Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Advances in HER 2 Targeted Therapy in GI Cancers: Antibodies, Antibody drug Conjugates and Immunotherapy

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#LearnACI

Disclosures

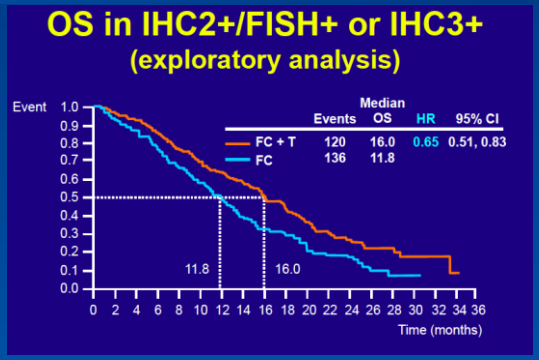
- **Consulting Fees**: AMGEN, Bayer, Lilly, Pieris, Roche, Astra-Zeneca, Bristol Myers Squibb, Astellas, Merck, Taiho, Daiichi Sankyo, Natera, Servier, Foundation Medicine

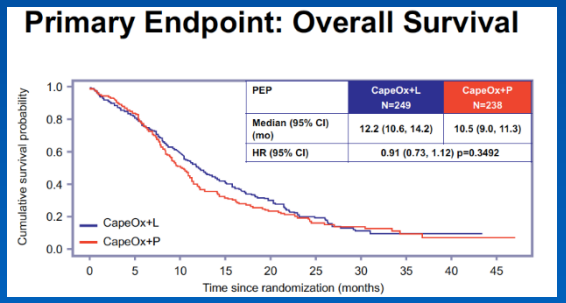
Agenda

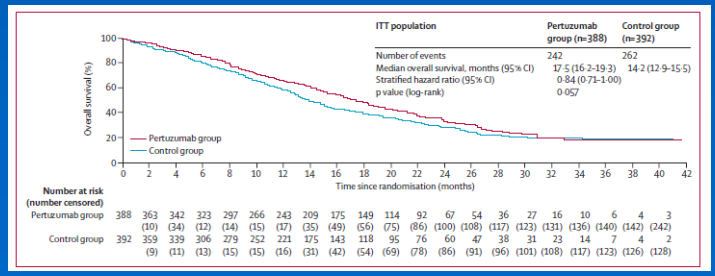
- **HER2 targeted therapy in esophagogastric cancer**
  - First line: trastuzumab, + pembrolizumab
  - Second / later line: trastuzumab deruxtecan
    - Novel agents
- **Colorectal cancer**
  - HER2 combinations, trastuzumab deruxtecan
- **Biliary cancers**
  - Extra hepatic cholangiocarcinoma

HER2: Esophagogastric Cancer is not Breast Cancer, First Line

- **Trastuzumab approved first line**
  - TOGA: Cape-Cis + trastuzumab improved RR, PFS, OS
  - Benefit limited to high expressors
- **First Line Lapatinib (LOGIC) + Cape / Oxaliplatin**
  - No difference in OS
  - 12.2 vs 10.5 mos (HR 0.91)
- **First Line Pertuzumab (JACOB) failed to improve OS + Trastuzumab / Cisplatin / FP**
  - 780 pts
  - OS 17.5 vs 14.2 mos (HR 0.84, p = 0.056)



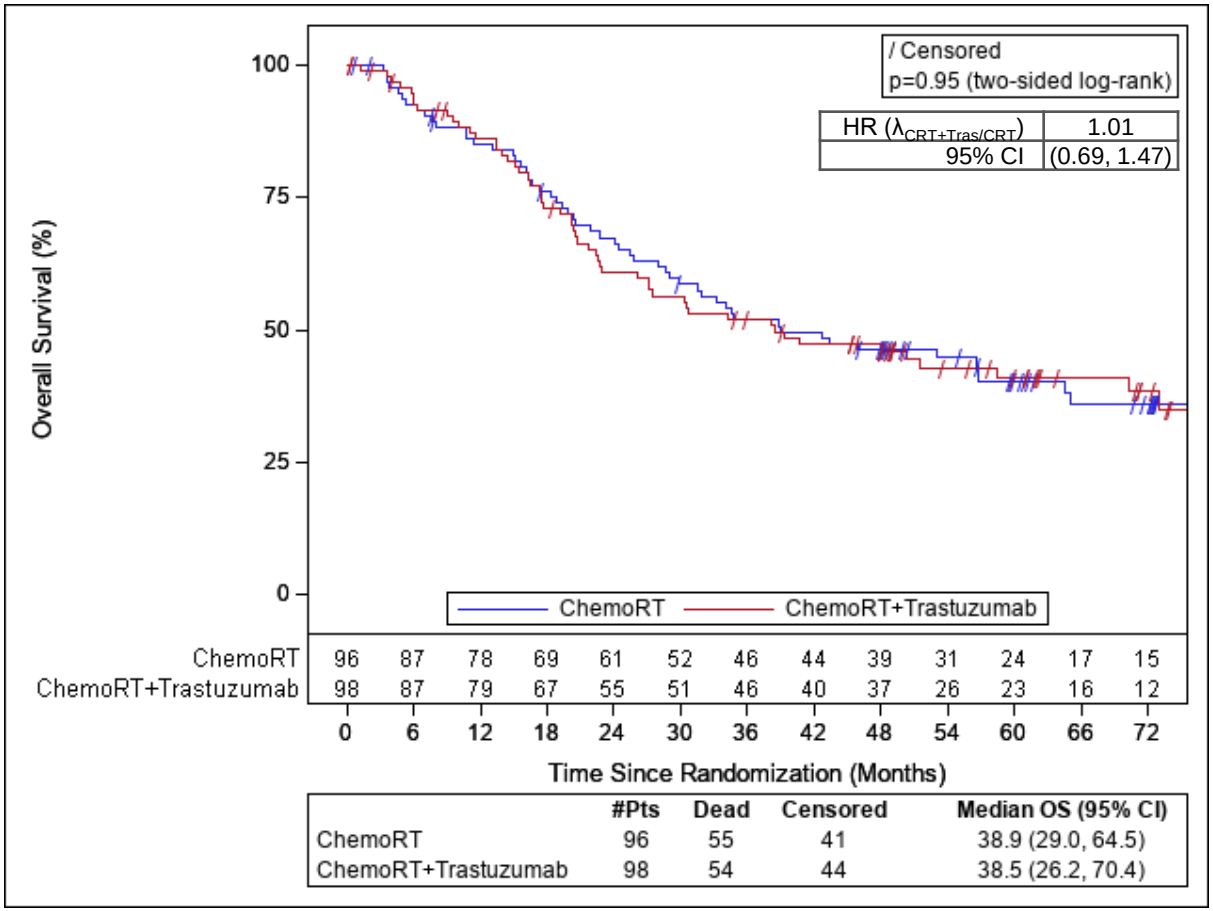




Bang Lancet 376: 687; 2010, Hecht JCO 34: 443; 2016, Tabernero Lancet Oncol 19: 1372; 2018

Adjuvant Trastuzumab added to Chemoradiotherapy/Surgery in HER2 + GEJ Cancer: RTOG 1010

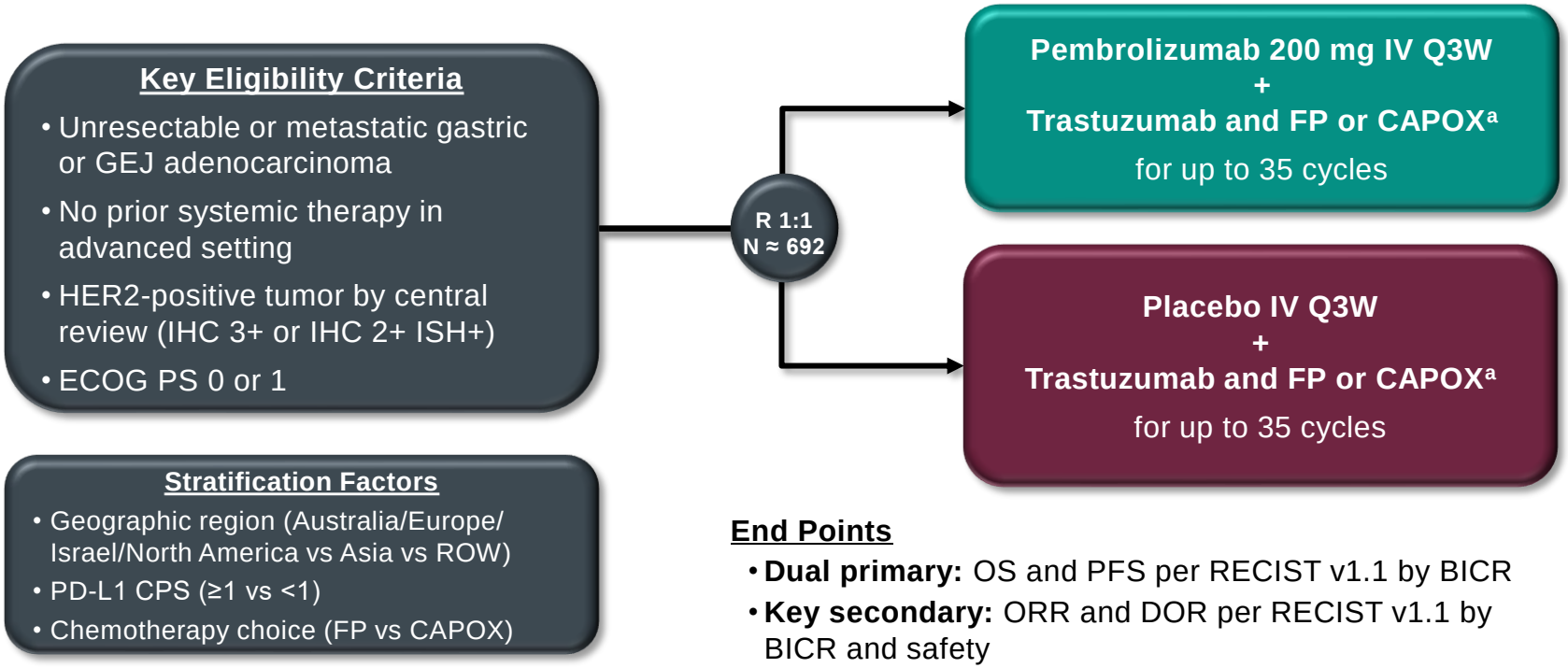
Overall Survival



Trastuzumab alone does not improve OS for HER+ esophageal GEJ cancer

NRG ONCOLOGY™

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

Janjigian Nature 600:727; 2021

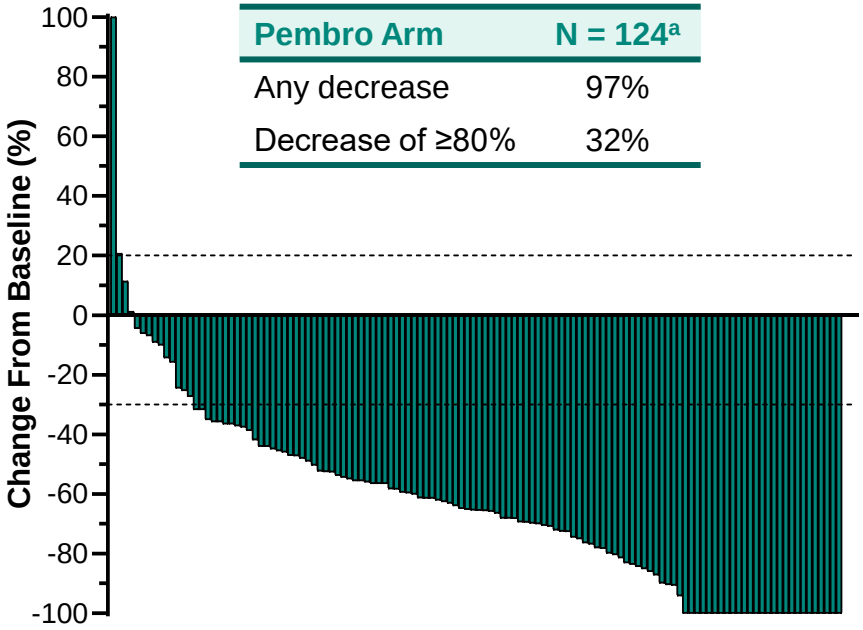
[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-811 ClinicalTrials.gov identifier, NCT03615326.

Baseline Characteristics at IA1

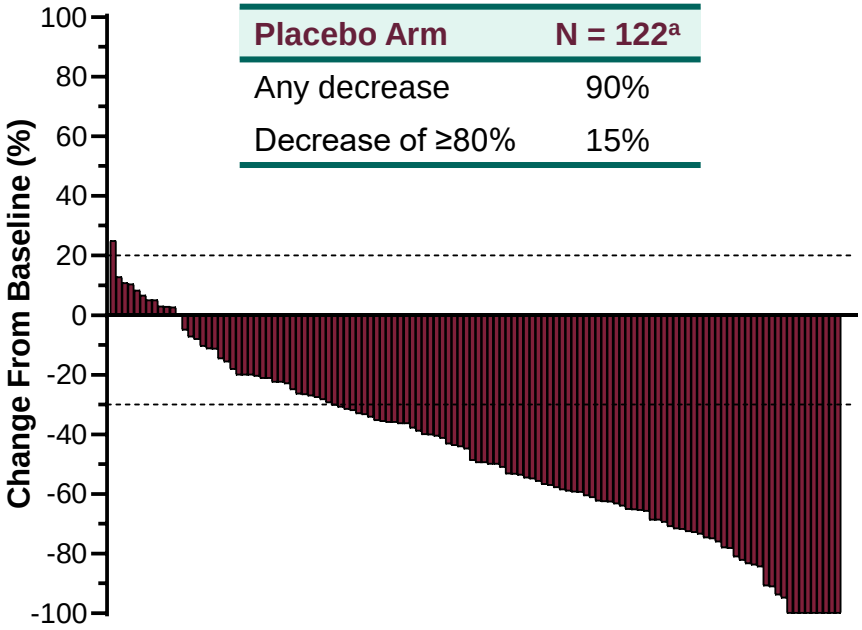
	Efficacy Population		ITT Population	
	Pembro Arm (N = 133)	Placebo Arm (N = 131)	Pembro Arm (N = 217)	Placebo Arm (N = 217)
Age, median (range)	62 y (19-84)	61 y (32-83)	62 y (19-84)	63 y (32-83)
Male sex	84%	79%	82%	80%
Region of enrollment				
Aus/Eur/Isr/NAm	31%	34%	31%	31%
Asia	30%	30%	35%	35%
ROW	39%	37%	34%	35%
ECOG PS 1	51%	55%	53%	59%
Primary location of stomach	72%	68%	71%	65%
Histologic subtype				
Diffuse	21%	20%	22%	18%
Intestinal	61%	48%	54%	47%
Indeterminate	18%	32%	24%	35%
PD-L1 CPS ≥1	88%	85%	85%	83%
HER2 IHC 3+	82%	79%	83%	78%
Choice of chemotherapy				
CAPOX	86%	88%	87%	86%
FP	14%	12%	13%	14%

Percentages may not total 100% because of rounding. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Best Percentage Change From Baseline in Size of Target Lesions at IA1, Efficacy Population



Pembro Arm	N = 124[a]
Any decrease	97%
Decrease of ≥80%	32%

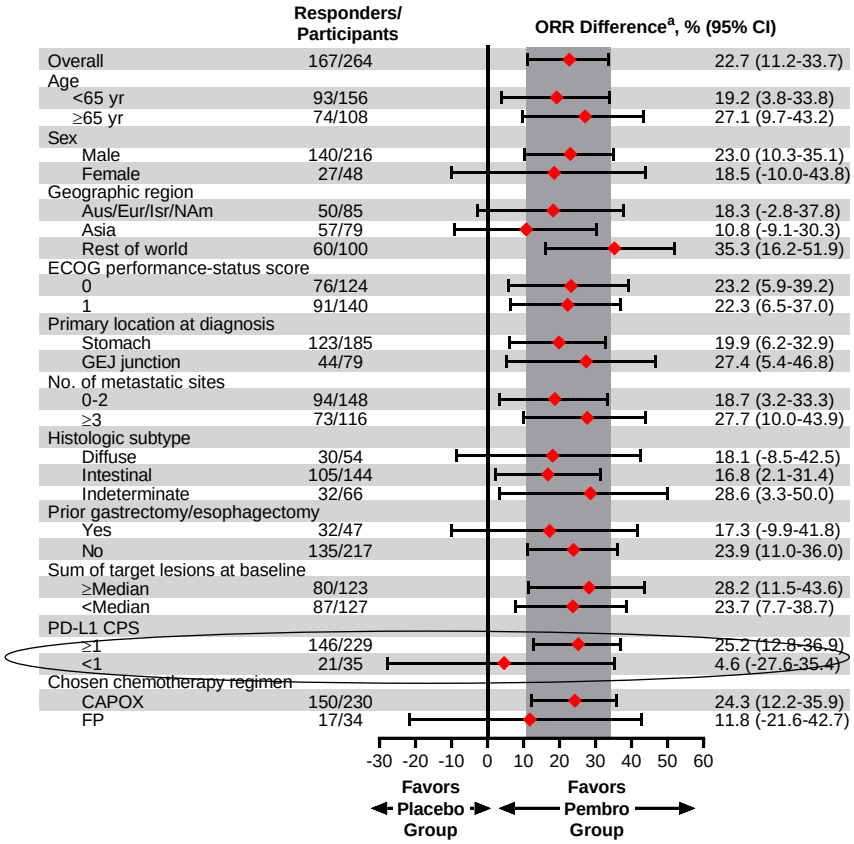


Placebo Arm	N = 122[a]
Any decrease	90%
Decrease of ≥80%	15%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions.
The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Confirmed Response at IA1, Efficacy Population

% (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[a]	**22.7% (11.2-33.7)** ***P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)



[a]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors.
The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Confirmed Response at IA1, Efficacy Population

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[a]	**22.7% (11.2-33.7)** ***P*** **= 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

DOR[b]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median (range)	10.6 mo (1.1+ to 16.5+)	9.5 mo (1.4+ to 15.4+)
≥6-mo duration	70%	61%
≥9-mo duration	58%	51%

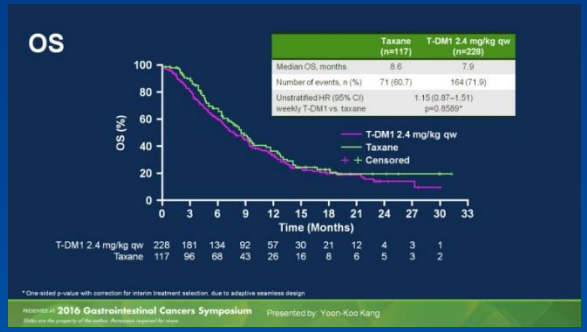
Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

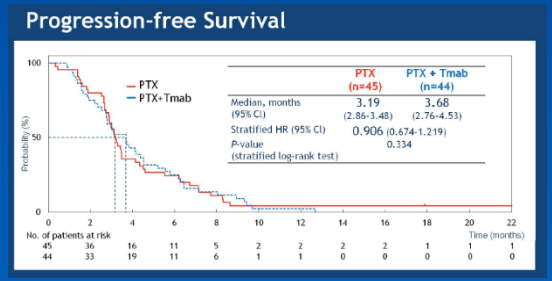
Pembro approved based on response rate increase

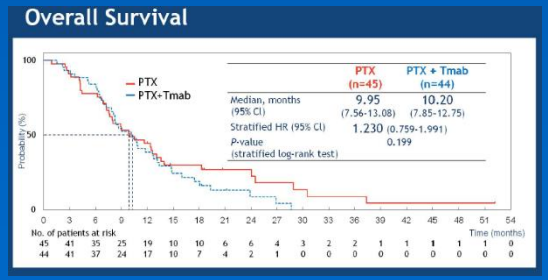
[a]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [b]Calculated in participants with best response of CR or PR; medians and ≥6-mo and ≥9-mo durations estimated using the Kaplan-Meier method. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

HER2: Second Line

- **Trastuzumab emtansine (TDM-1) no better than a taxane in 345 pts (OS 7.9 vs 8.6 mos, HR 1.15)**
- **Continuation of Trastuzumab into 2nd line does not benefit**
  - Paclitaxel + / - Trastuzumab
  - PFS primary endpoint
  - No difference PFS, OS
  - Persistent HER2 amplified cTDNA in 60%
- **De novo and acquired HER2 resistance are likely: Loss of HER2 expression may occur**

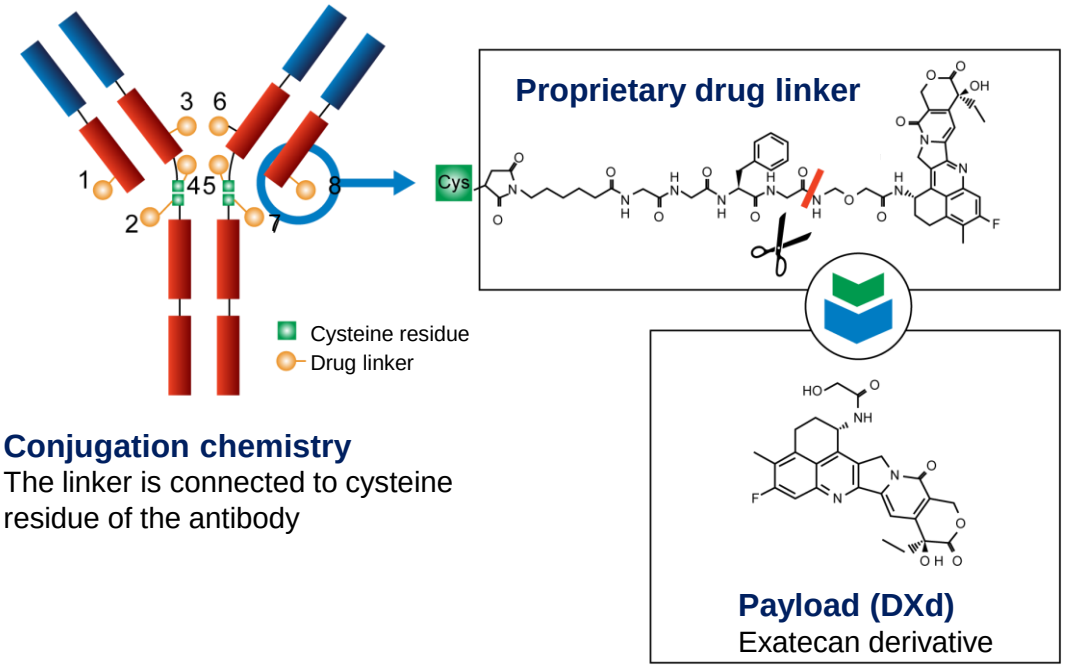






Thuss Patience Lancet Oncol 18: 640; 2017, Makiyama J Clin Oncol 38: 2018 (suppl, Abst 4011)

Trastuzumab Deruxtecan Structure and Mechanism of Action[1]



Conjugation chemistry
The linker is connected to cysteine residue of the antibody

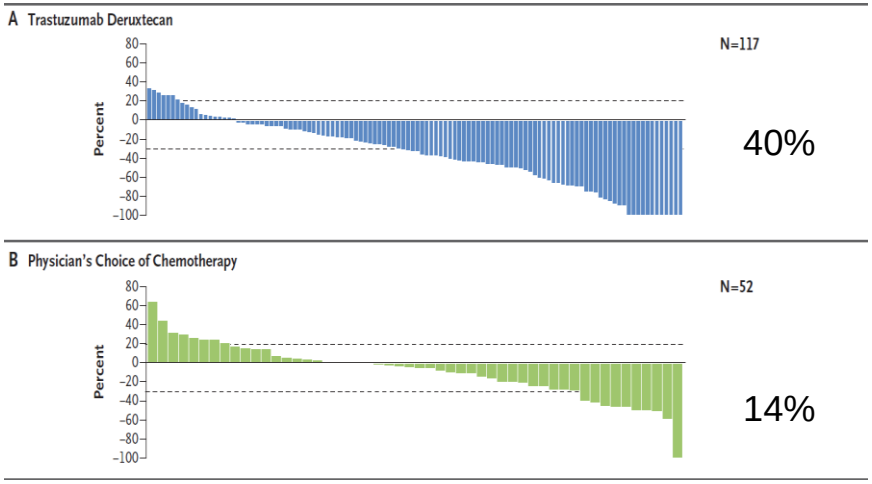
- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

- **Trastuzumab deruxtecan designed with goal of improving critical attributes of an ADC**

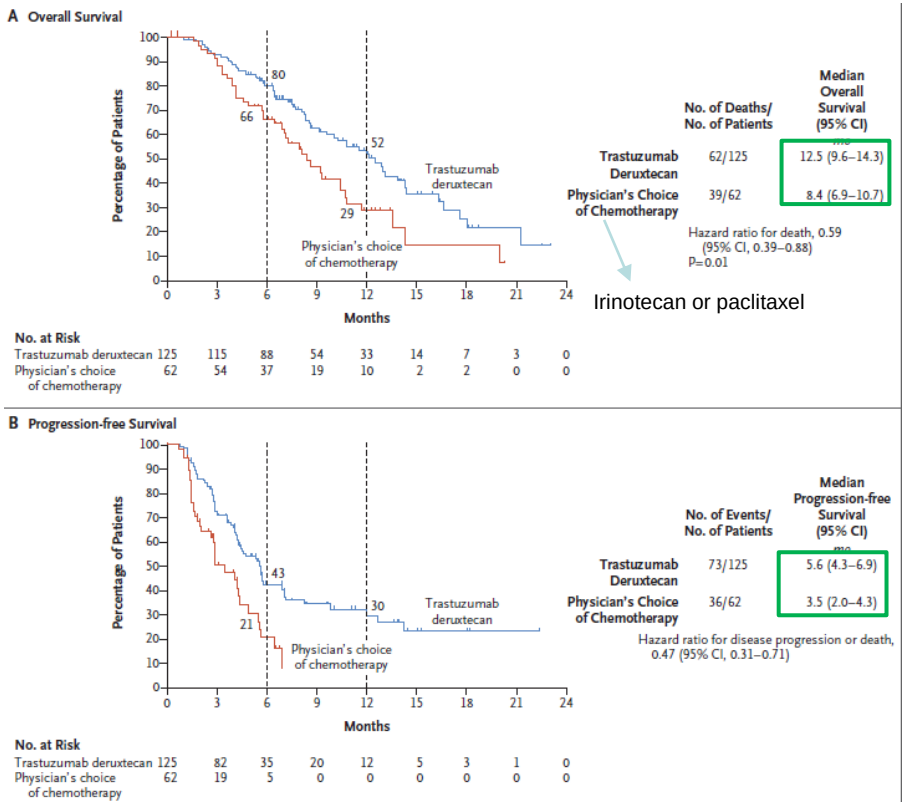
1. Iwata H et al. ASCO 2018. Abstract 2501.

Third Line – Trastuzumab Deruxtecan

DESTINY Gastric01
Third line or higher
N= 125 pts
R 2:1 versus chemotherapy monotherapy
100% Asian



FDA approved 1/2021,
Label: recommend confirming persistent HER2+



Shitara *et al*. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *NEJM* 2020

Trastuzumab Deruxtecan: IHC3+ vs IHC2+

Figure S5. Subgroup Analysis of Difference in ORR by ICR With T-DXd and Physician's Choise.

Subgroup Name	T-DXd N	T-DXd Responders	T-DXd %	PC N	PC Responders	PC %
Primary cohort	119	61	51.3	56	8	14.3
Region						
Japan	95	48	50.5	45	7	15.6
Korea	24	13	54.2	11	1	9.1
Lines of prior systemic therapy						
2	60	29	48.3	33	4	12.1
3	34	18	52.9	17	3	17.6
≥4	25	14	56.0	6	1	16.7
Age						
<65 years	52	30	57.7	22	1	4.5
≥65 years	67	31	46.3	34	7	20.6
Sex						
Female	30	14	46.7	12	2	16.7
Male	89	47	52.8	44	6	13.6
ECOG PS						
0	59	31	52.5	29	3	10.3
1	60	30	50.0	27	5	18.5
HER2 status in central laboratory						
Primary cohort: IHC 3+	91	53	58.2	44	5	11.4
Primary cohort: IHC 2+/ISH+	28	8	28.6	12	3	25.0
Primary tumor location						
Gastric	104	52	50.0	49	7	14.3
GEJ	15	9	60.0	7	1	14.3
Histological subtype						
Intestinal	86	41	47.7	37	8	21.6
Diffuse	27	18	66.7	14	0	0.0
No. of metastatic sites						
<2	21	13	61.9	6	1	16.7
≥2	98	48	49.0	50	7	14.0
Previous total gastrectomy						
Yes	21	12	57.1	8	1	12.5
No	98	49	50.0	48	7	14.6

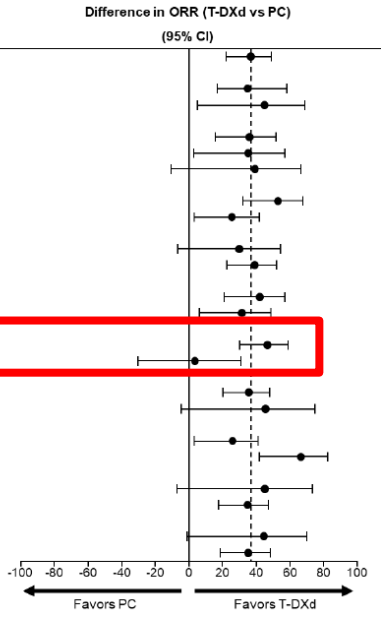
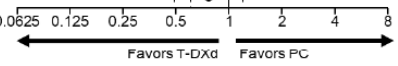


Figure S6. Subgroup Analyses of OS With T-DXd and Physician's Choice.

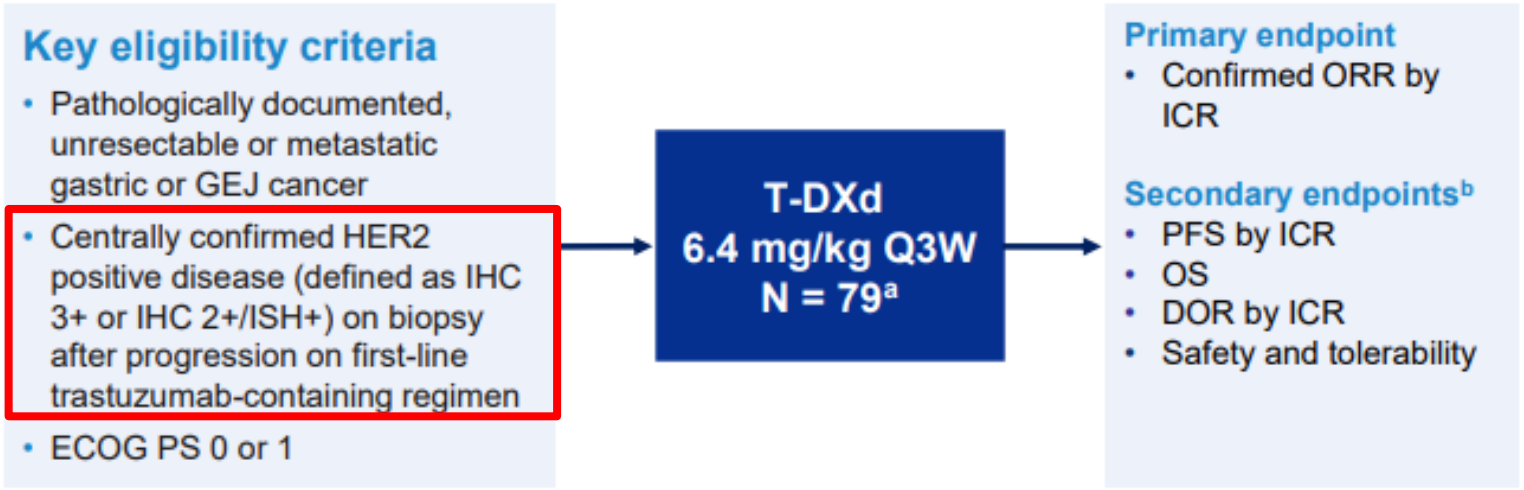
Subgroup Name	N	No. of Events (%)	HR (95% CI)
Primary cohort	187	101 (54.0)	0.59 (0.39-0.88)
Region			
Japan	149	81 (54.4)	0.57 (0.36-0.89)
Korea	38	20 (52.6)	0.69 (0.25-1.88)
Lines of prior systemic therapy			
2	104	55 (52.9)	0.85 (0.49-1.47)
3	52	29 (55.8)	0.39 (0.18-0.85)
≥4	31	17 (54.8)	0.38 (0.13-1.11)
Age			
<65 years	82	45 (54.9)	0.82 (0.44-1.53)
≥65 years	105	56 (53.3)	0.44 (0.26-0.76)
Sex			
Female	45	30 (66.7)	0.78 (0.37-1.66)
Male	142	71 (50.0)	0.53 (0.33-0.87)
ECOG PS			
0	92	48 (52.2)	0.57 (0.32-1.02)
1	95	53 (55.8)	0.59 (0.33-1.04)
HER2 status in central laboratory			
Primary cohort: IHC 3+	143	70 (49.0)	0.47 (0.29-0.77)
Primary cohort: IHC 2+/ISH+	44	31 (70.5)	1.14 (0.52-2.50)
Primary tumor location			
Gastric	163	89 (54.6)	0.59 (0.38-0.91)
GEJ	24	12 (50.0)	0.68 (0.21-2.15)
Histological subtype			
Intestinal	127	69 (54.3)	0.65 (0.39-1.07)
Diffuse	46	25 (54.3)	0.38 (0.17-0.86)
No. of metastatic sites			
<2	34	15 (44.1)	0.40 (0.13-1.23)
≥2	153	86 (56.2)	0.61 (0.39-0.95)
Previous total gastrectomy			
Yes	31	15 (48.4)	0.16 (0.05-0.47)
No	156	86 (55.1)	0.77 (0.49-1.20)



76.4% IHC3+

Shitara *et al*. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *NEJM* 2020

DESTINY GASTRIC-02
Western Phase II



Van Cutsem et al. Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen. ESMO 2021

DESTINY GASTRIC-02

	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

Van Cutsem et al. Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen. ESMO 2021

DESTINY GASTRIC-02

Adjudicated Drug-Related ILD/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	2 (2.5)	3 (3.8)	0	0	1 (1.3)	6 (7.6)

- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 53-85 days), with a median duration of 38.0 days (range, 15-142 days)
- 83% of adjudicated drug-related ILD/pneumonitis cases were low grade (Grade 1-2)

Van Cutsem et al. Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen. ESMO 2021

Phase 2 DESTINY-Gastric01 Trial: Trastuzumab Deruxtecan in Advanced HER2+ GC/GEJC

- Pathologically documented locally advanced or metastatic gastric or GEJ cancer
- Progression on and after ≥2 prior regimens
- Adequate tumor sample
- Measurable disease based on RECIST 1.1

N = ≈220

R 2:1

Primary cohort (HER2+ and progressed on trastuzumab-containing regimen)

Experimental: trastuzumab deruxtecan (IV infusion every 3 weeks)

Active comparator: physician's choice of irinotecan 150 mg/m^2 biweekly or paclitaxel 80 mg/m^2 weekly

Exploratory: trastuzumab deruxtecan (IV infusion every 3 weeks) in ≤20 patients with naive HER2 IHC 2+/ISH- disease

Exploratory: trastuzumab deruxtecan (IV infusion every 3 weeks) in ≤20 patients with naive HER2 IHC 1+ disease

Outcomes

- Primary: ORR by ICR
- Secondary: percentage of participants in the experimental and active comparator groups with PFS, OS, DOR, DCR, TTF, ORR, C_{max}, AUC_{last}, and AUC_{0-21}

https://clinicaltrials.gov/ct2/show/NCT03329690

Phase 2 DESTINY-Gastric01 Trial: ORR in Low-Expressors

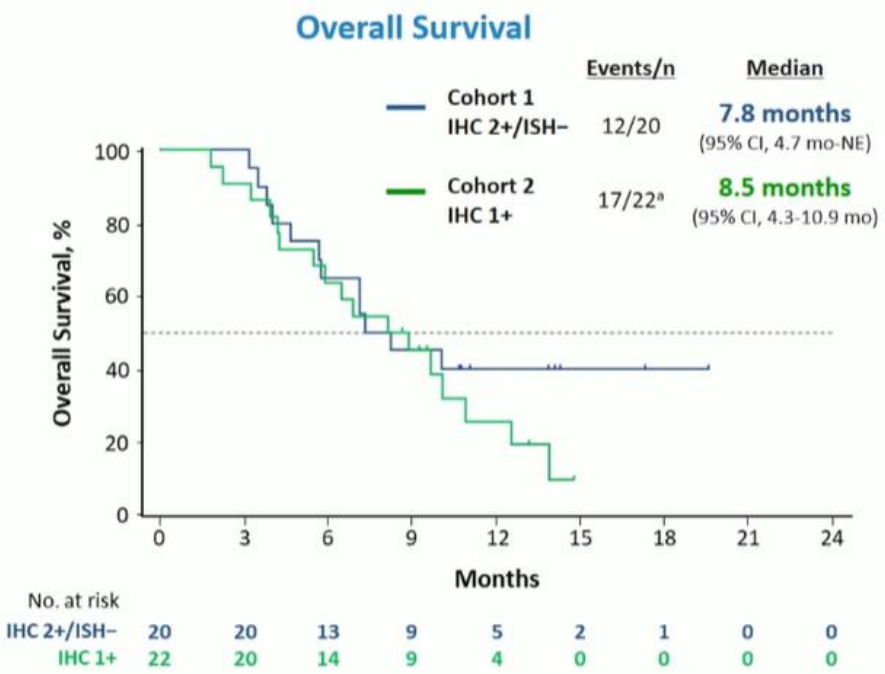
	Primary Cohort[1]		Exploratory Cohorts	
	T-DXd (n = 119)	PC Overall (n = 56)	Cohort 1 IHC 2+/ISH− (n = 19)	Cohort 2 IHC 1+ (n = 21)
ORR by ICR (CR + PR)	**51.3% (n = 61)** 95% CI, 41.9-60.5; *P* < .0001[a]	**14.3% (n = 8)** 95% CI, 6.4-26.2	**36.8% (n = 7)** 95% CI, 16.3%-61.6%	**19.0% (n = 4)** 95% CI, 5.4%-41.9%
Confirmed ORR by ICR (CR + PR)	**42.9% (n = 51)** 95% CI, 33.8-52.3	**12.5% (n = 7)** 95% CI, 5.2-24.1	**26.3% (n = 5)** 95% CI, 9.1%-51.2%	**9.5% (n = 2)** 95% CI, 1.2%-30.4%
CR	8.4% (n = 10)	0	0	0
PR	34.5% (n = 41)	12.5% (n = 7)	26.3% (n = 5)	9.5% (n = 2)
SD	42.9% (n = 51)	50.0% (n = 28)	63.2% (n = 12)	61.9% (n = 13)
PD	11.8% (n = 14)	30.4% (n = 17)	10.5% (n = 2)	28.6% (n = 6)
NE	2.5% (n = 3)	7.1% (n = 4)	0	0
Confirmed DCR (CR + PR + SD)	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1	89.5% (n = 17) 95% CI, 66.9%-98.7%	71.4% (n = 15) 95% CI, 47.8%-88.7%
Median confirmed DOR	11.3 months 95% CI, 5.6 months-NE	3.9 months 95% CI, 3.0-4.9 months	7.6 months 95% CI, 4.1 months-NE	12.5 months 95% CI, NE-NE

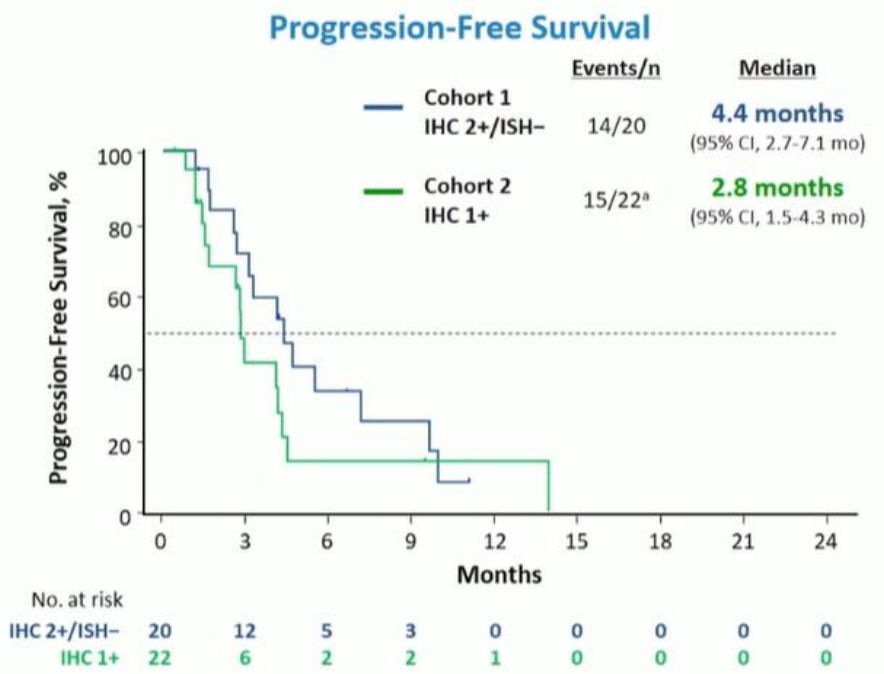
Includes data for the response-evaluable set: all randomized (for primary cohort) patients who received ≥ 1 dose of study drug and had measurable tumors based on independent central review at baseline.
[a]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region.

1. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

Yamaguchi, K et al. ESMO 2020

Phase 2 DESTINY-Gastric01 Trial: OS & PFS in Low-Expressors





[a] Two patients were excluded from analysis due to a missing HER2 status by central laboratory.

Yamaguchi, K et al. ESMO 2020

Ongoing Trastuzumab-Deruxtecan Studies

- DESTINY-Gastric03 phase 2: Tras-Derux combinations with chemo, ICI [NCT04379596]

- DESTINY-Gastric04 phase 3: 2nd-line Tras-Derux vs Pac/Ram pending. [NCT04704934]

~10% pneumonitis risk → may be challenging to move this to earlier lines

Novel HER2-Directed Strategies

Antibody-drug conjugates

- Trastuzumab deruxtecan (T-Dxd) (DS-8201a)
- RC48-ADC: ongoing phase 2 trial (NCT03556345)

Monoclonal antibodies

- Margetuximab (+ PD-1 inhibitor)

Bispecific antibodies

- Zanidatamab (ZW25); targets two areas on HER2 (phase 2 in combination with SOC chemo [NCT03929666], and phase 1/2 with chemo and PD-1 inhibitor [NCT04276493])

Combination with immune checkpoint inhibitors

- With durvalumab, nivolumab, and pembrolizumab (phase 3 KEYNOTE-811)

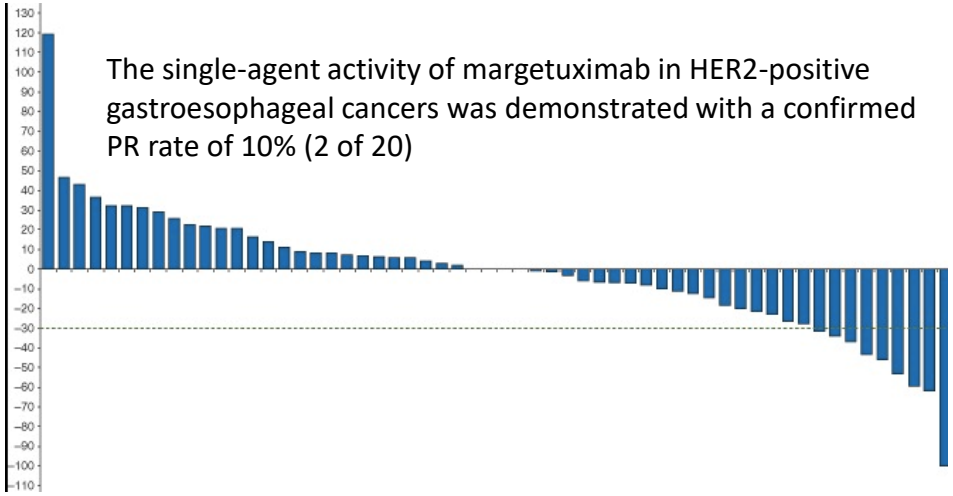
Novel HER2 Agents: Antibody Drug conjugates, Bi Specific antibodies

- **Margetuximab:**
  - Anti HER-2 with optimized Fc domain to increase activation of CD16A receptors on NK cells
  - Phase I / II + Pembro: 18% response rate second line
    - Higher in IHC 3+, retained HER-2 amplification, PDL-1+
  - Phase II/III first line: MAHOGANY
- **Zanidatamab: Targeting two epitopes on HER2**

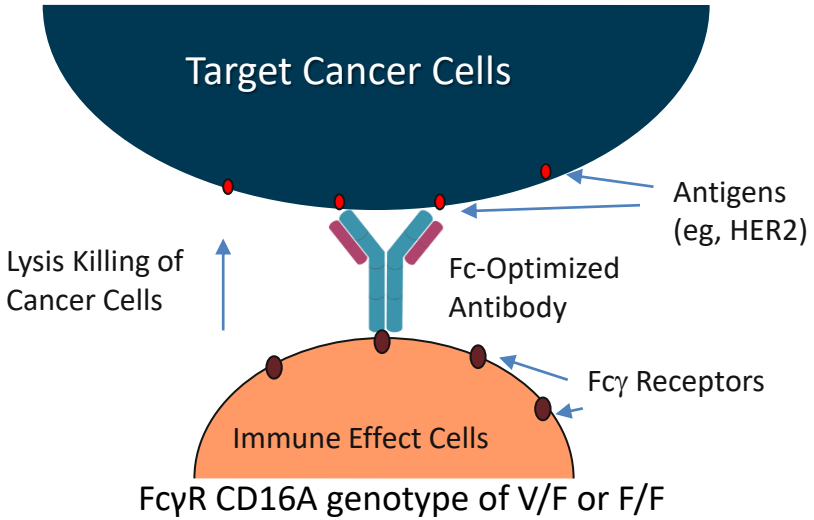
Catenacci Lancet Oncol 21: 1066; 2020

Margetuximab

- **Margetuximab had enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) compared with trastuzumab**



The single-agent activity of margetuximab in HER2-positive gastroesophageal cancers was demonstrated with a confirmed PR rate of 10% (2 of 20)



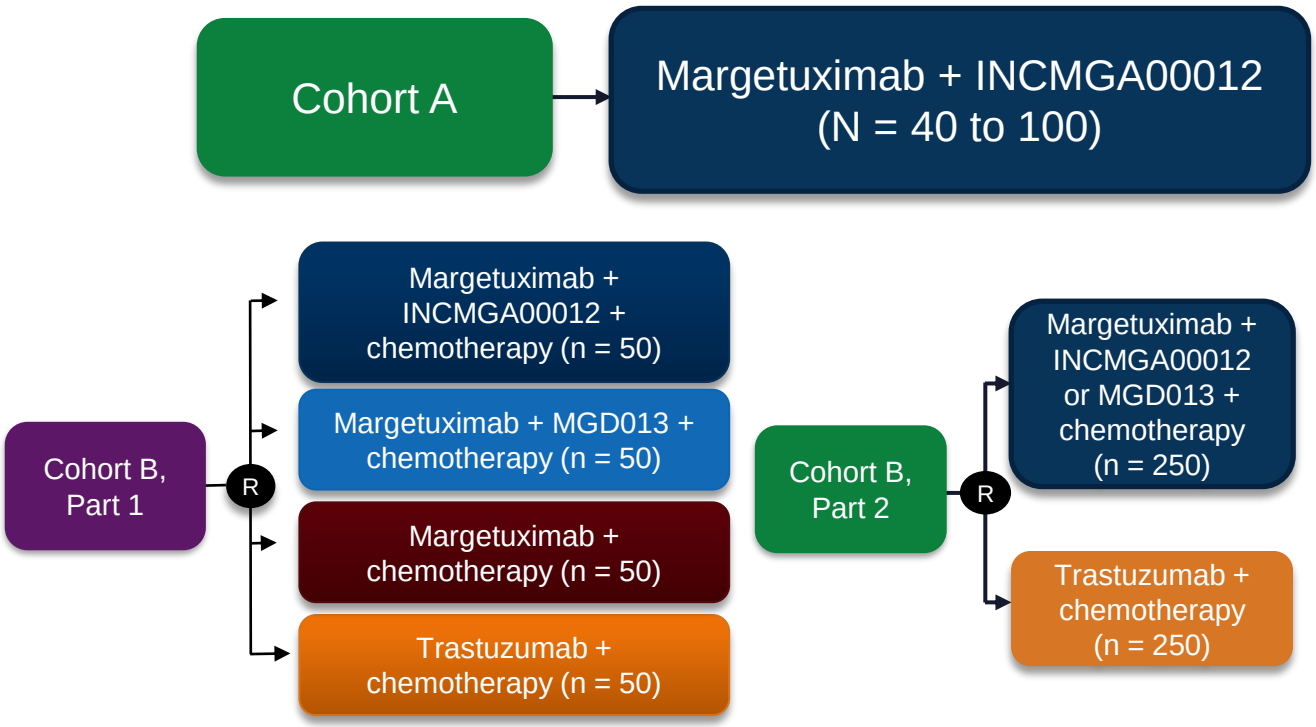
Phase 2/3 MAHOGANY: Combination margetuximab, INCMGA00012, MGD013, and chemotherapy in *HER2*+ gastric/GEJ cancer

1. Bang YJ et al. Ann Oncol. 2017;
2. https://clinicaltrials.gov/ct2/show/NCT04082364

MAHOGANY Phase 2/3 Trial in HER2-Positive Gastric/GEJ Cancer[1]

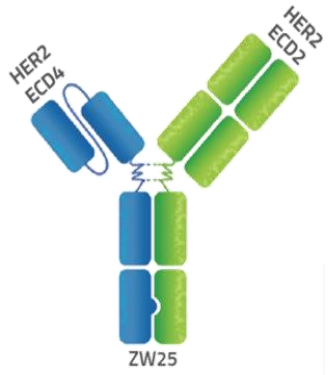
Inclusion Criteria

- Previously untreated advanced disease
  - Cohort A: HER2-positive (by IHC 3+) and PD-L1-positive (CPS ≥ 1%)
  - Cohort B: HER2-positive (by IHC 3+ or IHC 2+/FISH+)
- ECOG 0 or 1



- Primary outcomes: AE incidence (Cohort A), ORR (Cohorts A and B), OS (Cohort B)

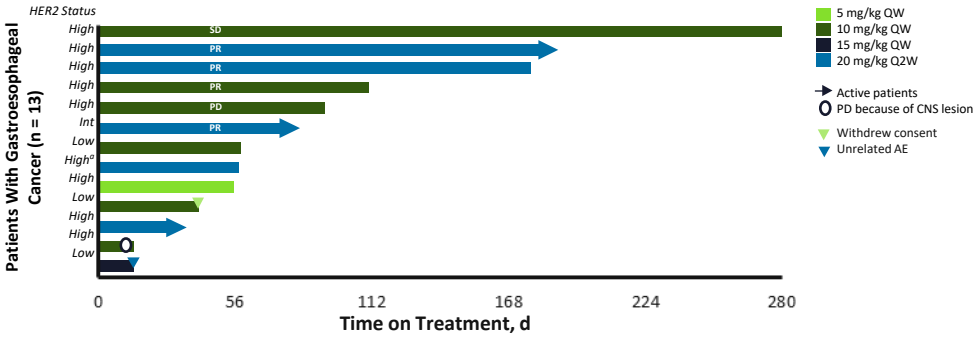
Zanidatamab (ZW25), a HER2-Targeted Bispecific mAb



Biparatopic binding targets two distinct HER epitopes
- Same domains as trastuzumab (ECD4) and pertuzumab (ECD2)

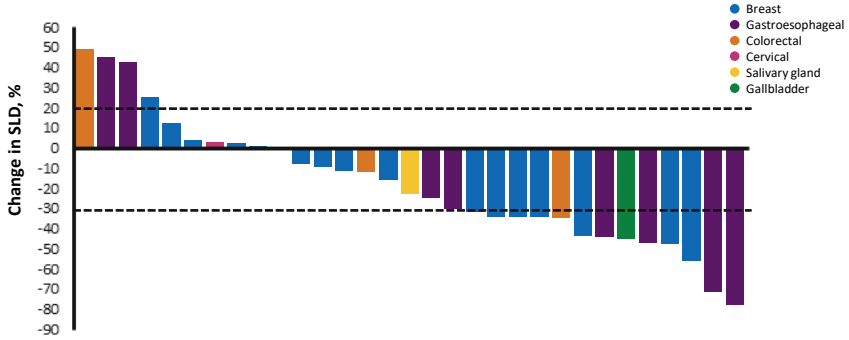
Unique mechanisms of action designed to expand activity
- Extended chain formation and dense HER2 receptor clustering
- Enhanced HER2 internalization and downregulation
- Increased tumor cell binding density and potent effector-mediated cytotoxicity
- Enhanced blockade of ligand-dependent and ligand-independent tumor growth

Gastroesophageal Cancer: Time on Treatment



Change in Target Lesions Across Cancer Types

Decrease in target lesions in majority of patients with measurable disease



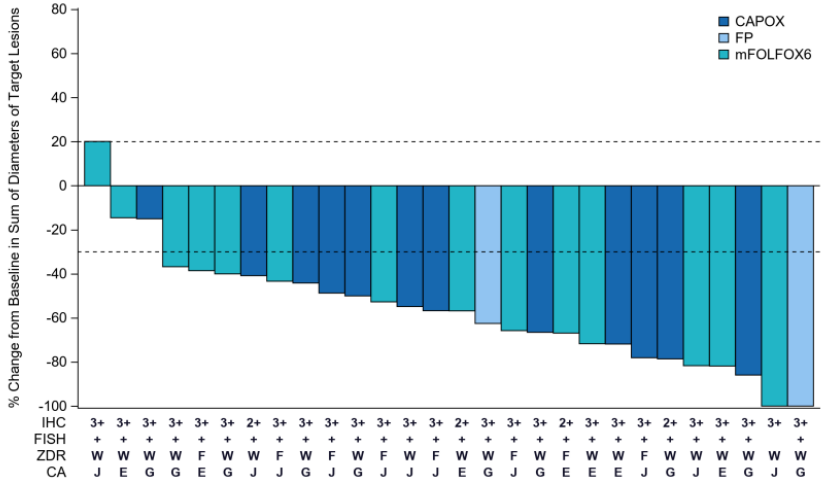
Beeram M, et al. EORTC-NCI-AACR 2018;
Meric-Bernstam F, et al. ASCO 2018

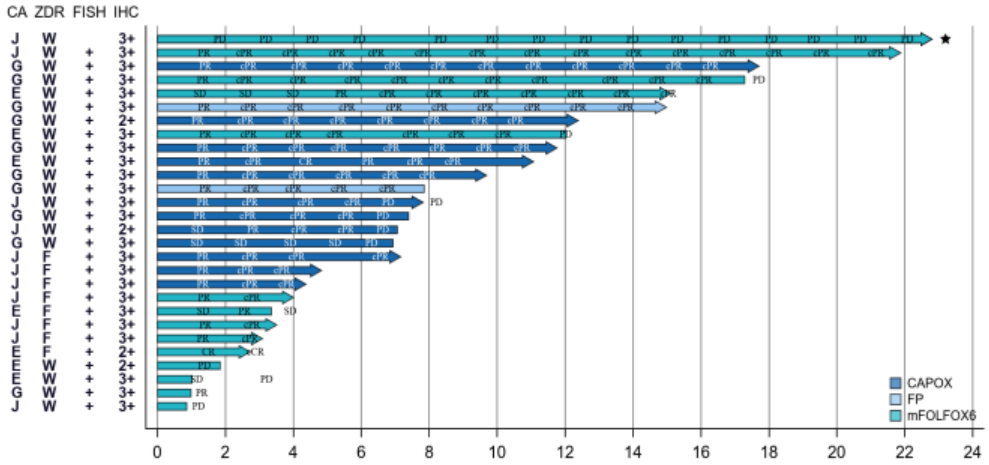
Zanidatamab (GI Symposium 2021 Abs 299): Gastric GEJ Cancer

	Zanidatamab Single Agent (N = 36)	Zanidatamab + Paclitaxel or Capecitabine (N = 26)
Median prior systemic therapies, n (range)	3 (1–7)*	2 (1–7)
Patients with prior HER2 therapies, n (%)	34 (94)	24 (92)
Grade 3+**	4 (11)	4 (15)
Response evaluable, n	34	20
Objective response, n (%)	13 (38)	12# (60)
Disease control rate, n (%)	21 (62)	17 (85)
Median duration of response, months (95% CI)‡	6.0 (1.9, 9.2)	8.9 (3.5, Not estimable)

Meric Bernstam JCO 39:164; 2021

Zanidatamab+Chemo First line





ORR 75% (21/28)
DCR 89% (25/28)

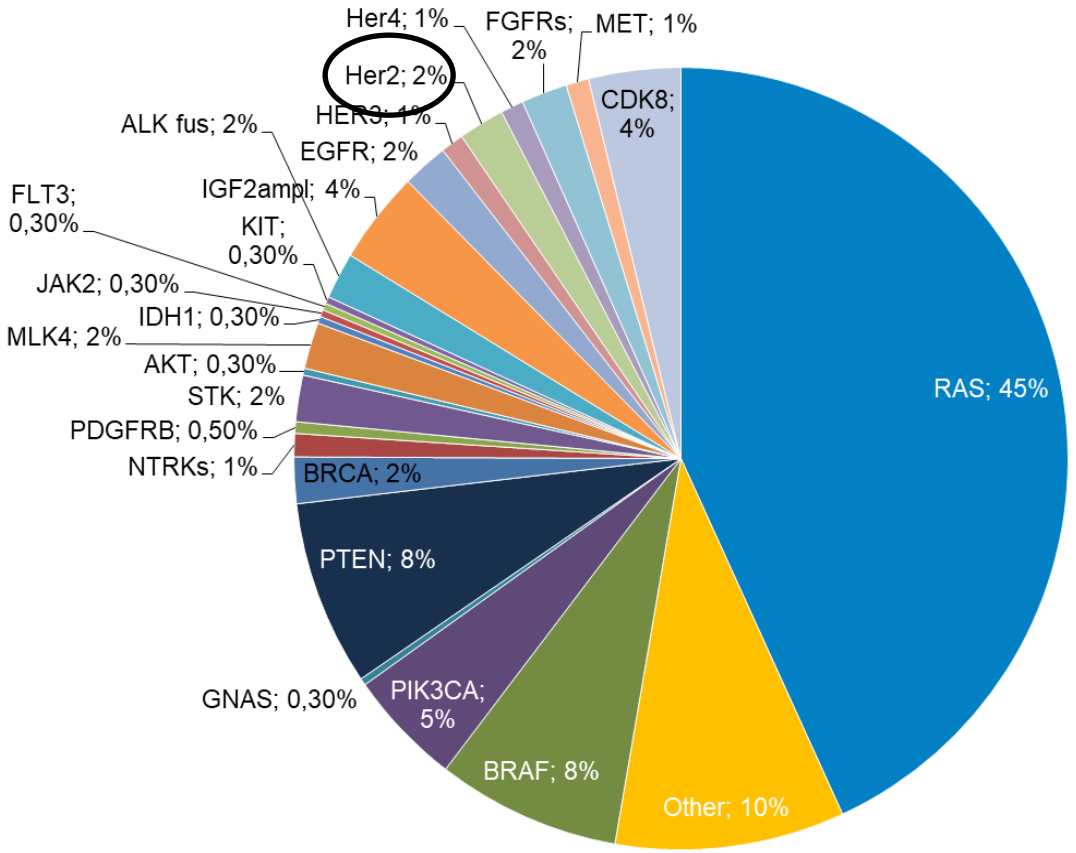
mDOR 16.4

Ku et al. ESMO 2021

CRC: Molecular subgroups

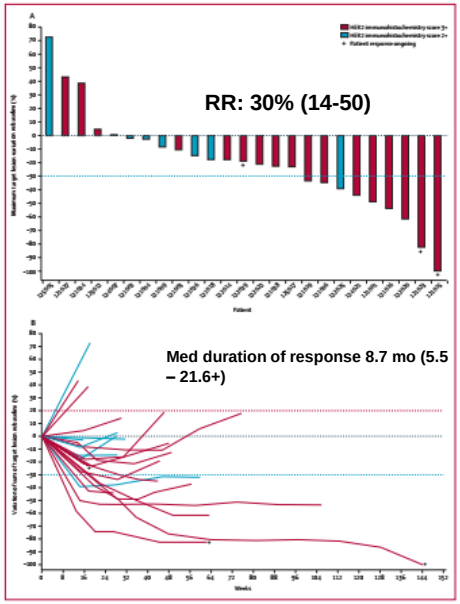
Molecular Subtypes in mCRC:

- **–RAS**
  - ***RAS G12C***
- **–MSI**
- **–BRAF**
- **–HER-2**
- ***–NTRK***
- ***–other***



Anti-HER2 combinations in chemo refractory HER2+ mCRC: Benefit limited to RAS WT

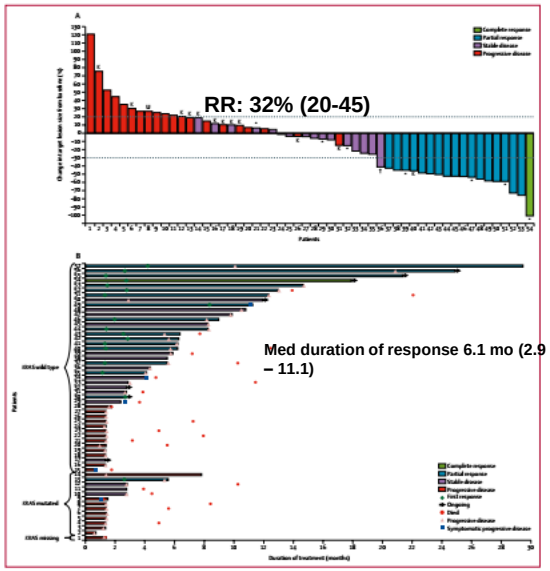
Trastuzumab + lapatinib



Patient selection (n=27):
- **IHC: 3+ HER2 score in more than 50% of cells**
- **IHC: 2+ and a HER2:CEP17 ratio > 2 in more than 50% of cells by FISH**

Sartore-Bianchi A et al, Lancet Oncol 2016

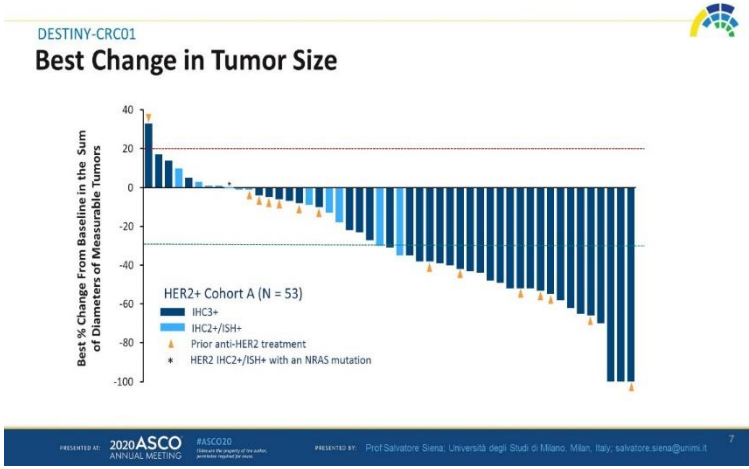
Trastuzumab + pertuzumab



Patient selection (n=57):
- **FISH or CISH + (*HER2/Ch17* > 2 or *HER2* GCN > 6)**
- **NGS: *HER2* amplification based on copy number gain**
- **IHC 3+**

Meric-Bernstam F et al, Lancet Oncol 2019

Trastuzumab-deruxtecan

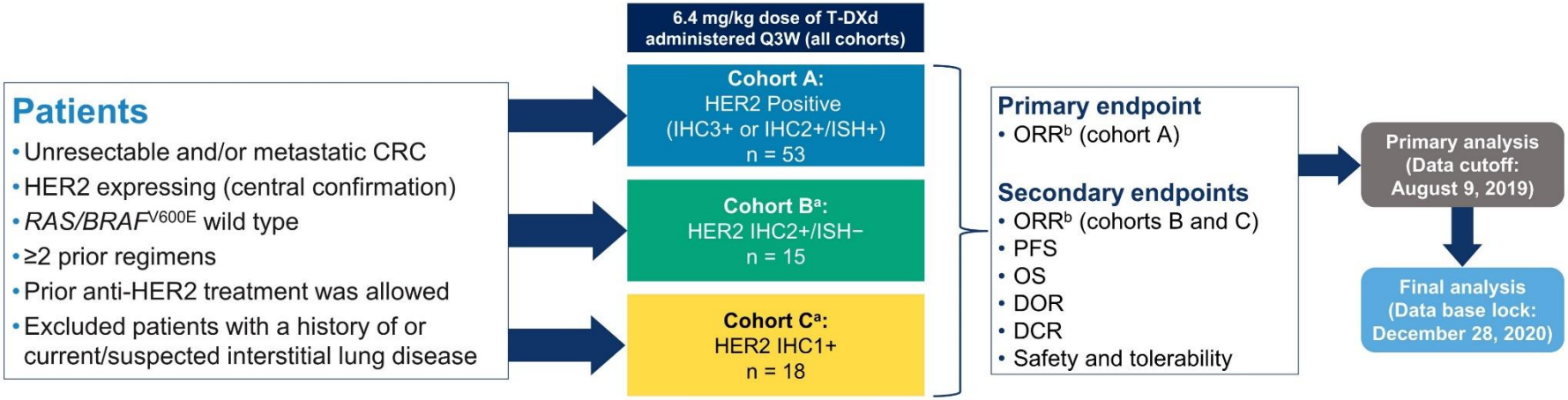


Siena S et al, ASCO 2020

SWOG 1613: vs Irinotecan/Cetuximab

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



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

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Prior Treatments

Prior Treatment, %	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Irinotecan	100	100	100	100
Fluorouracil / capecitabine	100 / 54.7	93.3 / 46.7	100 / 55.6	98.8 / 53.5
Oxaliplatin	100	93.3	100	98.8
Cetuximab or panitumumab	100	100	94.4	98.8
Bevacizumab	75.5	73.3	83.3	76.7
Prior anti-HER2 agents	30.2	0	0	18.6

- Median prior regimens for metastatic disease was 4 (range, 2–11)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

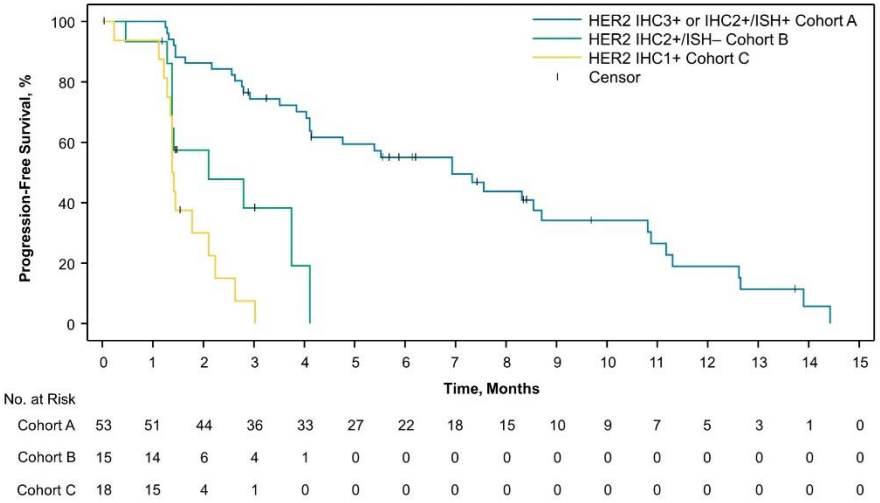
Efficacy Results

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	**24 (45.3)** [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients were missing postbaseline scans.

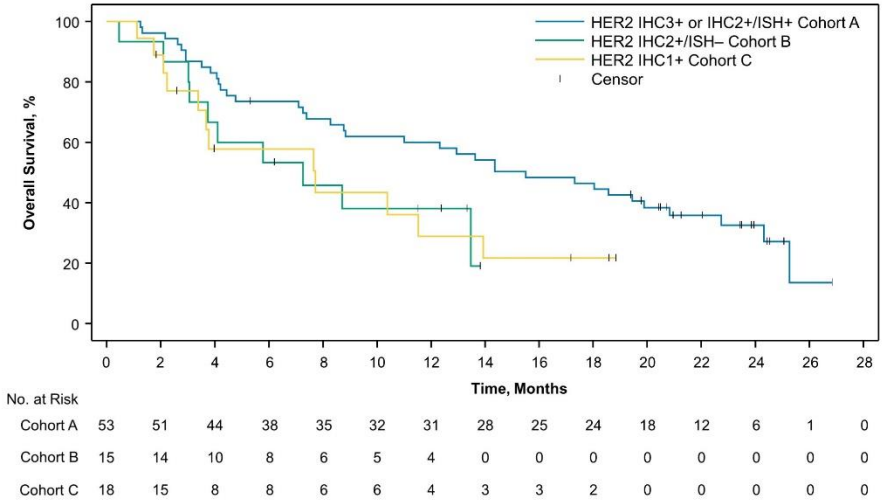
Progression-Free and Overall Survival

Progression-Free Survival



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival

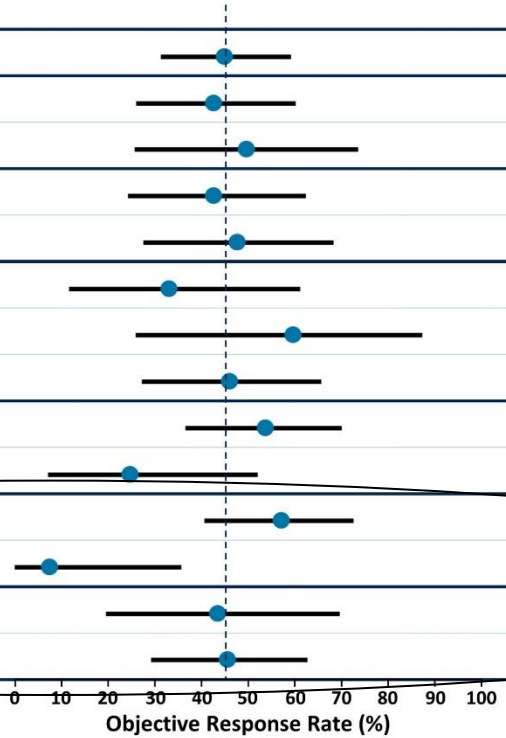


	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not-evaluable.

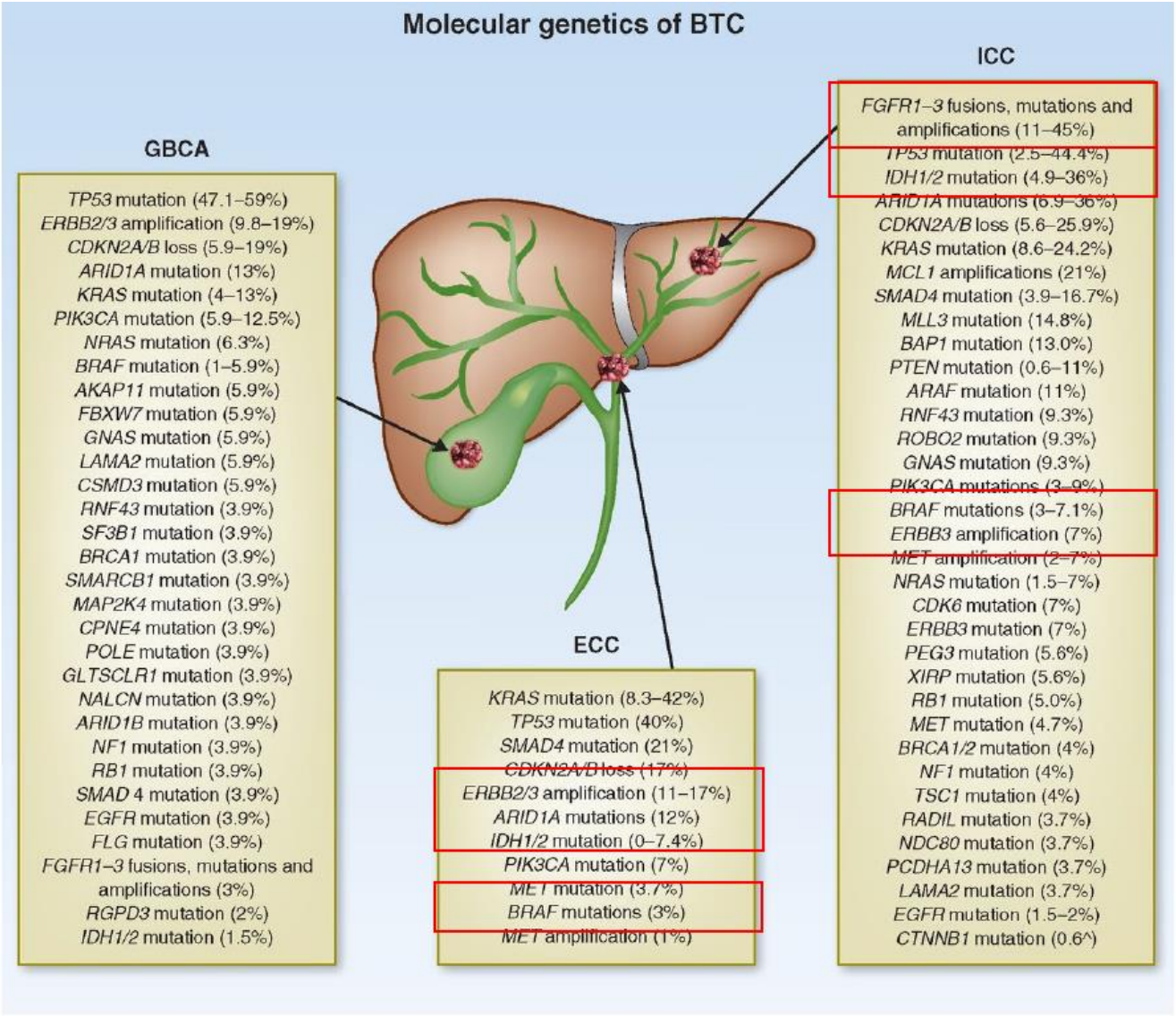
ORR by Subgroup in Cohort A

		ORR, %	[95% CI]
HER2+ Cohort A	**n = 53**	**45.3**	[31.6-59.6]
Age	<65 y (n = 35)	**42.9**	[26.3-60.6]
	≥65 y (n = 18)	**50.0**	[26.0-74.0]
Sex	Female (n = 28)	**42.9**	[24.5-62.8]
	Male (n = 25)	**48.0**	[27.8-68.7]
Region	Asia (n = 15)	**33.3**	[11.8-61.6]
	North America (n = 10)	**60.0**	[26.2-87.8]
	Europe (n = 28)	**46.4**	[27.5-66.1]
ECOG PS	0 (n = 37)	**54.1**	[36.9-70.5]
	1 (n = 16)	**25.0**	[7.3-52.4]
HER2 status	IHC3+ (n = 40)	**57.5**	[40.9-73.0]
	IHC2+/ISH+ (n = 13)	**7.7**	[0.2-36.0]
Prior HER2 treatment	Yes (n = 16)	**43.8**	[19.8-70.1]
	No (n = 37)	**45.9**	[29.5-63.1]



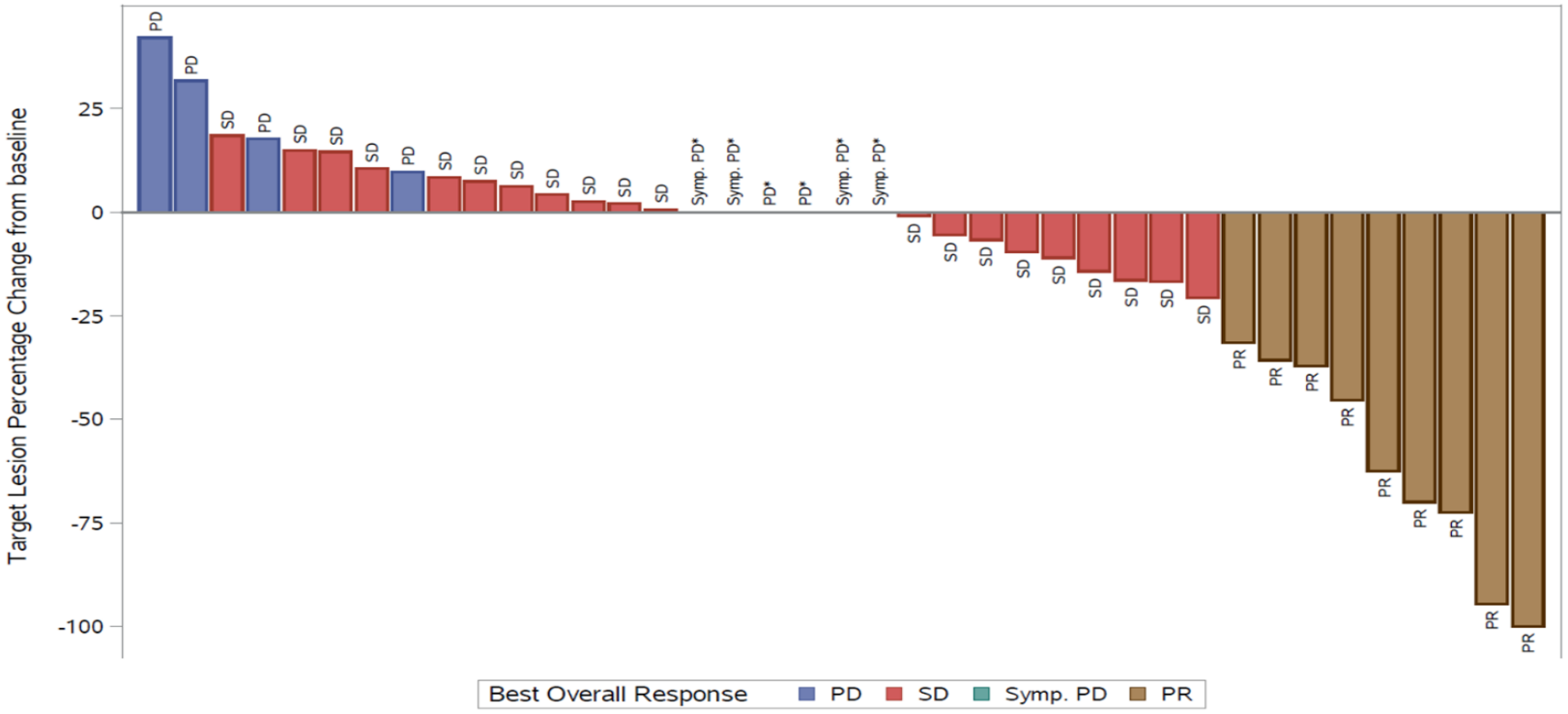
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate.
Reprinted from *The Lancet Oncology*, Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. 2021, with permission from Elsevier.

Genomics of Biliary Cancer



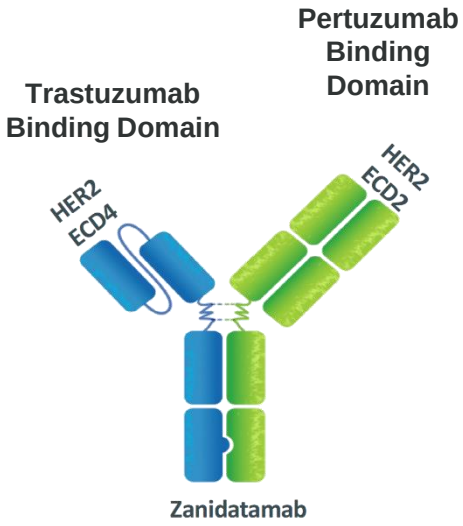
Valle et al Cancer Discovery 2017

Trastuzumab plus pertuzumab for HER2/neu-amplified BTC

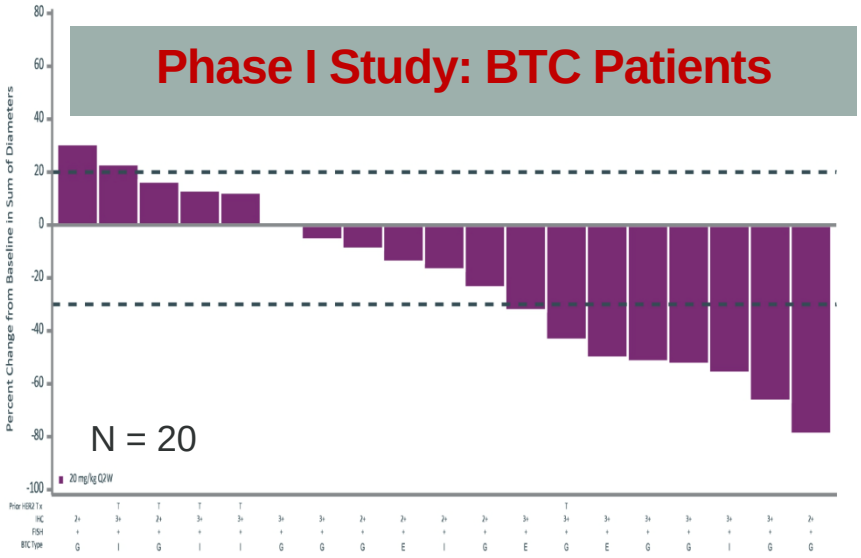


Javle M, et al. *J Clin Oncol* 2017;35(4_suppl):402–402

Zanidatamab: Bispecific HER2-Targeted Antibody



Phase I Study: BTC Patients



ORR 40% | **DCR 65%** | **DOR 7.4 mo**

Meric-Bernstam et al, *J Clin Oncol* 2021

Summary

- **HER2 is targetable in EG, CR, and biliary cancers**
- **Esophagogastric cancer**
  - First line: trastuzumab + pembrolizumab + chemo
  - Second / later line: trastuzumab deruxtecan
    - Combinations, earlier line use
  - Margetuximab, Zanidatimab, others
- **Colorectal cancer**
  - HER2 combinations, trastuzumab deruxtecan, tucatinib (TKI)
- **Biliary cancers**
  - Extra hepatic cholangiocarcinoma
- **Obtain NGS on all patients!**