
Confirmed ORR, n (%)	22 (76)	21 (49)	32 (78)	25 (58)	26 (63)	75%
PD-L1 CPS ≥1, n/N (%)	17/20 (85)	12/21 (57)	17/22 (77)	14/20 (70)	14/18 (78)	-
PD-L1 CPS <1, n/N (%)	5/7 (71)	8/15 (53)	11/15 (73)	5/13 (39)	7/16 (44)	-
Grade ≥3 AE, n (%)	17 (59)	27 (64)	32 (76)	39 (91)	33 (81)	34%
Treatment discontinuation due to AE, n (%)	3 (10)	9 (21)	14 (33)	22 (51)	11 (27)	2 (6,3)
Adjudicated drug-related ILD/pneumonitis[c]	NA	4 (10)	5 (12)	8 (19)	5 (12)	0

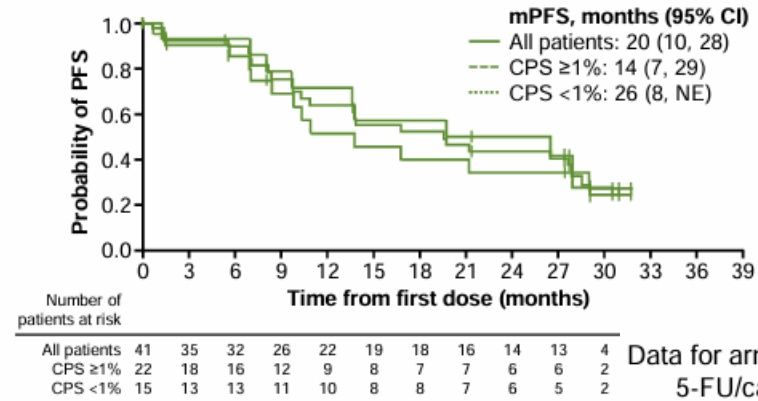
Arm 2A: SOC - trastuzumab + 5-FU/cap + cisplatin/oxaliplatin (n=29)



T-DXd 6.4 mg/kg n=43

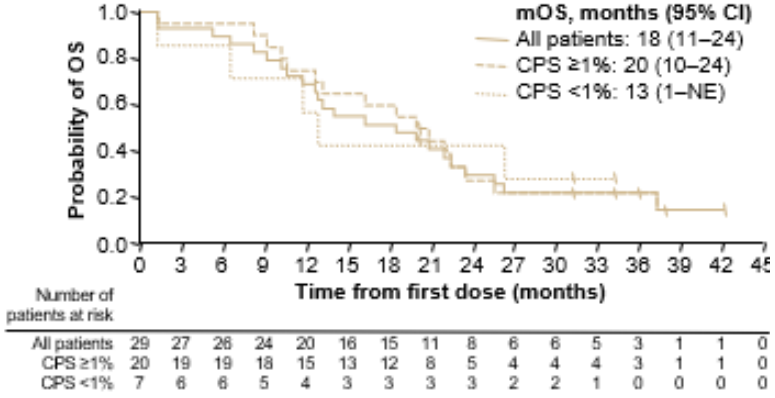


T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41

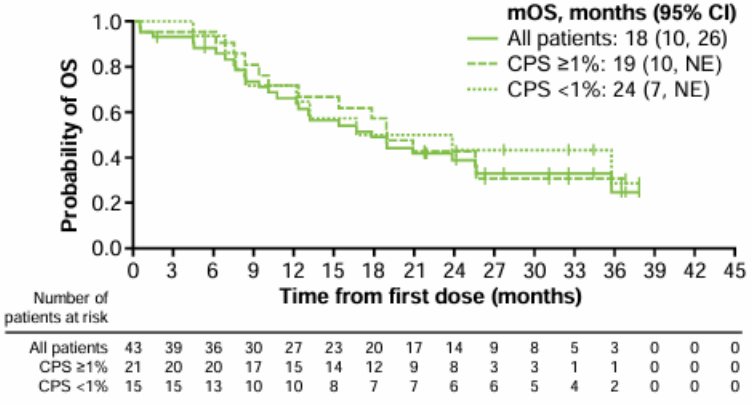


Data for arm T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro are immature

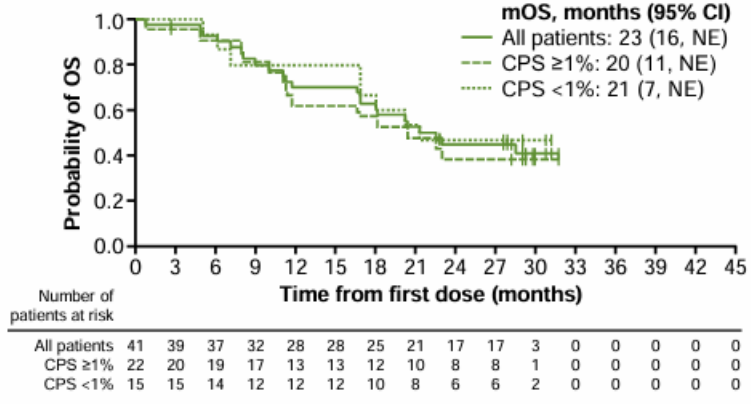
Arm 2A: SOC - trastuzumab + 5-FU/cap + cisplatin/oxaliplatin (n=29)



T-DXd 6.4 mg/kg n=43



T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41



First-line T-DXd combinations with fluoropyrimidine and/or pembrolizumab demonstrated promising antitumor activity in metastatic HER2+ GC/GEJA

Janjigian Y, et al. ESMO 2024

GC/GEJ A HER2+, ANTIBODY-DRUG CONJUGATE: DISITIMAB VEDOTIN (RC 48)+TISLELIZUMAB+S1. PHASE II

Efficacy and safety of Disitamab Vedotin (RC48) plus Tislelizumab and S-1 as 1st line therapy for HER2-overexpressing advanced gastric/GEJ adenocarcinoma (RCTS): a multicenter, single-arm, phase II trial (NCT05586061): Design

Key eligibility criteria
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy in advanced setting
- HER2 IHC 3+ or 2+, regardless of FISH
- ECOG PS 0-1
- Measurable tumor lesion per RECIST v1.1 criteria

Treatment
- RC48 2.5mg/kg IV Q3W
- Tislelizumab 200mg IV Q3W
- S-1 40-60 mg PO bid D1-14 Q3W

Until PD or unacceptable toxicity

Primary endpoint
- ORR by RECIST v1.1

Secondary endpoints
- DCR , PFS, DOR
- OS
- Safety

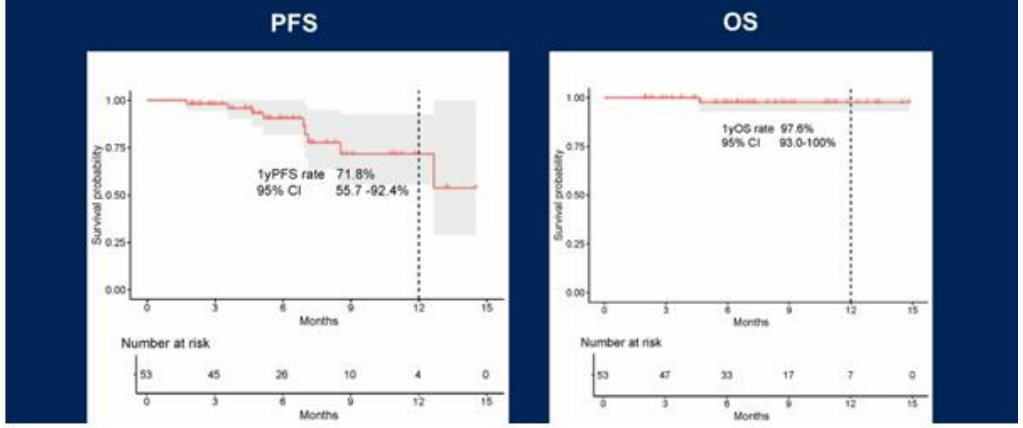
Exploratory endpoints
- Potential biomarkers

RCTS trial has met its primary endpoint

Objective response rates*

Response	n = 53	Best Overall Response	n = 44
ORR, n (%)		Confirmed ORR, n (%)	
CR	5 (9.4%)	CR	3 (6.8%)
PR	45 (84.9%)	PR	37 (84.1%)
SD	2 (3.8%)	SD	3 (6.8%)
PD	1 (1.9%)	PD	1 (2.3%)
ORR, % (95% CI)	94.3% (84.3-98.8%)	Confirmed ORR, % (95% CI)	90.9% (77.9-97.4%)
DCR, % (95% CI)	98.1% (89.9-100%)	Confirmed DCR, % (95% CI)	97.7% (87.7-99.9%)

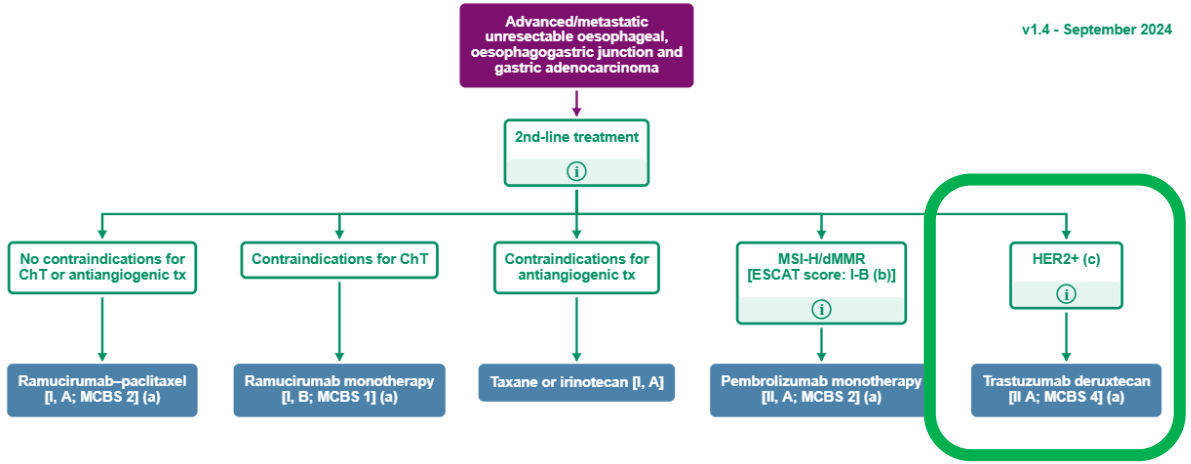
Premature overall survival with median follow-up of 6.7 months

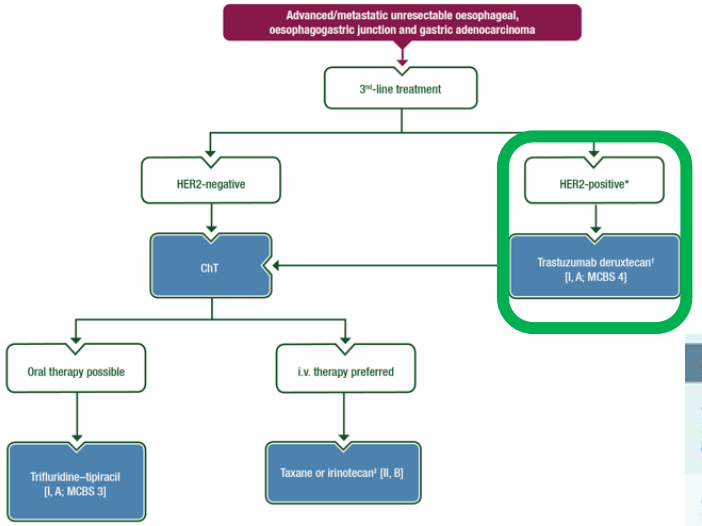


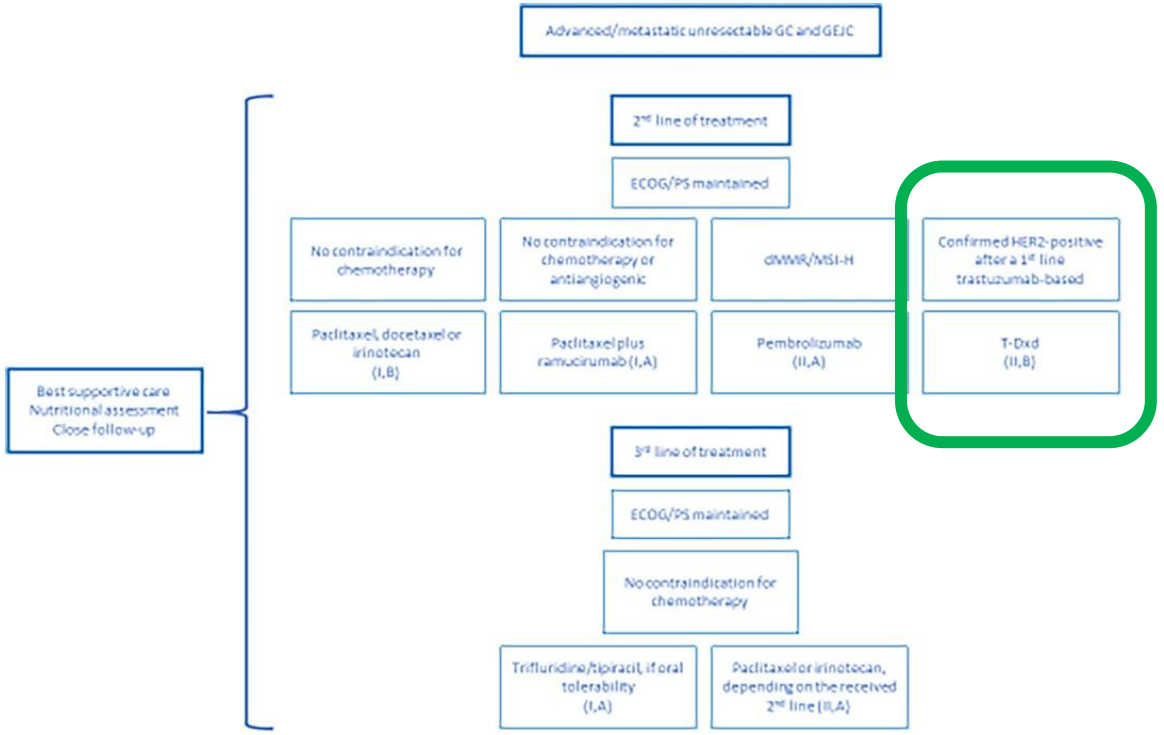
Grade 3/4 treatment-related adverse events occurred in 40.9% of patients: neutropenia, fatigue, and diarrhea

Li Song, et al. ASCO 2024

ESMO/SEOM GUIDELINES GASTRIC CANCER







HER2-positive	LoE, GoR
Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer	I, D
Trastuzumab deruxtecan is recommended for patients with HER2-positive advanced gastric cancer who have received a prior trastuzumab-based regimen [**ESMO-MCBS v1.1 score: 4**] Re-biopsy is recommended when possible	I, A

ESMO guidelines GC V 1.4 Sept 2024

Rivera F, et al. SEOM guidelines GC (2023). CTO 2024

CRC HER-2 ANTIBODY-DRUG CONJUGATE:
TRASTUZUMAB DERUXTECAN (DESTINY CRC01)

6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

Patients
- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- *RAS/BRAF*^{V600E} wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

Cohort A: HER2 Positive (IHC3+ or IHC2+/ISH+) n = 53

Cohort B*: HER2 IHC2+/ISH− n = 15

Cohort C*: HER2 IHC1+ n = 18

Primary endpoint
- ORR[b] (cohort A)

Secondary endpoints
- ORR[b] (cohorts B and C)
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

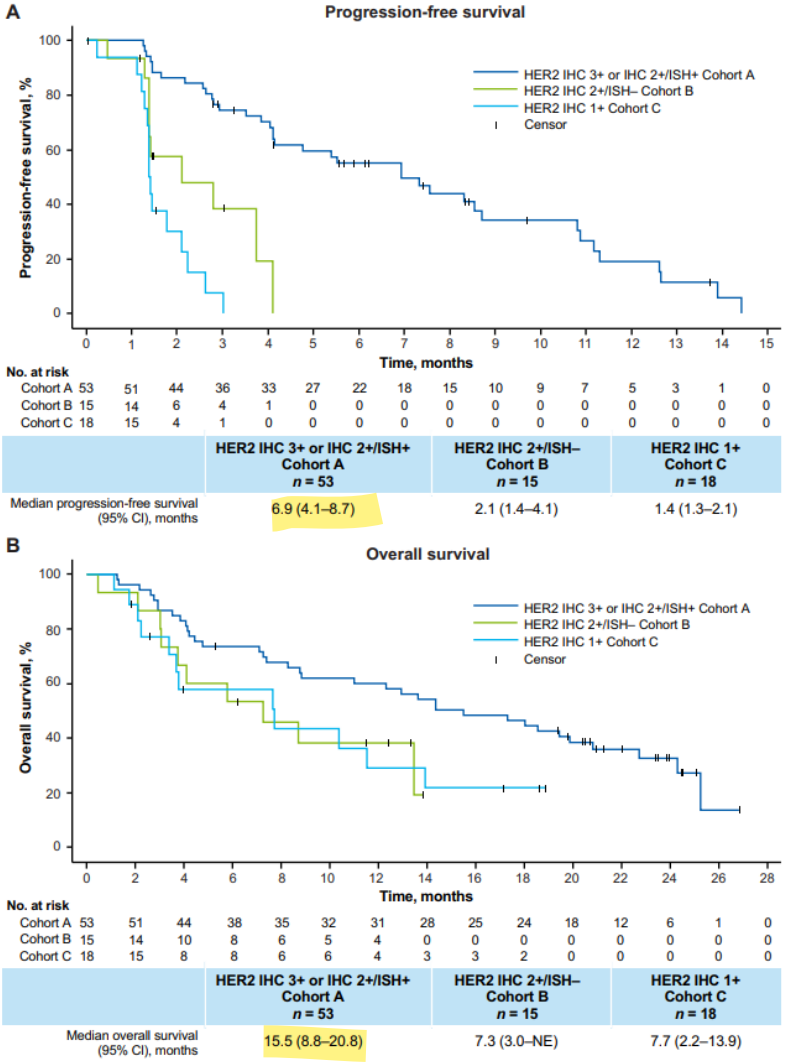
Primary analysis (Data cutoff: August 9, 2019)

Final analysis (Data base lock: December 28, 2020)

Primary analysis of cohort A[1]
- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

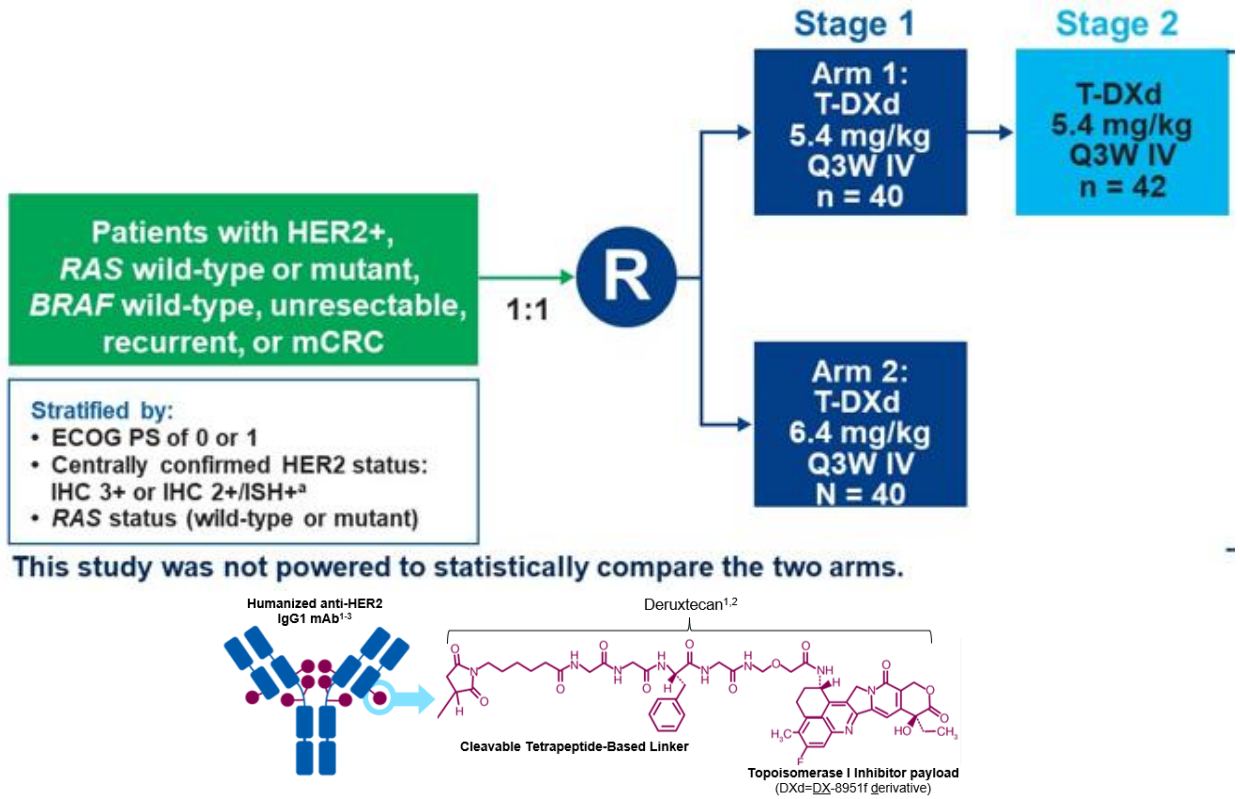
Patient disposition at final analysis[c]
- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

	HER2+ Cohort A (N = 53)
Confirmed ORR by ICR	**45.3% (n = 24)** (95% CI, 31.6%-59.6%)
CR	1.9% (n = 1)
PR	43.4% (n = 23)
SD	37.7% (n = 20)
PD	9.4% (n = 5)
Not evaluable	7.5% (n = 4)[a]
Disease control rate	83.0% (95% CI, 70.2%-91.9%)
Duration of response, median	Not reached (95% CI, 4.2 months-NE)



Yoshino T, et al. Nature C 2023

CRC HER-2 ANTIBODY-DRUG CONJUGATE:
TRASTUZUMAB DERUXTECAN (DESTINY CRC02)



	Trastuzumab deruxtecan 5·4 mg/kg group (n=82)	Trastuzumab deruxtecan 6·4 mg/kg group (n=40)
Confirmed objective response rate* (% [95% CI)	31 (37·8% [27·3–49·2])	11 (27·5% [14·6–43·9])
Complete response	0	0
Partial response	31 (38%)	11 (28%)
Stable disease	40 (49%)	23 (58%)
Progressive disease	8 (10%)	4 (10%)
Not evaluable	3 (4%)	2 (5%)
Confirmed disease control rate* (% [95% CI])	71 (86·6% [77·3–93·1])	34 (85·0% [70·2–94·3])
Confirmed clinical benefit rate* (% [95% CI])	37 (45·1% [34·1–56·5])	13 (32·5% [18·6–49·1])
Median duration of response*, months (95% CI)	5·5 (4·2–8·1)	5·5 (3·7–NE)
Median progression-free survival*, months (95% CI)	5·8 (4·6–7·0)	5·5 (4·2–7·0)
Patients with events	54 (66%)	27 (68%)
Median overall survival, months (95% CI)	13·4 (12·5–16·8)	NE (9·9–NE)
Patients with events	26 (32%)	13 (33%)
Median follow-up, months (IQR)	8·9 (6·7–10·5)	10·3 (5·9–12·7)
Median treatment duration†, months (IQR)	5·5 (3·6–8·4)	4·9 (2·8–8·5)
Median total dose†, mg/kg (IQR)	37·8 (26·9–59·4)	40·8 (25·4–66·1)
Median cycles initiated† (IQR)	7·0 (5·0–11·0)	7·0 (4·0–11·0)

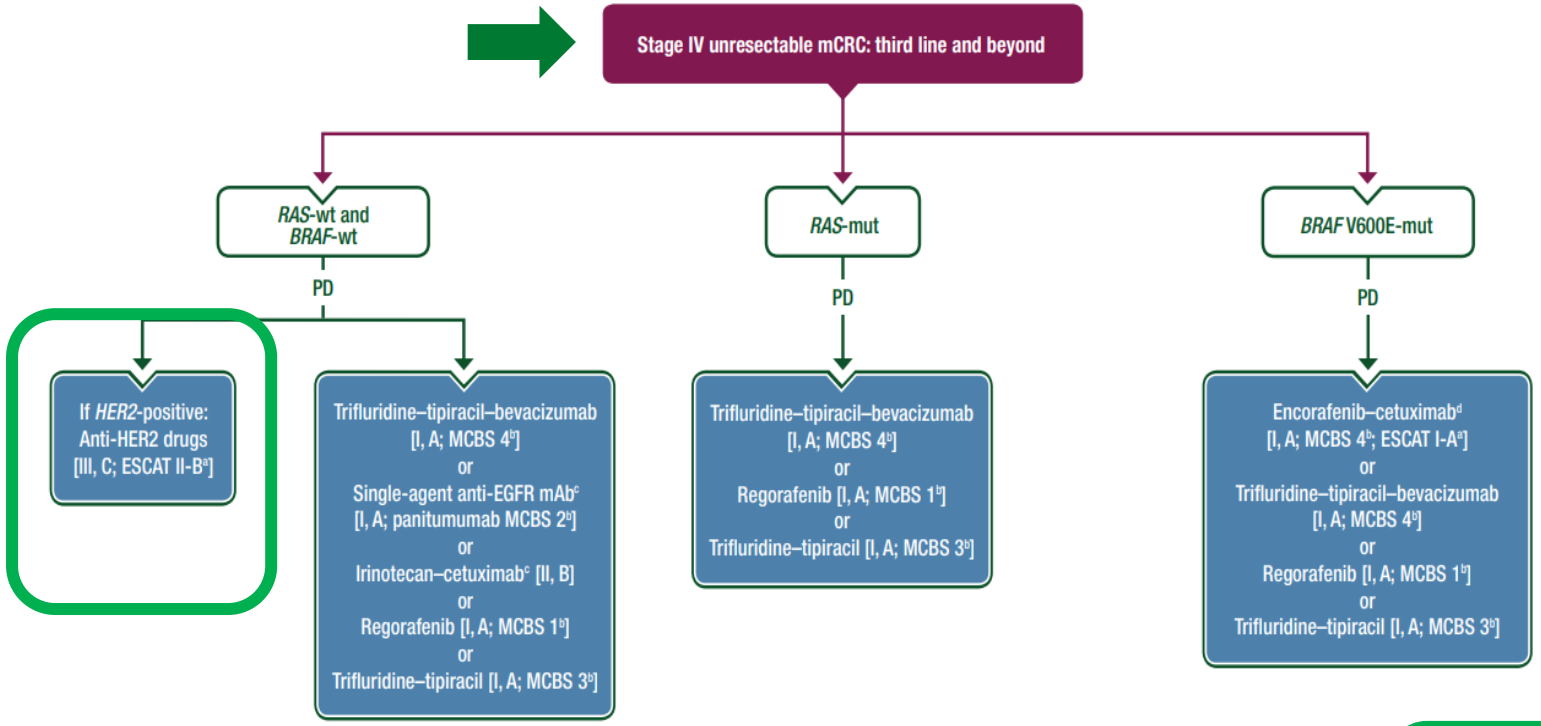
Data are n (%) except where otherwise stated. NE=not estimable. *Assessed by blinded independent central review. †Based on the total population treated with trastuzumab deruxtecan; 5·4 mg/kg, n=83; 6·4 mg/kg, n=39 (safety analysis set).

Prior anti-HER2 therapy	7/17 (41.2) [18.4-67.1]	4/10 (40.0) [12.2-73.8]
HER2 IHC 3+	30/64 (46.9) [34.3-59.8]	10/34 (29.4) [15.1-47.5]

These promising results support T-DXd 5.4 mg/kg as the optimal dose (as a single agent) in this patient population due to its positive benefit-risk profile

Raghav K, et al . The Lancet Oncology 2024

ESMO CLINICAL GUIDELINES CRC



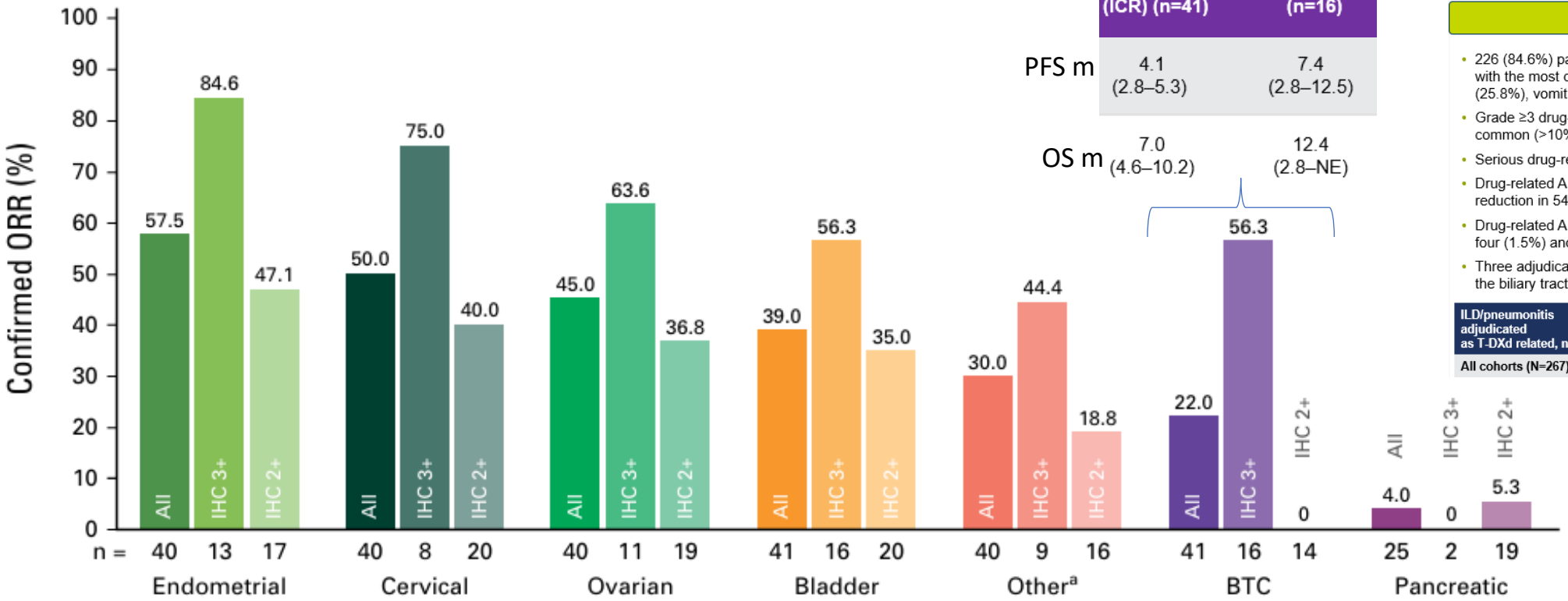
	ESCAT I	ESCAT II	ESCAT III
CRC CANCER	44% **KRAS** 4% **NRAS** 8.5% **BRAF**^{V600E} 4-5% **MSI-H** 0.5% **NKTR1**	2% **ERBB2**	17% **PI3K** hotspot mutations 5% **ATM** mutations 1.7% **MET** amplifications 1% **AKT1**^{E17K} 1% **TMB-High** in MSS 0.3% **RET** fusions 0.2% **ALK** fusions

Cervantes A, et al. ESMO guidelines mCRC 2023

Mosele et al, Ann of Oncol 2020. Mateo et al, Ann Oncol 2018

BTC CANCER HER2+, ANTIBODY-DRUG CONJUGATE: TRASTUZUMAB DERUXTECAN (DESTINY-PANTUMOR 02. PHASE II TRIAL)

A



	All patients (ICR) (n=41)	HER2 IHC 3+ (n=16)
PFS m	4.1 (2.8–5.3)	7.4 (2.8–12.5)
OS m	7.0 (4.6–10.2)	12.4 (2.8–NE)

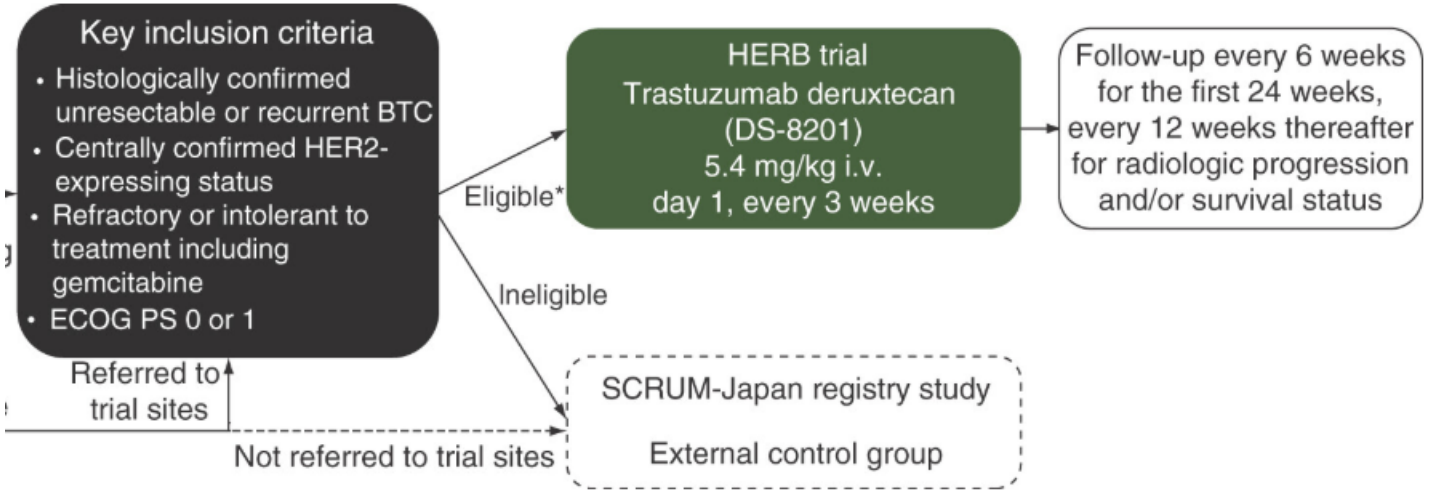
Safety (n=267)[1]

- 226 (84.6%) patients experienced ≥1 investigator-assessed drug-related AE with the most common being nausea (55.1%), anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), and fatigue (24.7%)
- Grade ≥3 drug-related AEs occurred in 109 (40.8%) patients and the most common (>10%) were neutropenia (10.9%) and anemia (10.9%)
- Serious drug-related AEs occurred in 36 (13.5%) patients.
- Drug-related AEs led to discontinuation in 23 (8.6%) patients and dose reduction in 54 (20.2%) patients
- Drug-related AEs and non–drug-related AEs resulting in death occurred in four (1.5%) and 19 (7.1%) patients, respectively
- Three adjudicated drug-related ILD/pneumonitis deaths ([1.1%], one each ir the biliary tract, endometrial, and other tumors cohorts) occurred

ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All cohorts (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Meric-Bernstam F, et al. J Clin Oncol 2023

BTC CANCER HER2+, ANTIBODY-DRUG CONJUGATE: TRASTUZUMAB DERUXTECAN (HERB PHASE II TRIAL)



	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR (90% CI) (95% CI)	**36.4% (19.6-56.1)*** (17.2–59.3)	12.5% – (0.3–52.7)	30.0% – (14.7–49.4)
Confirmed DCR (95% CI)	81.8% (59.7–94.8)	75.0% (34.9–96.8)	80.0% (61.4–92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)

Event	Any grade, n (%)	Grade ≥ 3, n (%)
Anemia	22 (68.8)	17 (53.1)
Neutrophil count decreased	18 (56.3)	10 (31.3)
White blood cell count decreased	18 (56.3)	10 (31.3)
Platelet count decreased	14 (43.8)	3 (9.4)
Nausea	14 (43.8)	0 (0)
Alopecia	13 (40.6)	0 (0)
Anorexia	12 (37.5)	1 (3.1)
Lymphocyte count decreased	11 (34.4)	7 (21.9)
Fatigue / Malaise	11 (34.4)	0 (0)
Interstitial lung disease / Pneumonitis	8 (25.0)	4 (12.5)
Hypoalbuminemia	7 (21.9)	1 (3.1)
Vomiting	7 (21.9)	0 (0)
Mucositis oral	5 (15.6)	0 (0)

HER2-positive pts (n=22)

No. of events, n (%)	21 (95.5)
mPFS, months (95% CI)	**5.1 (3.0–7.3)**
6-month PFS rate (95% CI)	40.9% (20.9–60.1)
Median follow-up: 7.1 mo (IQR 4.7–14.6).	

No. of events, n (%)	18 (81.8)
mOS, months (95% CI)	**7.1 (4.7–14.6)**
6-month OS rate (95% CI)	63.6% (40.3–79.9)
Median follow-up: 7.1 mo (IQR 4.7–14.6).	

HER2-low-expressing pts (n=8)

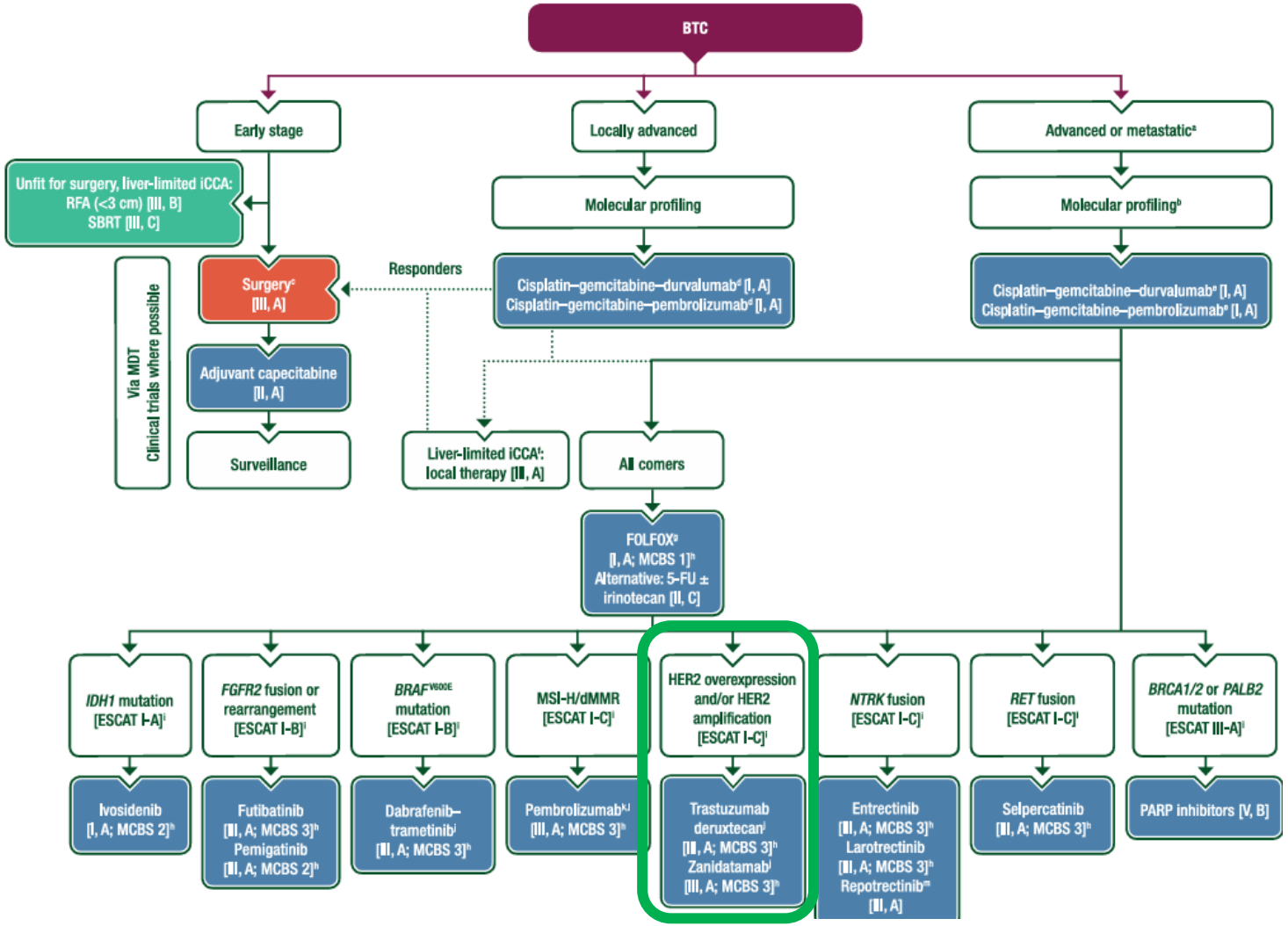
No. of events, n (%)	8 (100)
mPFS, months (95% CI)	**3.5 (1.2–5.5)**
6-month PFS rate (95% CI)	0% (–)

No. of events, n (%)	8 (100)
mOS, months (95% CI)	**8.9 (3.0–12.8)**
6-month OS rate (95% CI)	75.0% (31.5–93.1)

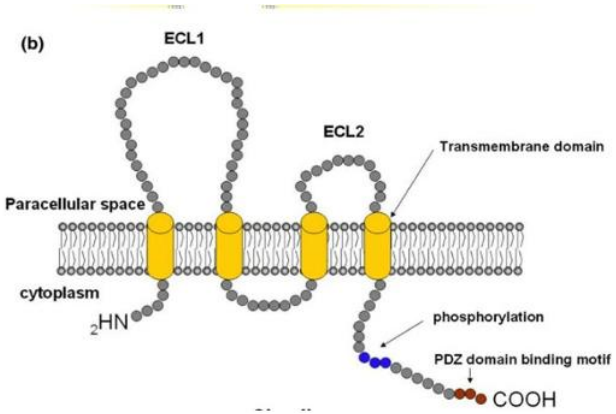
Ohba A, et al . JCO 2024

Ohba A, et al . ASCO 2022

ESMO CLINICAL PRACTICE GUIDELINE INTERIM UPDATE ON THE MANAGEMENT OF BILIARY TRACT CANCER 2024

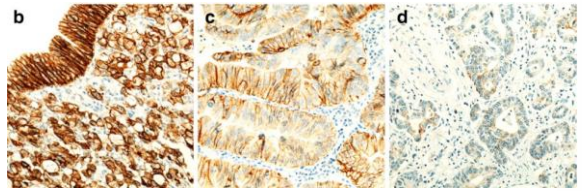


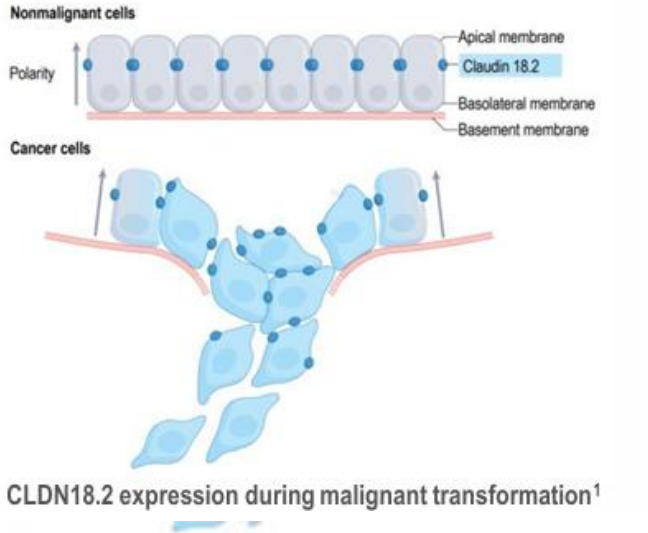
- Trastuzumab deruxtecan should be considered in patients with HER2 overexpression and/or *HER2* amplification who have progressed on or are intolerant to prior treatment [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA approved, not EMA approved].



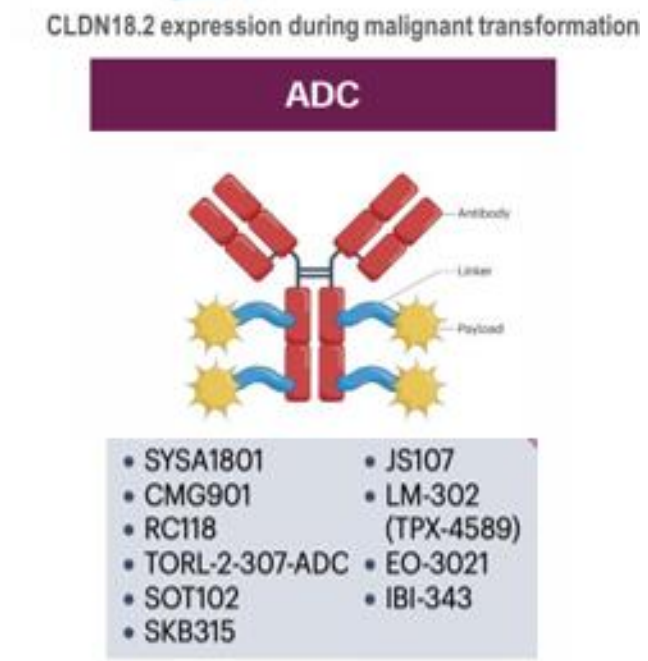
CLAUDINA 18.2 ADCs

GASTRIC CANCER/GEJ A CLDN18.2+





- Claudin 18.2 (CLDN18.2)
  - 30-45% expressed in patients with gastric adenocarcinoma. > Female, > difusse type, > HER2 negative. Trend of relatively low CPS.
  - A new therapeutic target for gastric cancer that has been clinically validated.
  - Zolbetuximab + CAPOX/FOLFOX (GLOW/SPOTLIGHT)[2,3] represents a new 1L standard-of-care treatment option for patients with HER2−, LA unresectable or mG/GEJ adenocarcinoma whose tumors are CLDN18.2+.
  - Different antibody-drug conjugates are in development in gastric cancer



1. Nat Rev Clin Oncol. 2024 May;21(5):354-369. 2. Shah MA et al. *Nat Med.* 2023;29(8):2133–2141;
2. 3. Shitara K et al. *Lancet*. 2023;401(10389):1655–1668.

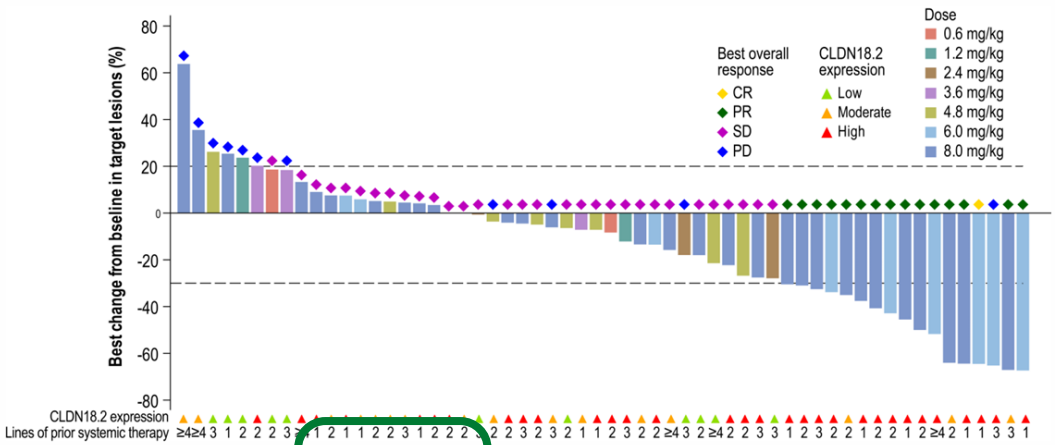
GASTRIC CANCER/GEJ A CLDN18.2+, ANTIBODY-DRUG CONJUGATE: SHR-A1904 PHASE 1 STUDY

- SHR-A1904:
  - A novel ADC comprised of a humanized IgG1 mAb targeting CLDN18.2, a cleavable linker, and a topoisomerase I inhibitor payload. High membrane permeability. Potent cell-killing efficacy.

Key eligibility criteria
- Pathologically confirmed advanced solid tumors;
- Had failed standard therapies or had no standard treatment available;
- Positive CLDN18.2 expression*;
- ECOG performance status of 0 or 1;
- At least one measurable lesion per RECIST v1.1.

- During dose escalation, 3 patients reported DLTs, including 2 patients at 4.8 mg/kg (grade 3 febrile neutropenia and grade 3 increased blood bilirubin) and 1 at 6.0 mg/kg (grade 3 gastric mucosal lesion). MTD was not reached.
- 6.0 and 8.0 mg/kg SHR-A1904 IV Q3W were selected for expansions

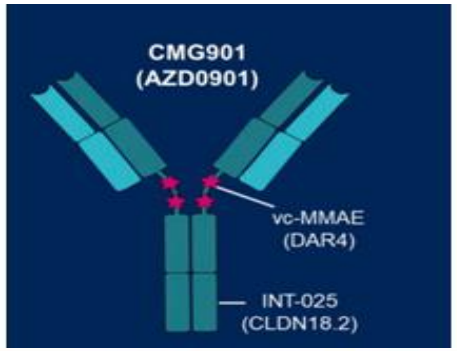
	0.6-4.8 mg/kg (N=20)	6.0 mg/kg (N=15)	8.0 mg/kg (N=38)	All (N=73)
Any TRAE, n (%)	20 (100.0)	13 (86.7)	36 (94.7)	69 (94.5)
Grade ≥3	8 (40.0)	4 (26.7)	27 (71.1)	39 (53.4)
Serious	4 (20.0)	3 (20.0)	17 (44.7)	24 (32.9)
Leading to treatment interruption	6 (30.0)	2 (13.3)	13 (34.2)	21 (28.8)
Leading to dose reduction	0	3 (20.0)	1 (2.6)	4 (5.5)
Leading to treatment discontinuation	0	1 (6.7)	2 (5.3)	3 (4.1)
Leading to death	0	0	0	0

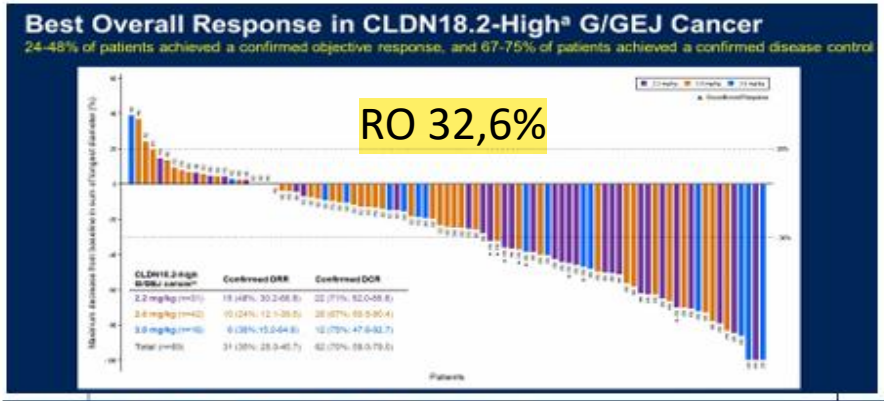


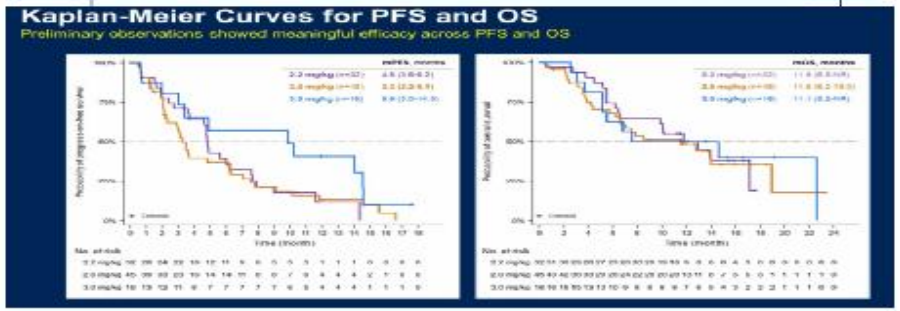
	6.0 mg/kg (N=9)	8.0 mg/kg (N=30)	All (N=58)
ORR, n (%; 95% CI)	5 (**55.6**; 21.2–86.3)	11 (**36.7**; 19.9–56.1)	16 (27.6; 16.7–40.9)
DCR, n (%; 95% CI)	8 (**88.9**; 51.8–99.7)	26 (**86.7**; 69.3–96.2)	47 (81.0; 68.6–90.1)

Rui-Hua Xu, et al. ESMO 2024

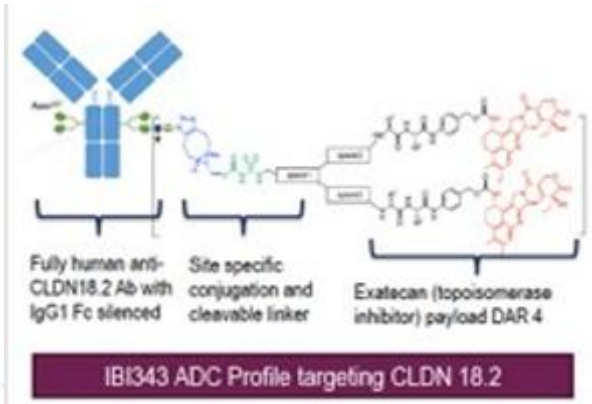
GC/GEJ A CLDN18.2+ ANTIBODY-DRUG CONJUGATE:
CMG901 AND IBI343 PHASE I

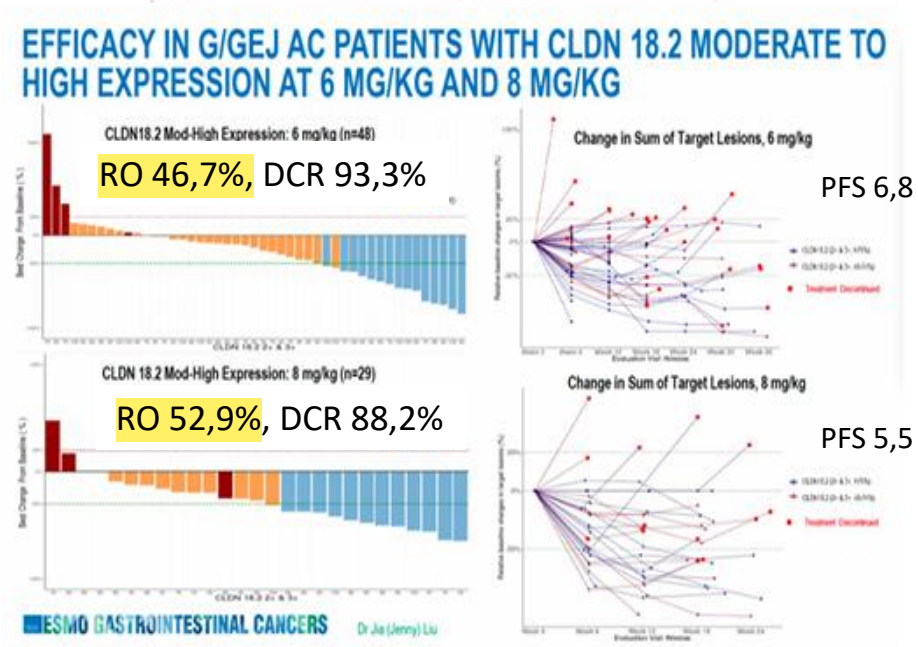






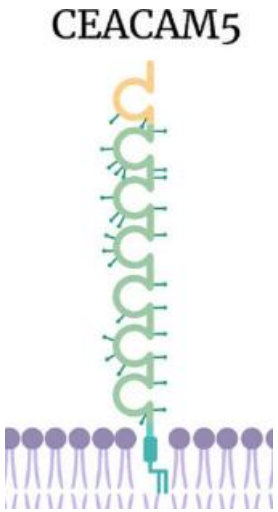
PFS 4,76 m





Riu-Hua XU, et al , ASCO 2024

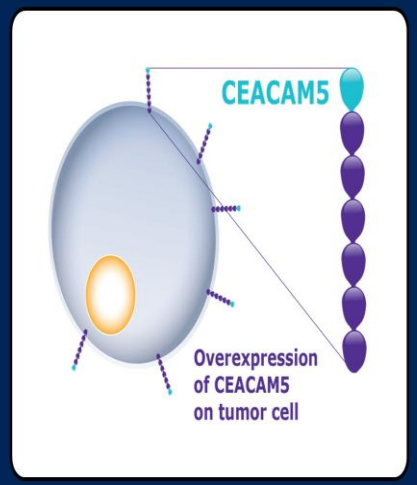
Liu JJ, et al , ESMO 2024



CEACAM5 ADCs

CCR, CEACAM5+ :
PROCEADE CRC-01. M9140 ADC$_S$ (ANTI-CEACAM5 WITH EXATECAN PAYLOAD)

Carcinoembryogenic antigen-related cell adhesion molecule 5 (CEACAM5) as an attractive ADC target



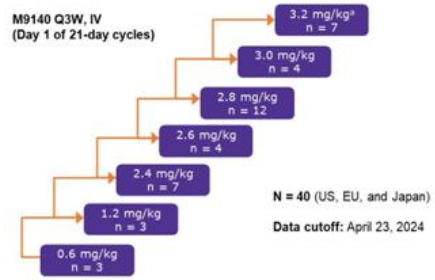
- CEACAM5 is a cell surface glycoprotein that modulates cell adhesion, differentiation, and proliferation[1]
- CEACAM5 has limited expression in adult healthy tissues but is overexpressed in various adenocarcinomas, particularly in CRC (>90% of patients)[2,3]
- Exploiting CEACAM5 overexpression in certain cancers has the potential to offer a promising approach for ADC-based therapy

ADC, antibody–drug conjugate; CRC, colorectal cancer
1. Beauchemin N, Arabzadeh A. *Cancer Metastasis Rev* 2013;32(3-4):643-671; 2. Zhang X, et al. *J Int Med Res* 2020;48(9):300060520959478; 3. Decary S, et al. *Clin Cancer Res* 2020;26(24):6589-6599.

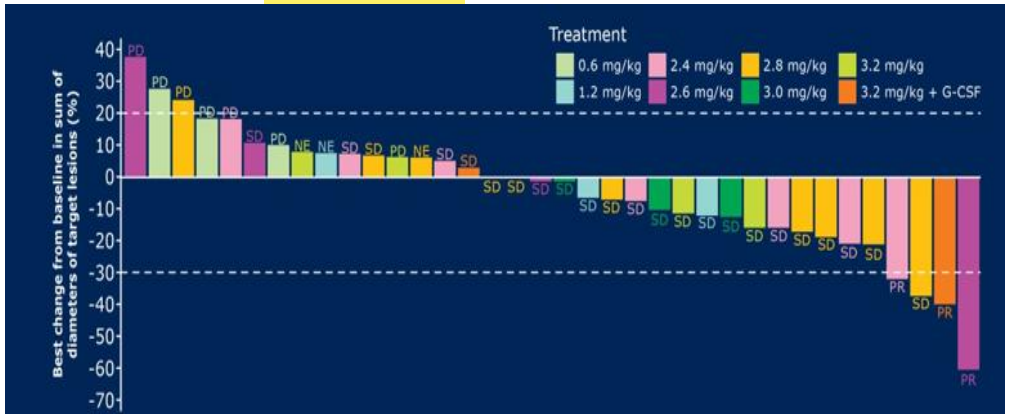
Key eligibility criteria

- Patients with confirmed LA/M CRC intolerant/refractory to or progressing after standard systemic therapies
- ECOG PS ≤1
- Patients with archived FFPE tumor tissue available. If archived tumor material not available, fresh biopsy required
- Patients were not selected on the basis of CEACAM5 expression

Dose escalation



- Hematological TLD$_S$ anemia, neutropenia, thrombocytopenia, leukopenia.
- No interstitial lung disease and ocular toxicities were observed
- MTD 2,8 mg/Kg
- PFS 6,7 m (95%CI: 4,6-8,4)
- DCR 70 % (PR3, SD 21)



Kopetz S, et al . ASCO 2024

CONCLUSIONES

- CG/GEJ: ESCAT IA (HER2, Claudina 18.2, PDL-1), ESCAT IIA (MSI).
- BTC: ESCAT IA (IDH), ESCAT IB (FGFR2, BRAF), ESCAT IC (HER2, NTRK, MSI, RET).
- CRC: ESCAT IA (RAS/BRAF/MSI/NTRK), ESCAT IIB (HER2).
- Medicina personalizada.
- ADC:
  - Necesidad mejorar perfil toxicidad/actividad: Linker y Payload.
  - Combinaciones ADC+QT+/-IO; ADCs biespecíficos.
- Amplio desarrollo diferentes targets con resultados prometedores:
  - HER2, HER3, TROP-2, Claudina 18.2, CEACAM5, c-Met.
- EC fase I-II-III en marcha en primera y sucesivas.
- Actualmente en T. Digestivos:
  - TDx aprobación condicional en GC/GEJ HER2 + que ha progresado a trastuzumab.
  - TDx alternativa en pacientes con BTC HER2+ que han progresado a 1ªL.
  - Tratamiento antiHER2 alternativa ≥ 3L CCRm HER2 +.

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025