GESTIONE CLINICA DEGLI ADC: QUALE IMPATTO ORGANIZZATIVO E SOSTENIBILITÀ NELL'AMBITO DELLA RETE ONCOLOGICA REGIONALE EMILIA ROMAGNA

Le prospettive future

Dott. Stefano Tamberi
UOC Oncologia Ravenna

Responsabile Scientifico
Carmine Pinto

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

Agenda

- **Biomarkers**
- First line in HER2 advanced gastric cancer
- TDX-D in second –third line
- HER2 test
- Questions for the future

✓ HER2 low
✓ Combination
✓ Management of toxicity
✓ Neoadjuvant/adjuvant setting

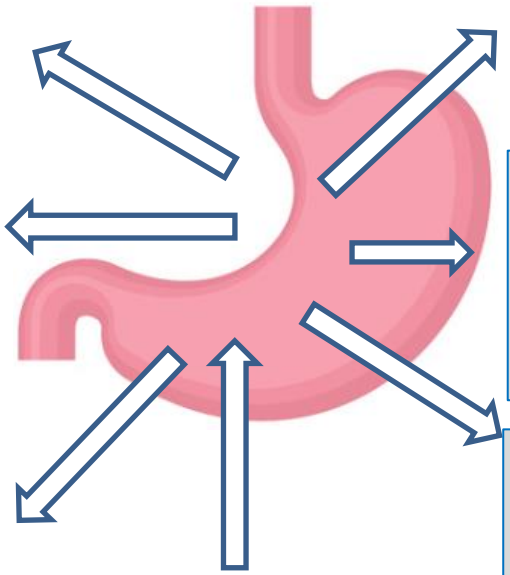
Key biomarkers in advanced gastric cancer

Established biomarkers

HER2 Positivity 5-25%
IHC 3+, IHC 2+ ISH ampl
CT+ trastuzumab I line
Trastuzumab deruxtecan II-III line

PD-L1 positivity ranges from 47.3% to 82.0%, serving as a predictive marker for response to ICI. Higher CPS (≥ 5, > 10) is associated with a higher likelihood of response to ICI treatment

MSI high/dMMR: 8–25% of patients exhibit MSI-High or dMMR, high response rates and improved survival when treated with ICI



NGS: TMB, MSI, ERBB2 amp, FGFR2b amp, MET, NTRK etc. **ctDNA**

Emerging biomarkers

FGFR2 amp: FGFR2 amplification is observed in 4–7.4% of patients and serves as a response predictor marker for bemarituzumab

FGFR2b positive : Approximately 30% of patients exhibit FGFR2b overexpression detected through IHC, which serves as a response predictor marker for bemarituzumab

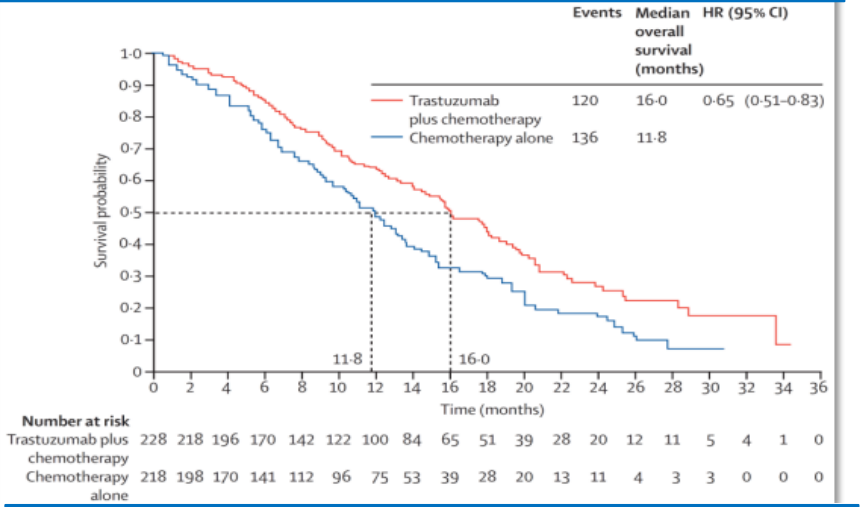
CLDN18.2 high: CLDN18.2 high expression is observed in 30–33% of patients and serves as a response predictive marker for zolbetuximab

Agenda

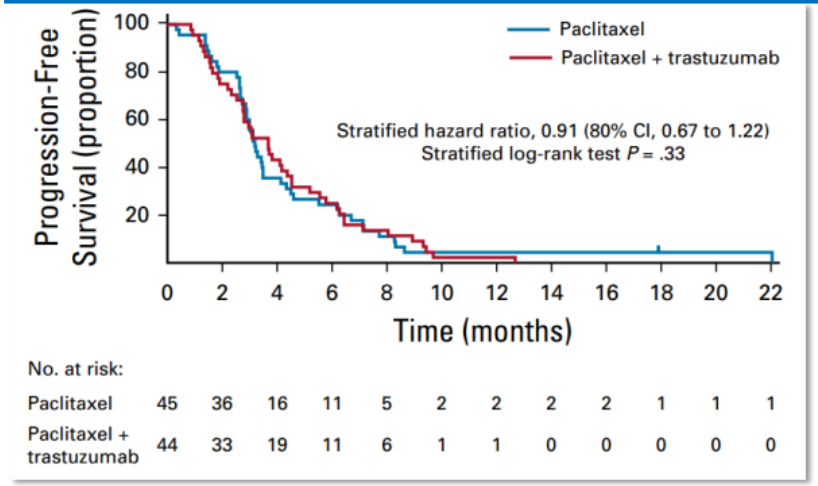
- Biomarkers
- **First line in HER2 advanced gastric cancer**
- TDX-D in second –third line
- HER2 test
- Questions for the future

✓ HER2 low
✓ Combination
✓ Management of toxicity
✓ Neoadjuvant/adjuvant setting

Trastuzumab + CT vs CT



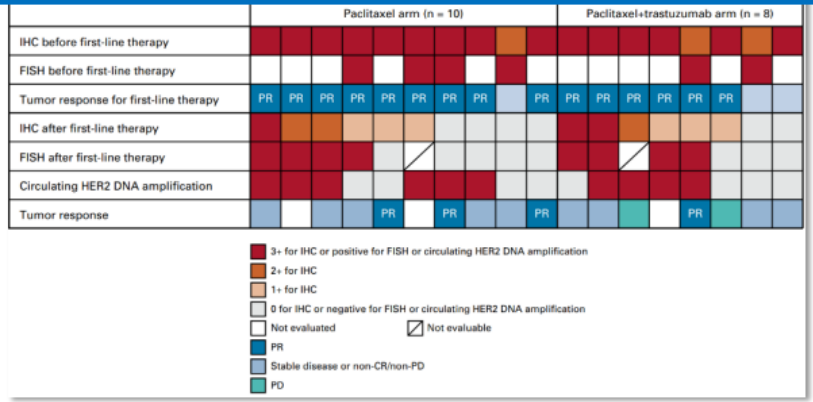
Trastuzumab beyond PD is not effective



Other agents not effective

Clinical Trial	First Reported Year	Drug	HER2 Definition	Phase	Line of Therapy	Intervention (Comparison)	Results
ToGA	2009	Trastuzumab	IHC 3+ and/or ISH-positive	P3	First-line	Trastuzumab + chemo (Chemotherapy)	Improvement of median OS 13.8 m vs. 11.1 m, $p = 0.0046$
TyTAN	2013	Lapatinib	ISH-positive	P3	Second-line	Lapatinib + chemo (Chemotherapy)	No difference in median OS 11.0 m vs. 8.9 m, $p = 0.1044$
TRIO-013/LOGiC	2013	Lapatinib	IHC 3+ and/or ISH-positive	P2/3	First-line	Lapatinib + chemo (Chemotherapy)	No difference in median OS 12.2 m vs. 10.5 m, $p = 0.91$
GATSBY	2016	T-DM1	IHC 3+ or IHC 2+ISH-positive	P2/3	First-line	T-DM1 (Chemotherapy)	No difference in median OS 7.9 m vs. 8.6 m, $p = 0.31$
JACOB	2017	Pertuzumab	IHC 3+ or IHC 2+ISH-positive	P3	First-line	Pertuzumab + Trastuzumab + chemo (Trastuzumab + chemo)	No difference in median OS 17.5 m vs. 14.2 m, $p = 0.057$

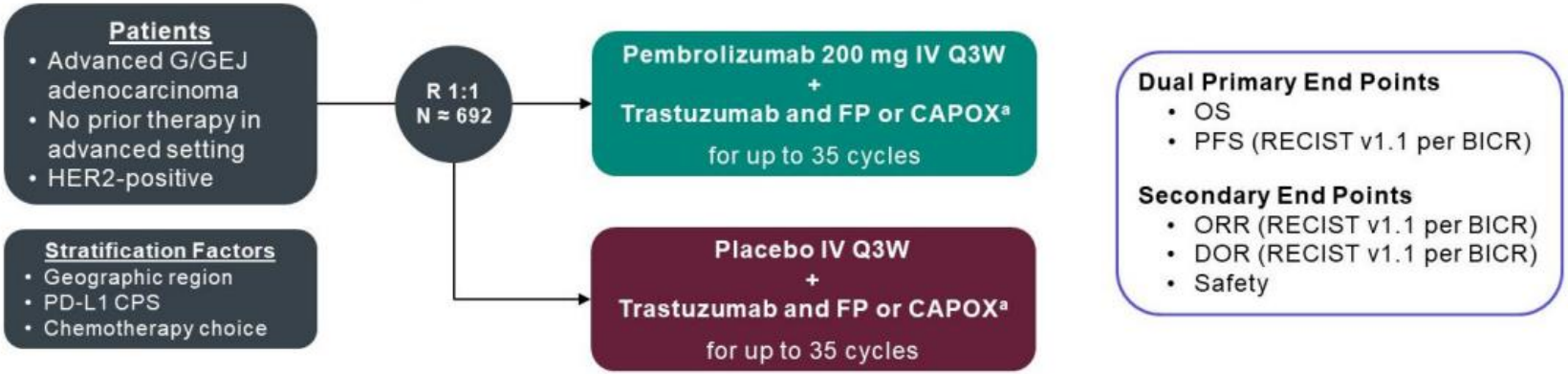
Loss of HER2 expression in about 1 of 3



Immunotherapy in first line HER2+ mGC

KEYNOTE-811 – PEMBROLIZUMAB + TRASTUZUMAB

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)



[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: 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).

Immunotherapy in first line HER2+ mGC

Approval 1st-line GC / EGJ cancer
- **HER2-positive**
- **PD-L1 CPS ≥ 1**

Summary of confirmed objective response in the effi

Variable	Pembrolizumab Group (N=133)	
Objective response — % (95% CI)*	74.4 (66.2–81.6)	5
Disease control — % (95% CI)†	96.2 (91.4–98.8)	8
Best overall response — no. (%)		

This approval by the EC follows the positive recommendation from the Committee for Medicinal Products for Human Use received in July 2023 and was based on results from the Phase 3 KEYNOTE-811 trial. In the study, KEYTRUDA plus trastuzumab and chemotherapy significantly improved progression-free survival (PFS), and objective response rate (ORR), compared to trastuzumab and chemotherapy alone in this patient population. In the study, more than 80% of patients had tumors that were PD-L1 positive.

difference in objective response rate in participants with PD-L1 combined positive score ≥1"

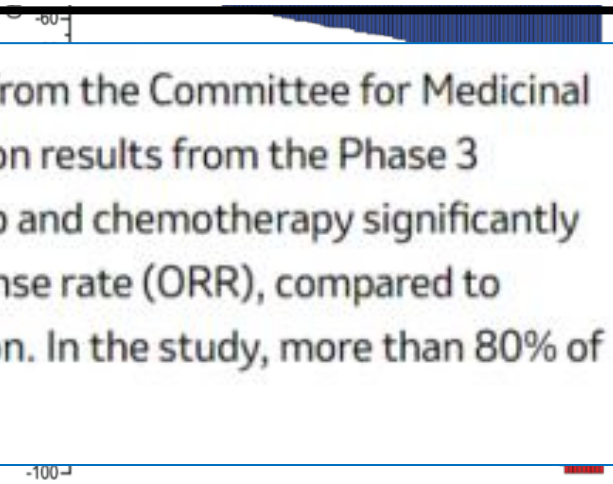
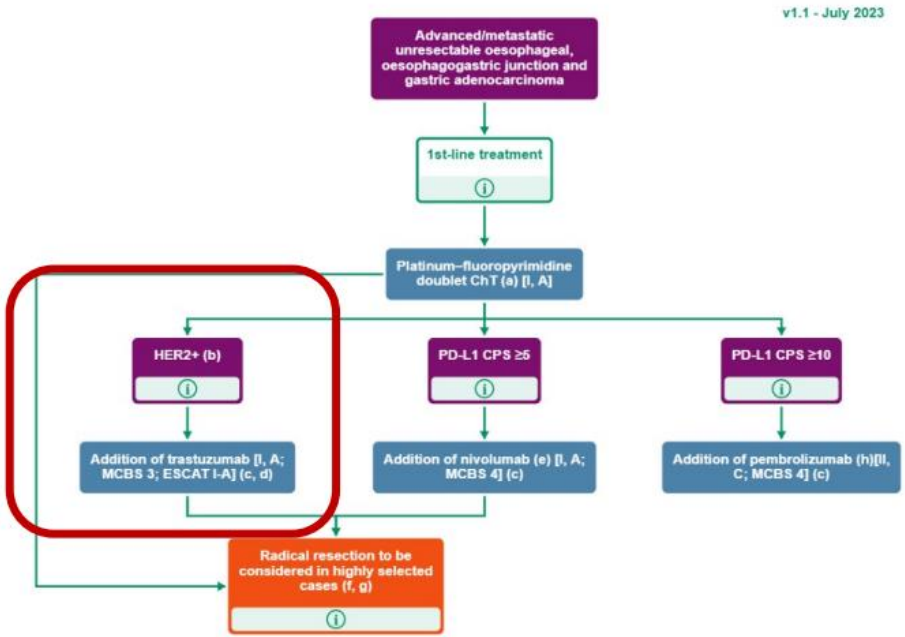


Fig. 1. Best percentage change from baseline in the size of target lesions among particip
the efficacy population

ESMO guidelines



- CT + trastuzumab standard first line
- IO+ trastuzumab+ CT standard for CPS≥1 in the next future
- Trastuzumab beyond progression is not effective
- Failure of other antiHER2 agents (pertuzumab, lapatinib TDM-1)

Agenda

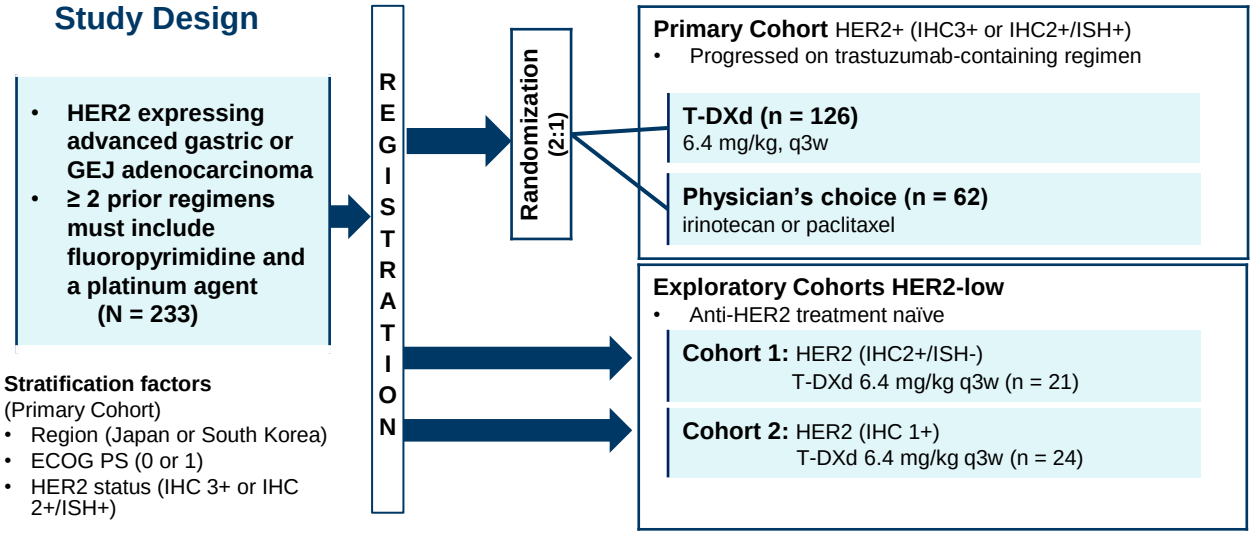
- Biomarkers
- First line in HER2 advanced gastric cancer
- **TDX-D in second –third line**
- HER2 test
- Questions for the future

✓ HER2 low
✓ Combination
✓ Management of toxicity
✓ Neoadjuvant/adjuvant setting

DESTINY-Gastric01
Study of Trastuzumab Deruxtecan in HER2 Expressing Gastric Cancer

A phase 2, multicenter, open-label trial of trastuzumab deruxtecan (T-DXd) in patients with HER2 expressing advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma (Asia)

Study Design



Stratification factors
(Primary Cohort)
- Region (Japan or South Korea)
- ECOG PS (0 or 1)
- HER2 status (IHC 3+ or IHC 2+/ISH+)

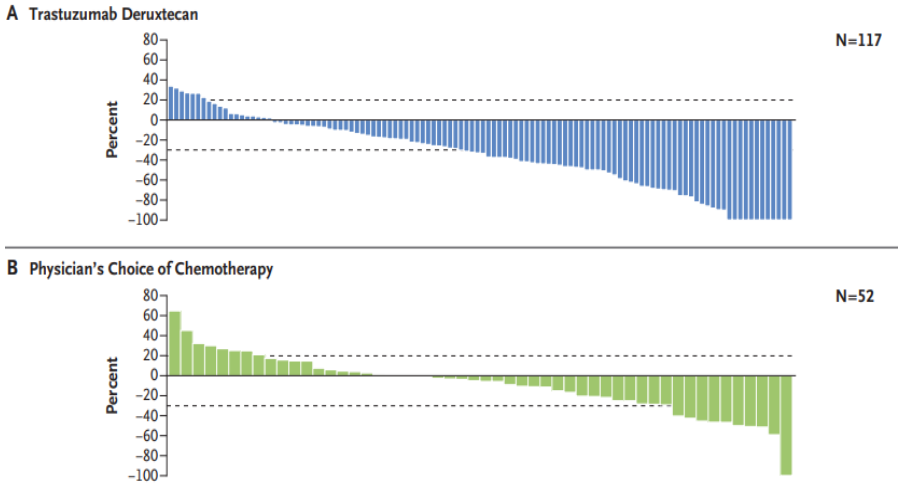
Primary Endpoint
- Objective response rate (ORR) by independent central review (ICR) in the primary cohort based on RECIST v1.1

Secondary Endpoints
- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DOR)
- Confirmed disease control rate (DCR)
- Time to treatment failure (TTF)
- Safety and pharmacokinetics
- ORR for each exploratory cohort, investigator assessed

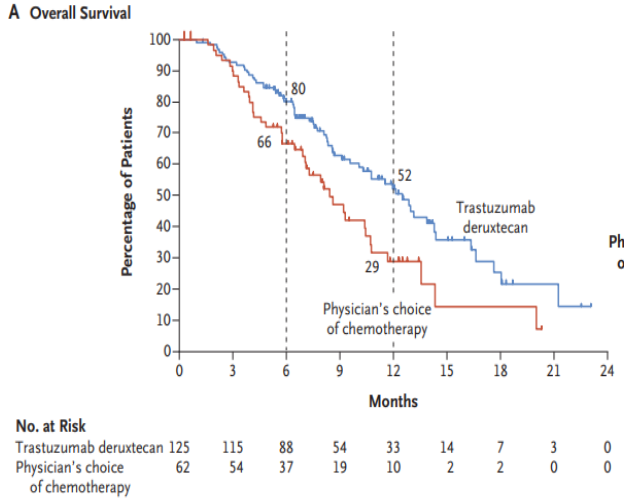
1. Shitara K, et al. *N Engl J Med.* 2020 Jun 18;382(25):2419-2430.
2. Yamaguchi K, et al. Presented at: American Society of Clinical Oncology (ASCO) 2021 Virtual Meeting. June 4-8, 2021. Poster 4048.

Destiny Gastric 01

Overall response rate 43% vs 12%



Overall survival (median) 12.5 vs 8,4 months



	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

Previous treatment — no. (%)		
Therapy containing trastuzumab	125 (100)	62 (100)
Therapy containing taxane	105 (84)	55 (89)
Therapy containing ramucirumab	94 (75)	41 (66)
Irinotecan or other topoisomerase I inhibitor	8 (6)	5 (8)
Immune checkpoint inhibitor	44 (35)	17 (27)

No. of previous systemic therapies for advanced or metastatic disease — no. (%)		
2	66 (53)	38 (61)
3	34 (27)	18 (29)
≥4	25 (20)	6 (10)

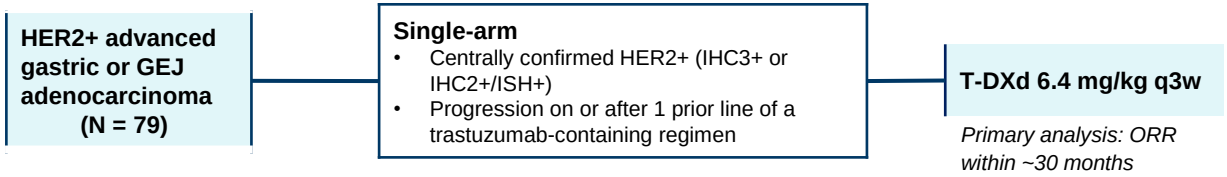
Shitara K et al. *NEJM* 2020;382:2419-30

DESTINY-Gastric02

Study of Trastuzumab Deruxtecan in HER2+ Gastric/GEJ Cancer[1]

A phase 2, multicenter, open-label trial of trastuzumab deruxtecan (T-DXd) in patients with HER2+, unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on or after a trastuzumab-containing regimen (North America, Europe)

Study Design



Primary Endpoint

- Confirmed objective response rate (ORR) by independent central review (ICR) based on RECIST v1.1

Secondary Endpoints

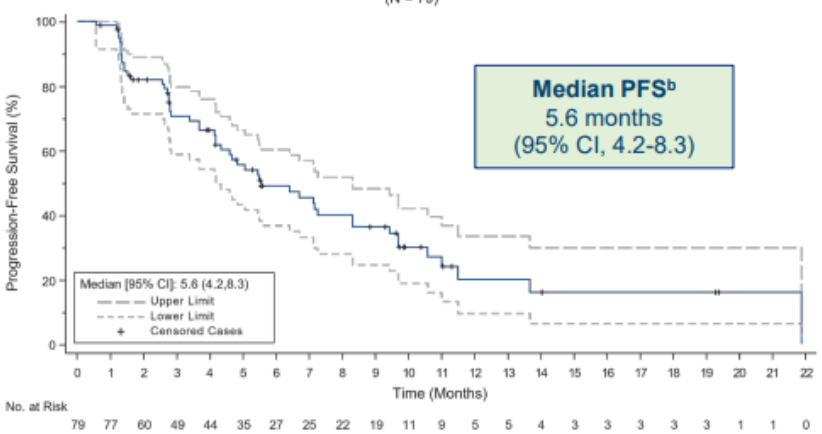
- Progression-free survival (PFS) by ICR and investigator assessment
- ORR by investigator assessment
- Overall survival (OS)
- Duration of response (DOR)

Destiny Gastric 02

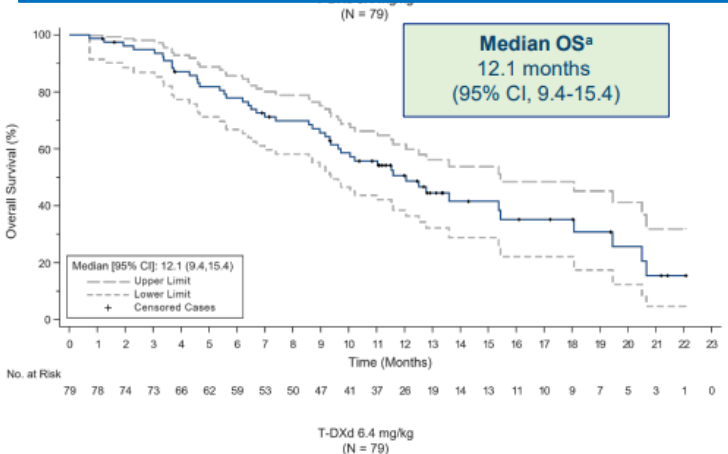
Overall response rate 42%

Confirmed ORR,[c] % (n)	**41.8 (33)** (95% CI, 30.8-53.4)
Confirmed best overall response, % (n)	
CR	**5.1 (4)**
PR	**36.7 (29)**
SD	**39.2 (31)**
PD	**16.5 (13)**
Not evaluable	**2.5 (2)**
Median DOR, months	8.1 (95% CI, 5.9-NE)[d]
Confirmed DCR,[e] % (n)	81.0 (64) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.7)

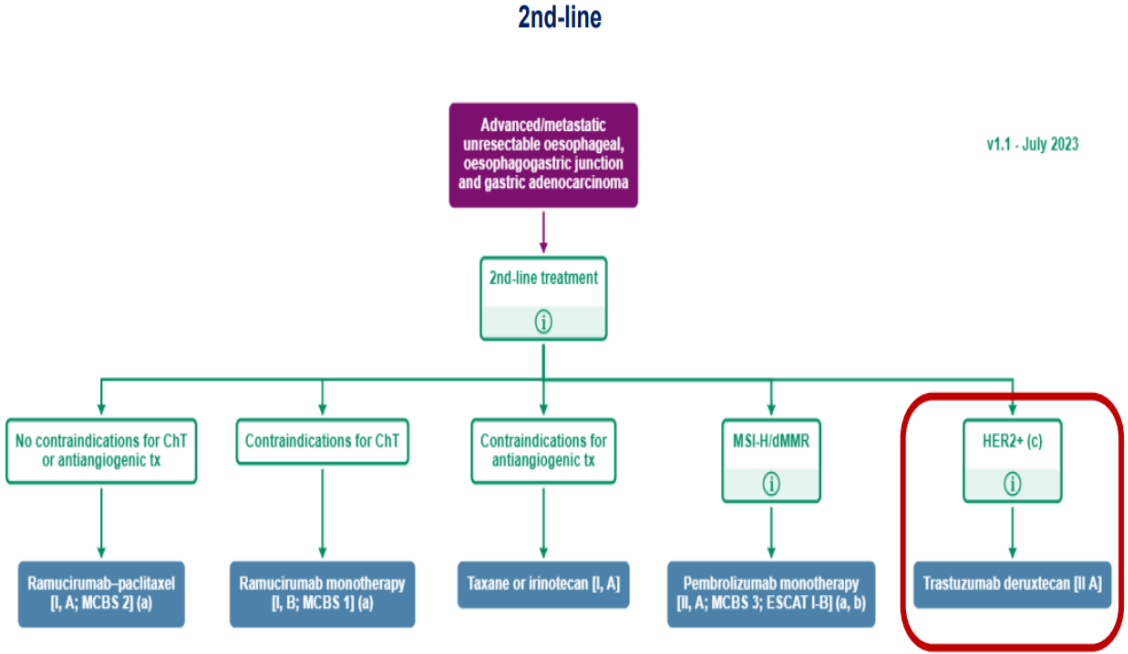
PFS (median) 5.6 m

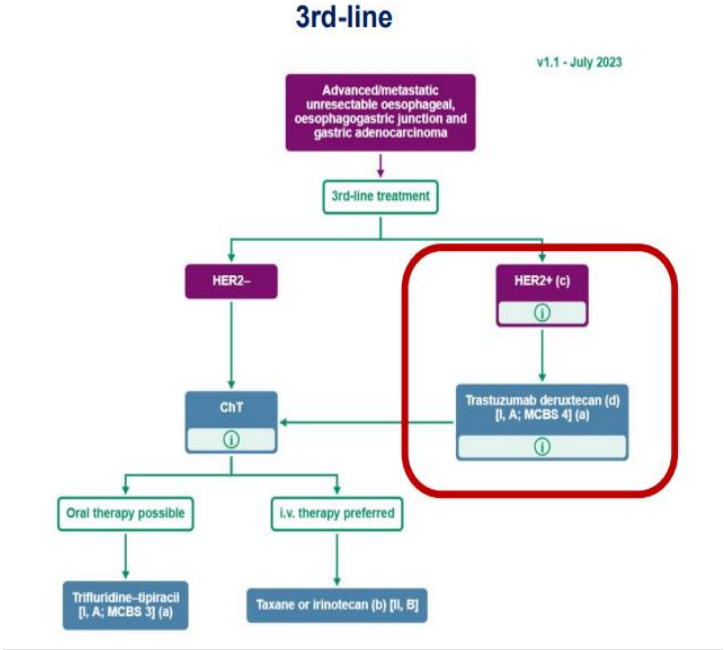


Overall survival (median) 12.1 m



ESMO guidelines



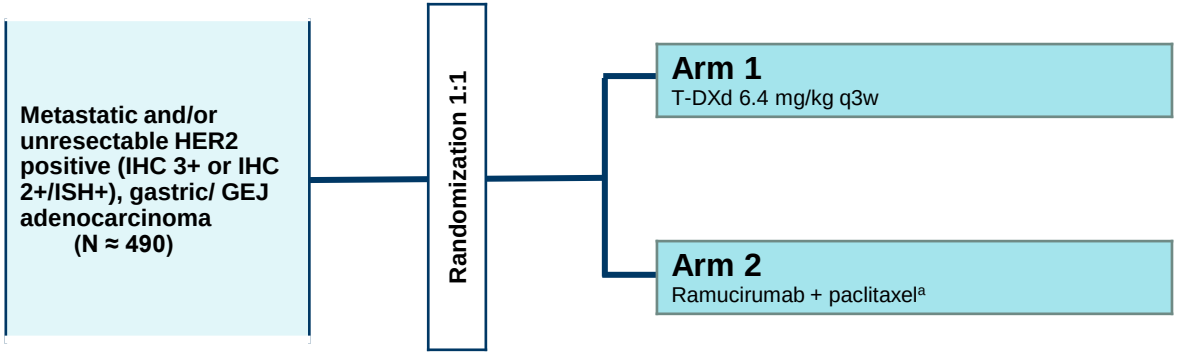


DESTINY-Gastric04 (DS8201-A-U306)

Study of Trastuzumab Deruxtecan in HER2+ Metastatic and/or Unresectable Gastric/GEJ Cancer

A phase 3, multicenter, 2-arm, randomized, open-label study of trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic and/or unresectable gastric or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen (Europe, Asia, South America)

Study Design



[a]Ramucirumab 8 mg/kg on Days 1 and 15 in combination with paclitaxel 80 mg/m^2 on Days 1, 8 and 15 of a 28-day cycle.

Primary Endpoint

- Overall survival (OS)

Secondary Endpoints

- Progression-free survival (PFS)
- Objective response rate (ORR)
- Duration of response (DOR)
- Disease control rate (DCR)
- Safety
- Pharmacokinetics (PK)

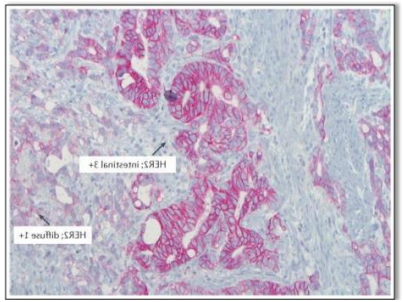
Agenda

- Biomarkers
- First line in HER2 advanced gastric cancer
- TDX-D in second –third line
- **HER2 test**
- Questions for the future

✓ HER2 low
✓ Combination
✓ Management of toxicity
✓ Neoadjuvant/adjuvant setting

HER2 test

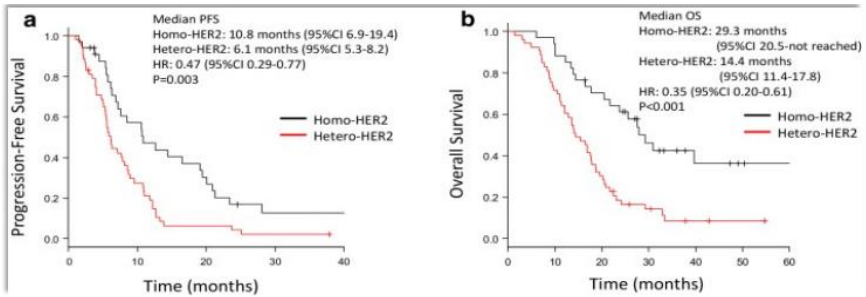
The challange of heterogeneity



TOGA HER2 heterogeneity by IHC score	
Heterogeneity = ≤ 30% staining	
IHC3+	30%

TOGA HER2 % of positive cells in IHC3 + patients				
% cells	<10%	10-30%	31-79%	≥80%
% patients	3%	27%	31%	39%

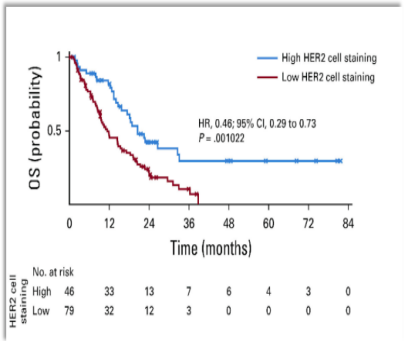
Heterogeneity and outcomes

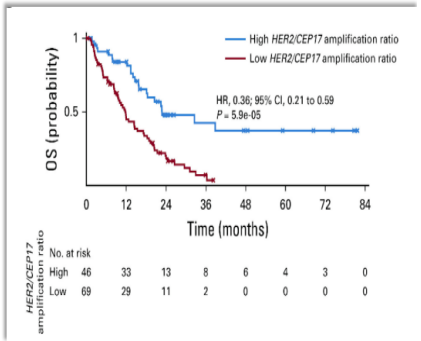


Japanese dataset HER2 treated GEA (n=87)
Homogenous HER2 3+ = all cells positive (40%)
↑ PFS and OS in HER2 3+ homogenous vs heterogenous

HER2 test

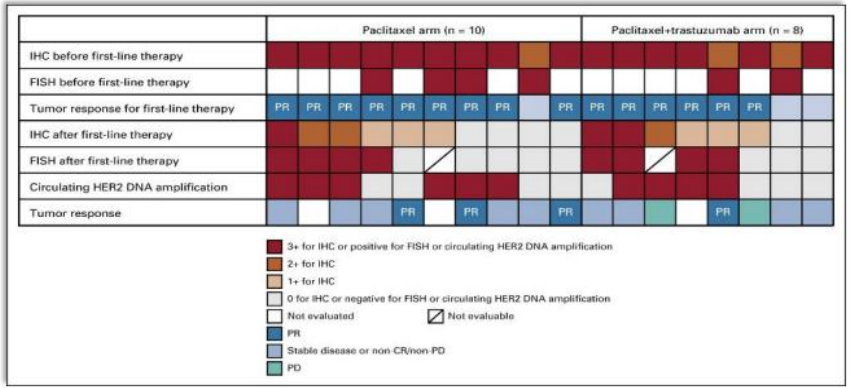
Can we define a better cut off?





German VARIANZ study Suggested optimised cut offs for benefit from 1L trastuzumab 40% cells positive for HER2 CEP17:HER2 ratio ≥3.0

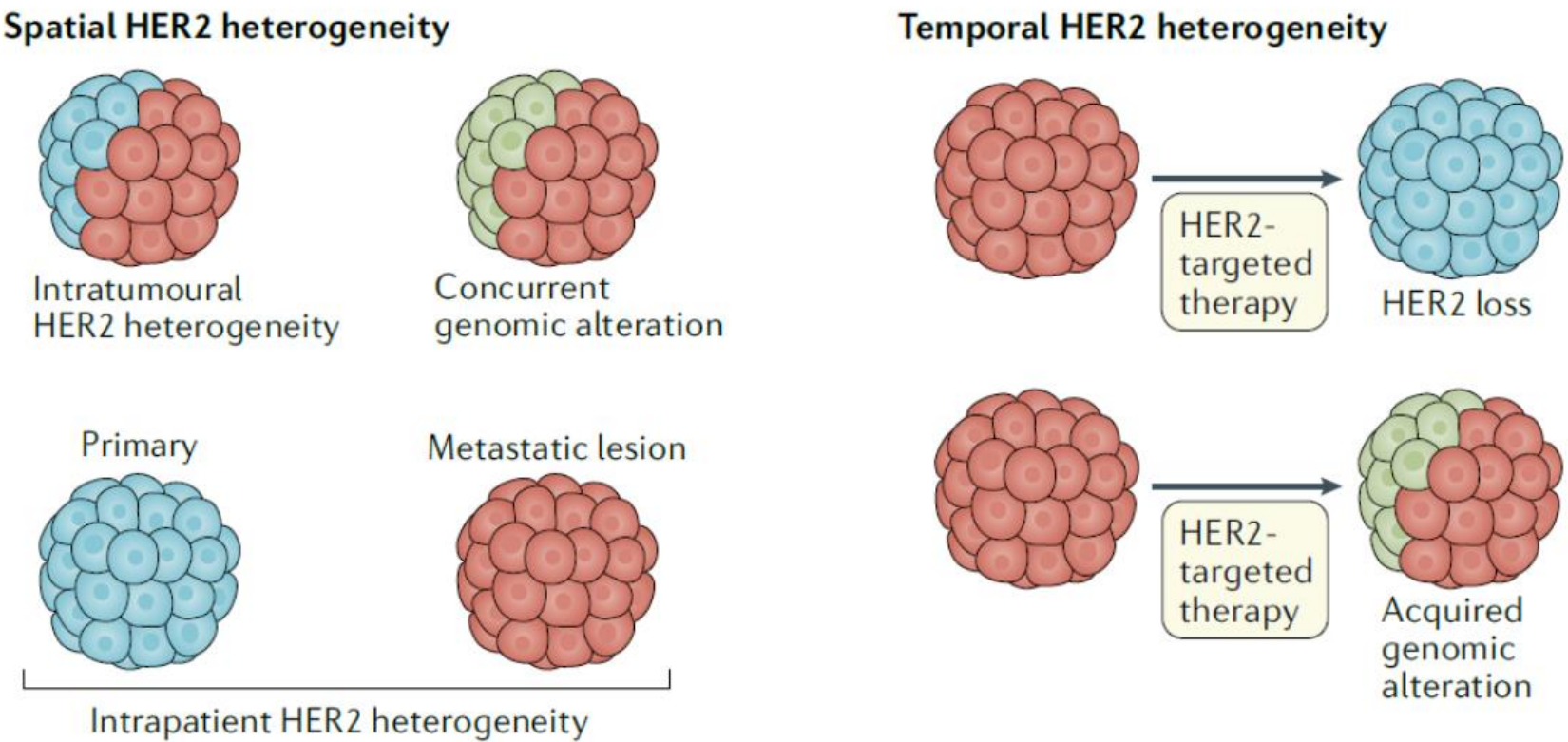
The dynamic nature of Her2



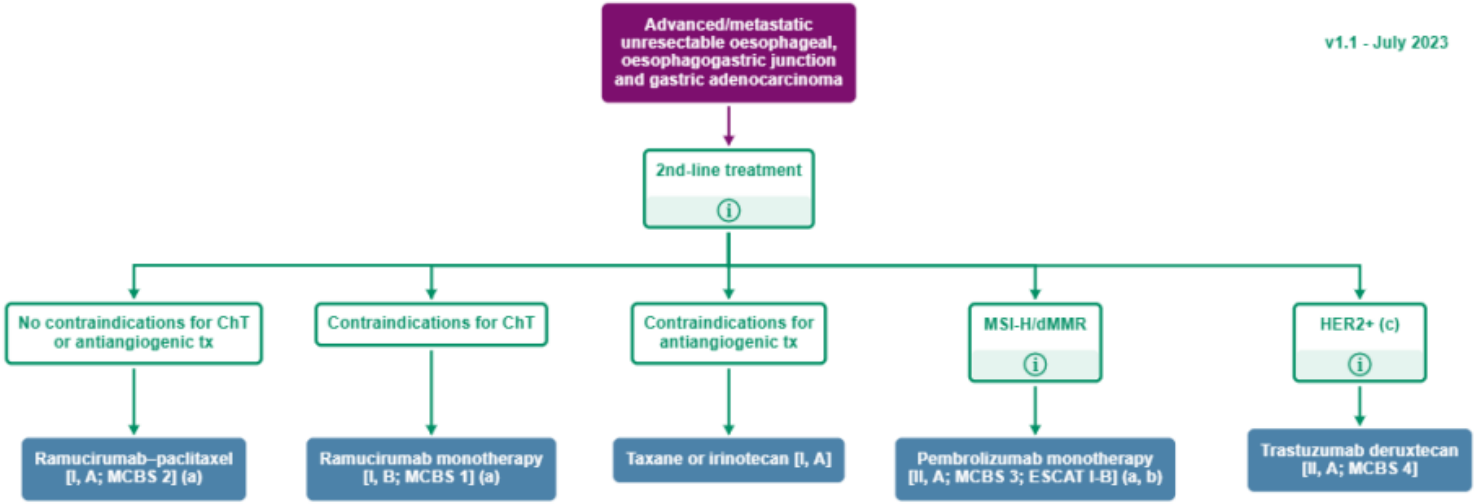
Italian registry study Change in HER2 status positive to negative 32% More common in IHC2+ than IHC3+ patients

T-ACT trial Paclitaxel vs paclitaxel/trastuzumab 69% of patients did not have retained HER2 expression after 1L trastuzumab

Precision medicine in HER2 + gastric cancer



ESMO guidelines



- Trastuzumab deruxtecan is recommended for patients with HER2-positive advanced gastric cancer who have received a prior trastuzumab-based regimen [I, A; **ESMO-MCBS v1.1 score: 4**]. Re-biopsy is recommended when possible.

Agenda

- Biomarkers
- First line in HER2 advanced gastric cancer
- TDX-D in second –third line
- HER2 test
- **Questions for the future**

✓ HER2 low
✓ Combination
✓ Neoadjuvant/adjuvant setting

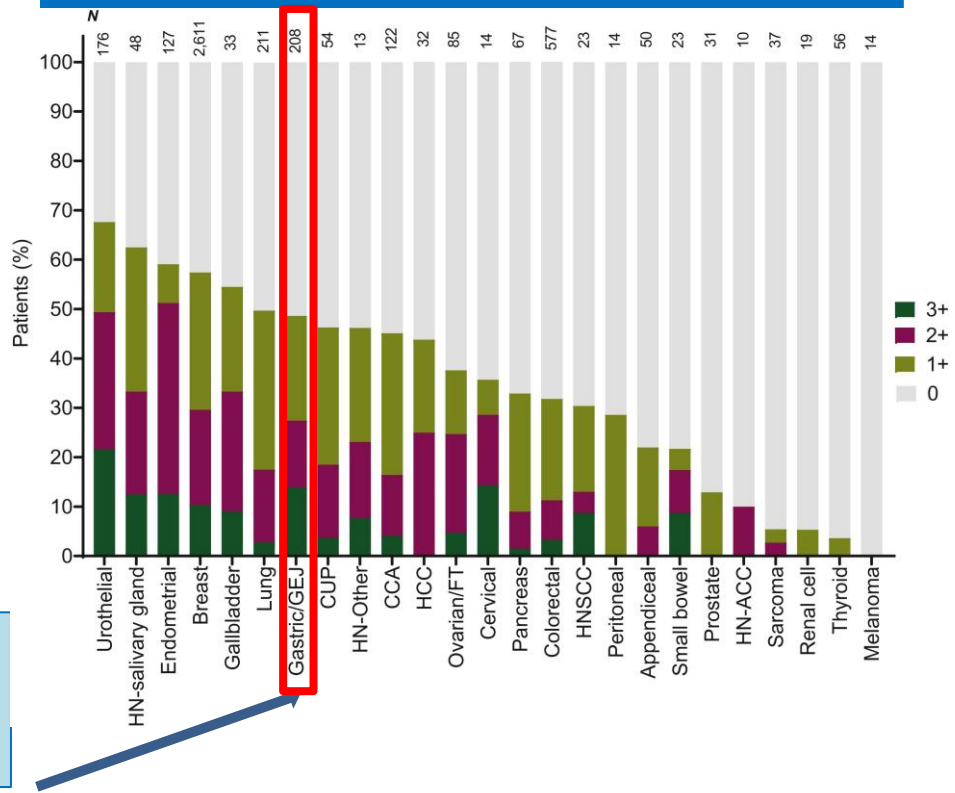
Questions for the future: HER2 low

HER2 low Italian study

1210 formalin-fixed paraffin-embedded samples
HER2-low was 28.3% (95% CI 25.8% to 31.0%) overall, and was **higher in biopsy specimens** compared with surgical resection specimens (34.9 vs 21.0%) (p<0.0001).
HER2-low prevalence ranged from 19.1% to 40.6% among centres (p=0.0005)
J Clin Pathol. 2023 Apr

HER2 expression by IHC was evaluated in 4701 patient.
Annals of Oncology Aug 2023

HER2 low MD Anderson



Questions for the future: HER2 low

HER2 low MD Anderson

B

		HER2 Metastasis *n*, %			
		HER2-negative	HER2-low	HER2-positive	Total
HER2 Primary *n*, %	HER2-negative	20 (95.2)	0	1 (4.8)	21
	HER2-low	0	0	1 (100.0)	1
	HER2-positive	1 (33.3)	1 (33.3)	1 (33.3)	3
Total		21 (84.0)	1 (4.0)	3 (12.0)	25

	0	1+	2+	3+	total
Gastric/GEJ	107 **(51.4)**	44 (**21.2**)	28 (**13.5**)	29 (**13.9**)	208

34.6 % patients had HER2 low tumor

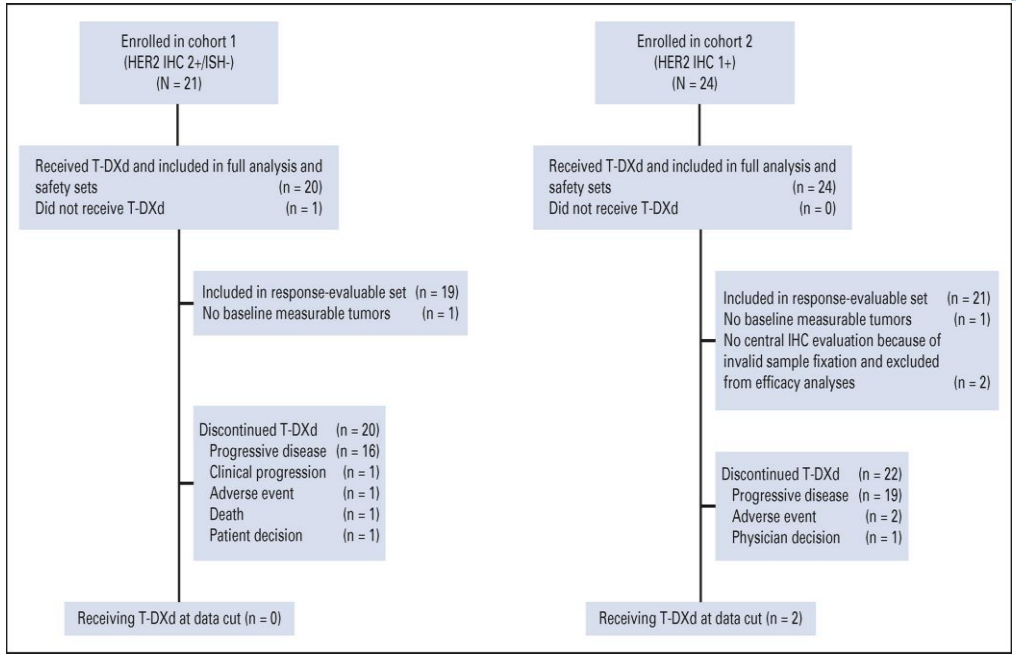
HER2 status between primary and metastatic

HER2-positive (HER2 3+ or 2+/ISH amplified) versus HER2-negative (all other HER2 status)

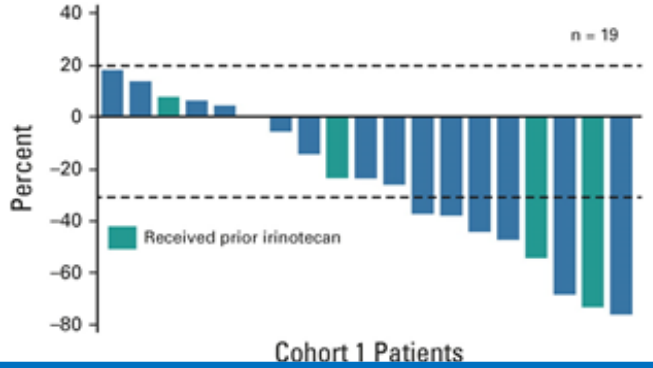
Only 25/208 paired primary and metastatic samples were identified out of 48 samples of gastric/GEJ Most patients with HER2-negative gastric/GEJ cancers remained negative at re-testing on metastatic samples (95.2%), whereas only 33% of HER2-positive cancers remained unchanged

Annals of Oncology Aug 2023

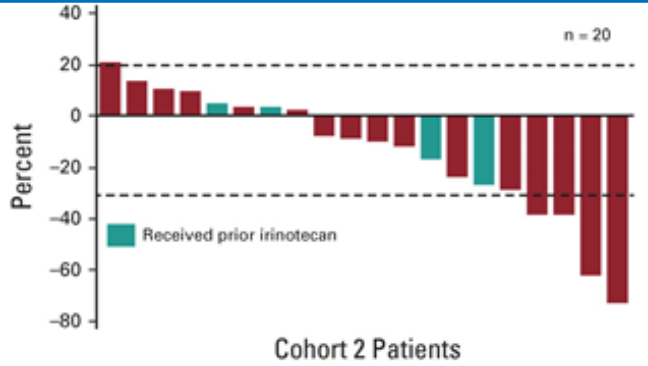
Trastuzumab Deruxtecan in Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial



Cohort 1 ORR 26.4%



Cohort 2 ORR 9.6%



J Clin Oncol 41:816-825. 2022

DESTINY-Gastric03 (D967LC00001)

Study of Trastuzumab Deruxtecan combinations in HER2 overexpressing Gastric/GEJ/Esophageal Cancer[1]

A phase 1b/2, multicenter, open-label, dose-escalation and dose-expansion trial of trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients with HER2 overexpressing, unresectable or metastatic gastric/gastroesophageal junction (GEJ) and esophageal adenocarcinoma (North America, South America, Europe, Asia)

Study Design

Population

- Metastatic or unresectable HER2 positive (IHC 3+ or 2+/ISH+) by local assessment GC/GEJ/esophageal adenocarcinoma[b]
- ≥2L following trastuzumab-containing therapy

Part 1 – Dose escalation (3 + 3)[a]

Allocate

- Arm 1A: T-DXd + 5-FU Q3W
- Arm 1B: T-DXd + capecitabine Q3W
- Arm 1D(a): T-DXd + 5-FU + oxaliplatin Q3W
  Arm 1D(b): T-DXd + capecitabine + oxaliplatin Q3W
- Arm 1C: T-DXd + durvalumab Q3W
- Arm 1E(a): T-DXd + 5-FU + durvalumab Q3W
  Arm 1E(b): T-DXd + capecitabine + durvalumab Q3W

Endpoints

Primary: Safety and RP2D
Secondary: Confirmed ORR per RECIST v1.1, DoR, PFS, OS, PK
Exploratory: ctDNA and tissue samples for candidate biomarkers

Population

- Previously untreated metastatic or unresectable HER2 positive (IHC 3+ or 2+/ISH+) by local assessment GC/GEJ/esophageal adenocarcinoma[b]
- Stratified by HER2 status (IHC 3+ or IHC 2+/ISH+)

Part 2 – Dose expansion: RP2D from Part 1
N≈40 patients/arm

Randomize

- Arm 2A[c]: SoC (trastuzumab + FP[d] + platinum[e])
- Arm 2B[c]: T-DXd monotherapy[f] Q3W
- Arm 2C: T-DXd + chemotherapy (FP[d] ± oxaliplatin)
- Arm 2D: T-DXd + chemotherapy (FP[d]) + pembrolizumab Q3W
- Arm 2E: T-DXd + pembrolizumab Q3W

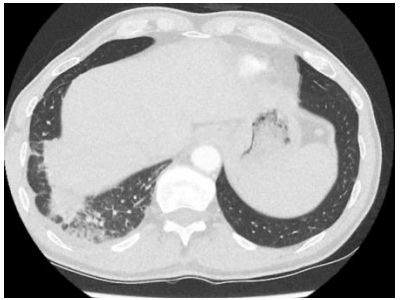
Endpoints

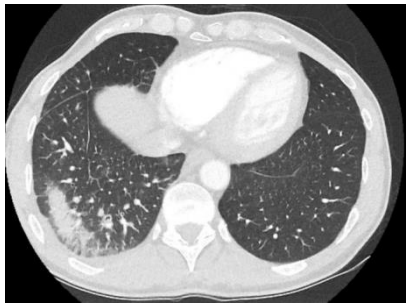
Primary: Confirmed ORR per RECIST v1.1
Secondary: Safety, DoR, PFS, OS, PK
Exploratory: ctDNA and tissue samples for candidate biomarkers

1. Janjigian Y, et al. Poster presented at: ESMO Virtual Congress; September 19-21, 2020. Poster 1500TiP.

Questions for the future

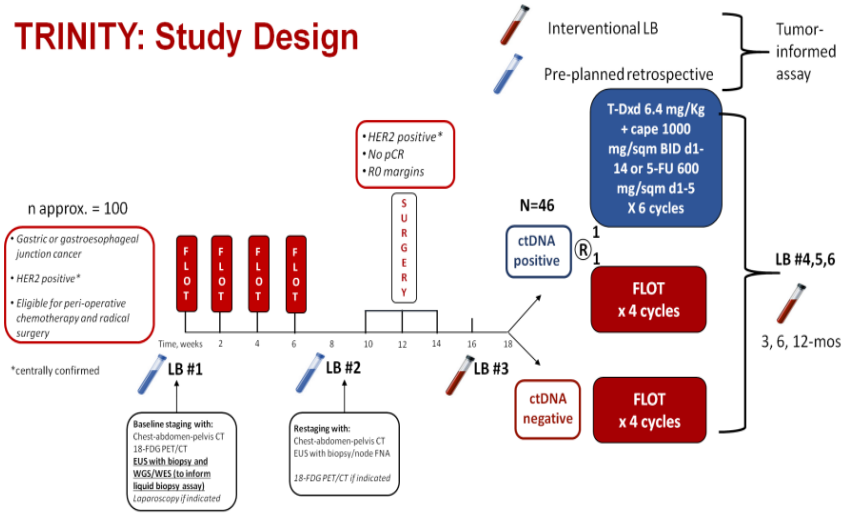
Management of toxicity





Interstitial lung disease ILD
7.6-10.4% of all grades
in gastric cancer trials
2.5% fatal in Destiny-02 (!)
Median time to onset ~80 days

Neoadiuvant/adjuvant setting



Conclusions

- TDX-D is the new standard tx in second and third line with higher ORR and OS
- Manageable toxicity (with experience)
- HER2 status a new landscape
- Waiting for the next data from phase III trials

INNOVAZIONE IN ONCOLOGIA

TRA RICERCA E SOSTENIBILITÀ

26 OTTOBRE

RAVENNA

08.30 Registrazione partecipanti

09.00 Apertura lavori
Saluti delle Autorità

09.30 Introduzione **S. Tamberi**

I SESSIONE
L'esperienza della Regione Emilia Romagna
Moderatori: M. C. Silvani, C. Masini

09.40 La commissione Regionale del farmaco **A.M. Marata**
10.00 GREFO: il presente e il futuro **G. Longo**
10.20 Gestione delle eccezioni prescrittive: Commissioni del farmaco a confronto
- CF AVR **L. Rossi, S. Tamberi**
- CF AVEC **A. C. Tardi, C. Descovich**
- CF AVEN **L. Daya, G. Mazzi**

10.50 Discussione

11.10 Pausa caffè

II SESSIONE
Il futuro tra innovazione e sostenibilità
Moderatori: F. Pieraccini, F. Falcini

11.40 Innovazione in oncologia e non solo **N. Magrini**
12.00 Sostenibilità in oncologia: una missione possibile? **E. Sangiorgi**
12.20 Il ruolo della Rete Oncologica dell'Emilia Romagna **R. De Palma**
12.40 Discussione

13.10 Pausa pranzo

III SESSIONE
Nuovi percorsi nell'innovazione
Moderatori: A. Frassoldati, G.L. Frassineti

14.30 Nuovi farmaci e tumori rari
Metodologia scientifica e nuovi percorsi di registrazione dei farmaci
V. Fausti
Discussant: **C. Rondoni**

15.00 Early access: il caso del tumore della mammella HER2 low
Trastuzumab Deruxtecan: le evidenze scientifiche **C. Zamagni**
Discussant: **L. Magnano**

15.30 Molecular tumor board e medicina di precisione
Profilazione genomica: è sempre il target il vero driver? **C. Bennati**
Discussant: **C. Masini**

16.00 Conclusioni **S. Tamberi**

Stefano Tamberi
Direttore Unità Operativa di Oncologia Ravenna
AUSL Romagna

FACULTY

Chiara Bennati, Ravenna
Lisa Daya, Carpi e Mirandola (MO)
Rossana De Palma, Bologna
Carlo Descovich, Bologna
Fabio Falcini, Forlì
Valentina Fausti, Meldola (FC)
Giovanni Luca Frassineti, Meldola (FC)
Antonio Frassoldati, Ferrara
Giuseppe Longo, Modena
Lucia Magnano, Bologna
Nicola Magrini, Roma
Anna Maria Marata, Modena
Carla Masini, Meldola (FC)
Giorgio Mazzi, Reggio Emilia
Fabio Pieraccini, Forlì
Cristina Rondoni, Ravenna
Lucia Rossi, Rimini
Elisa Sangiorgi, Bologna
Maria Chiara Silvani, Ravenna
Stefano Tamberi, Ravenna
Anna Chiara Tardi, Bologna
Claudio Zamagni, Bologna

RAZIONALE SCIENTIFICO

Il crescente sviluppo di nuovi farmaci in ambito oncologico necessita di una attenta e profonda riflessione sull'efficacia e sostenibilità dell'innovazione farmacologica. Il Convegno ha lo scopo di permettere un confronto tra decisori istituzionali, oncologi e farmacisti per approfondire cosa significhi "Innovazione", "Sostenibilità" e quali siano i percorsi adeguati a rendere disponibili le migliori terapie ai pazienti. Tuttavia, la riflessione si rende necessaria anche per specifici ambiti di innovazione terapeutica, in particolare le terapie target e il ruolo dei molecular tumor board, i tumori rari e la necessità di comuni percorsi per l'Early access. Il convegno permette quindi un aggiornamento e confronto su tematiche estremamente rilevanti per la sostenibilità del SSN