

# Advances in Esophageal Cancer Oncologic Therapy

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# Learning Objectives:

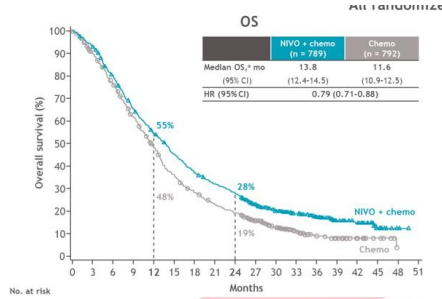
- Novel targeted therapies / immunotherapies in Metastatic Disease
- Changes in Standard of Care for Locoregional Disease



= Practice Changing !

**Disclosures** (Consulting/Speaker's Bureau/Honoraria): Astellas, Astrazeneca, BeOne, Ipsen, Jazz, Takeda

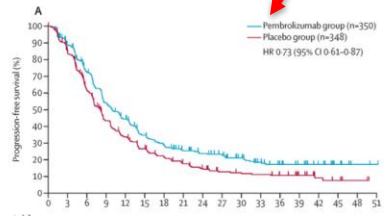
# Evolution of first-line therapy in gastric cancer



**2010**  
 ERBB2/HER2  
 Trastuzumab/Chemo

**2008**  
 Oxaliplatin

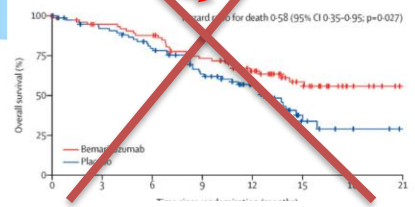
**1994**  
 5FU



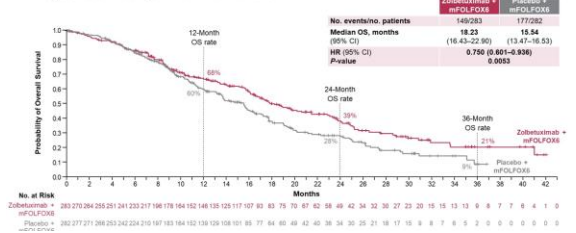
**2021**  
 PDL1  
 Irrespective of PDL1  
 Nivolumab/Chemo  
 ERBB2/HER2  
 Pembrolizumab/Trastuzumab/Chemo

**2023**  
 CLDN18.2  
 Zolbetuximab/Chemo  
 Pending FDA

~~FGFR2b~~

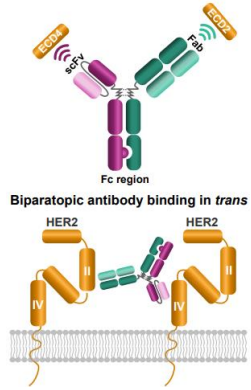


**Key Secondary End Point: OS**



Scheithauer et al Ann Hematol 1994; Al-Batran *et al* J. Clin Oncol 2008; Bang *et al* Lancet 2010; Janjigian YY, Shitara K *et al* Lancet 2021; Janjigian YY Nature 2021; Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

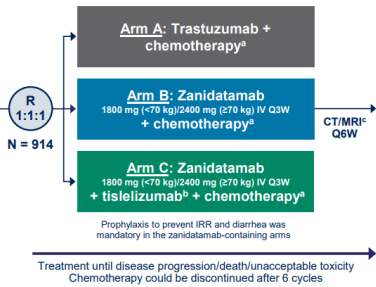
# HERIZON-GEA-01: Her-2 +



## HERIZON-GEA-01 Study Design

Global phase 3 trial of *zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ mGEA*

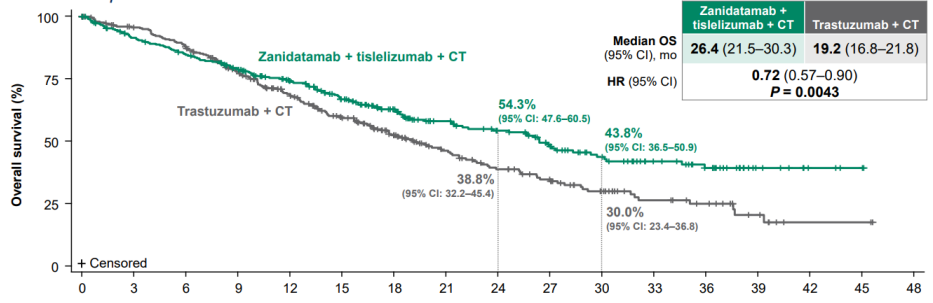
- Key Eligibility Criteria**
- Age ≥18 years
  - Unresectable, locally advanced, recurrent or metastatic GEA
  - HER2 IHC 3+ or IHC 2+ /ISH+ per central testing
  - ECOG PS 0 or 1
  - No prior treatment for locally advanced or metastatic disease
  - No prior HER2-targeted agents or immunotherapy in any setting
- Stratification Factors**
- Geographic region
  - HER2 status
  - ECOG PS



- Dual Primary Endpoints**
- PFS (per BICR)
  - OS
- Select Secondary Endpoints**
- cORR (per BICR)
  - Frequency and severity of AEs
- ClinicalTrials.gov: NCT05152147

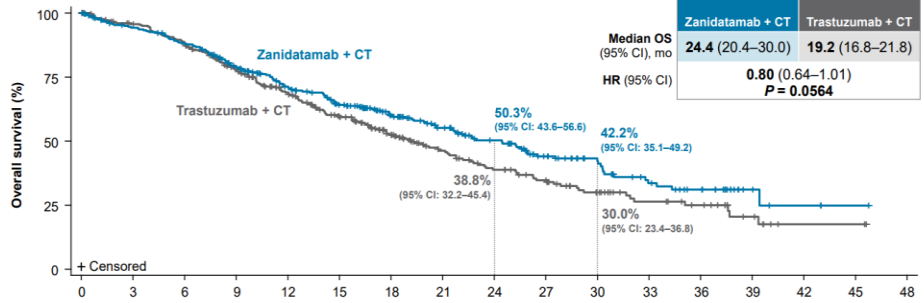
## Primary Endpoint: Overall Survival

Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT



## Primary Endpoint: Overall Survival

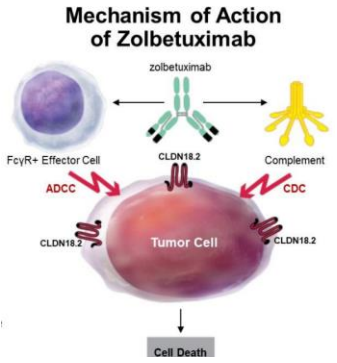
At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



**Zanidatamab > Trastuzumab**

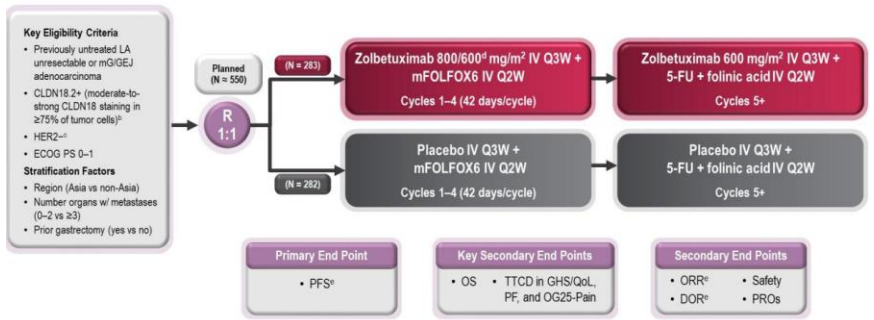
**UCI Health**

# Zolbetuximab: anti-CLDN18.2



## Study Design: SPOTLIGHT

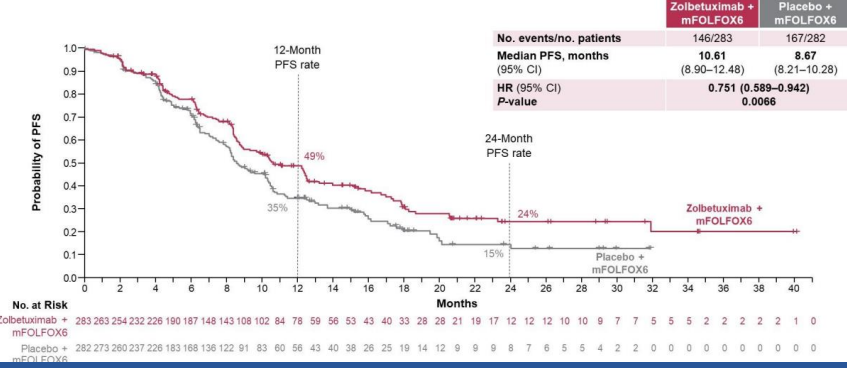
Global<sup>a</sup>, randomized, double-blinded, placebo-controlled, phase 3 trial



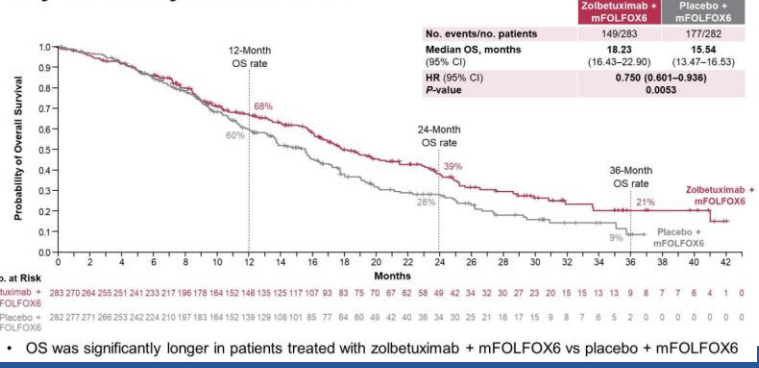
- Key Eligibility Criteria**
- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
  - CLDN18.2+ (moderate-to-strong CLDN18 staining in ≥75% of tumor cells)<sup>b</sup>
  - HER2-<sup>c</sup>
  - ECOG PS 0-1
- Stratification Factors**
- Region (Asia vs non-Asia)
  - Number organs w/ metastases (0-2 vs ≥3)
  - Prior gastrectomy (yes vs no)

- Primary End Point**
- PFS<sup>d</sup>
- Key Secondary End Points**
- OS
  - TTCd in GHS/OoL, PF, and OG25-Pain
- Secondary End Points**
- ORR<sup>e</sup>
  - Safety
  - DOR<sup>f</sup>
  - PROs

## Primary End Point: PFS by Independent Review Committee<sup>a</sup>



## Key Secondary End Point: OS

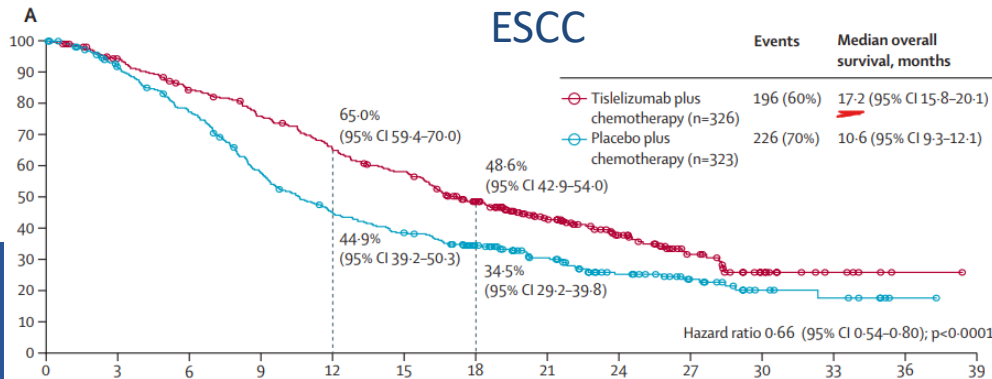
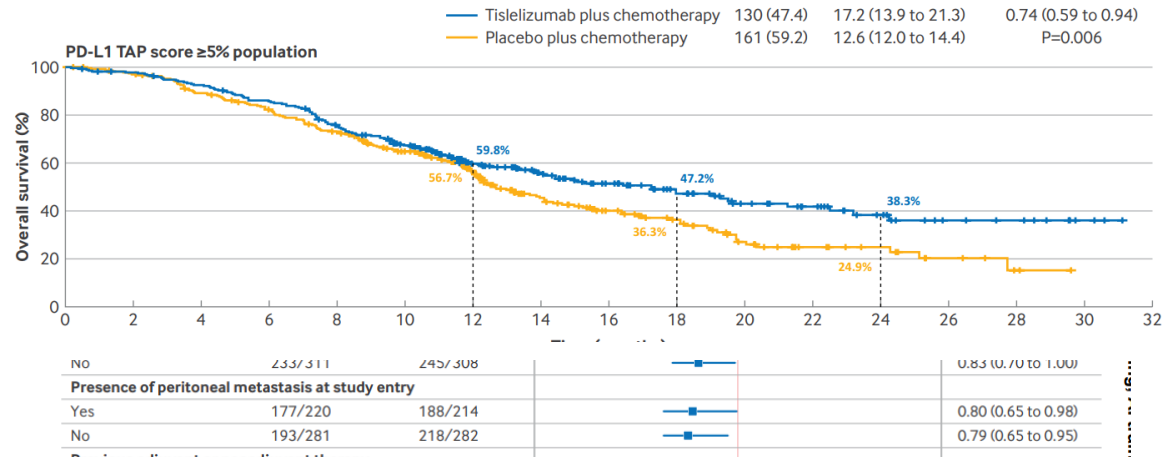


OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

# Tislelizumab: anti-PD1 (Rationale 305 and 306)

- Binds to PD-1, blocking its interaction with PD-(L)1 and PD-(L)2
- Designed to minimize binding to Fc-gamma (Fcγ) receptors on macrophages

## GEA



# Locoregional Disease

## The Beginning of the End (for XRT)

# Evolution of Esophageal Cancer Therapy

2006

2012

2017

2023

MAGIC

CROSS

FLOT-4

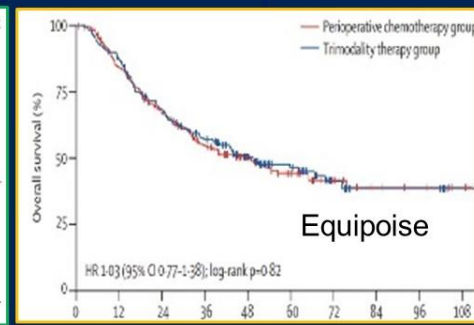
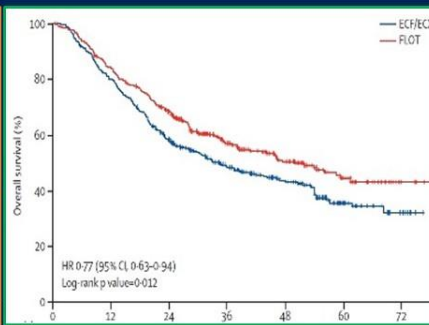
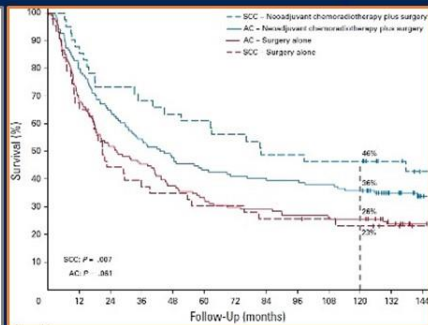
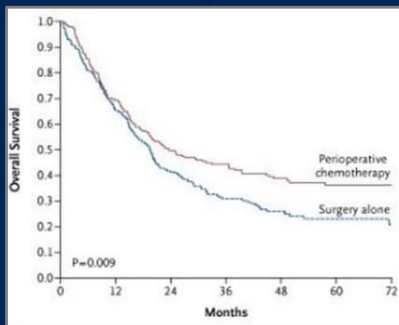
Neo-AEGIS

Peri-Op CT v.  
Surgery Alone

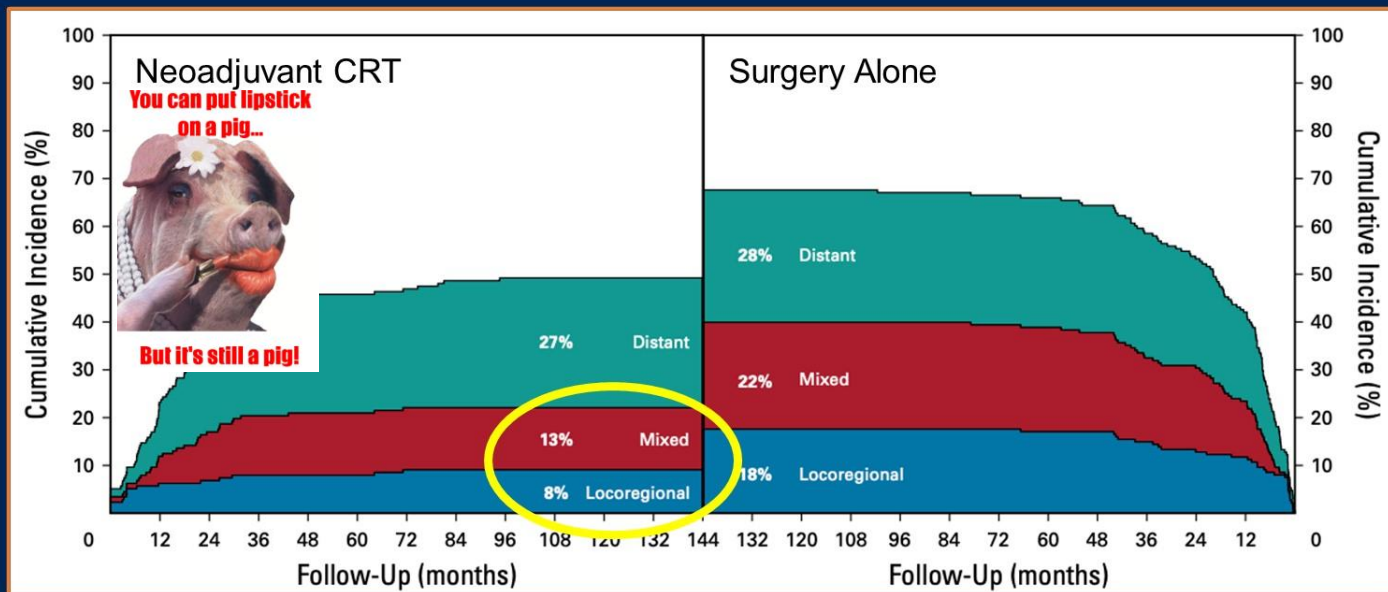
Pre-Op CRT v.  
Surgery Alone

Peri-Op ECF/ECX  
v. Peri-op FLOT

Peri-Op ECF/ECX/FLOT  
v. Pre-Op CRT



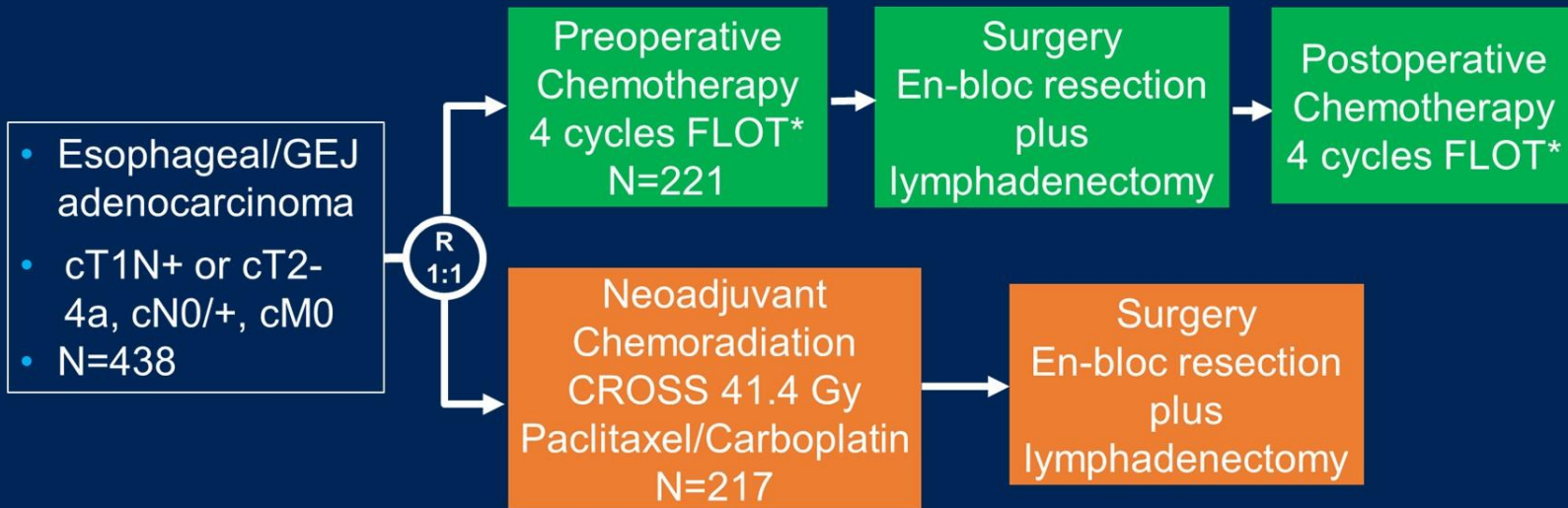
# CROSS Trial: Neoadjuvant Chemoradiotherapy



No benefit in distant relapse rates with low-dose radiosensitizing chemotherapy

Eyck BM, J Clin Oncol, 2021

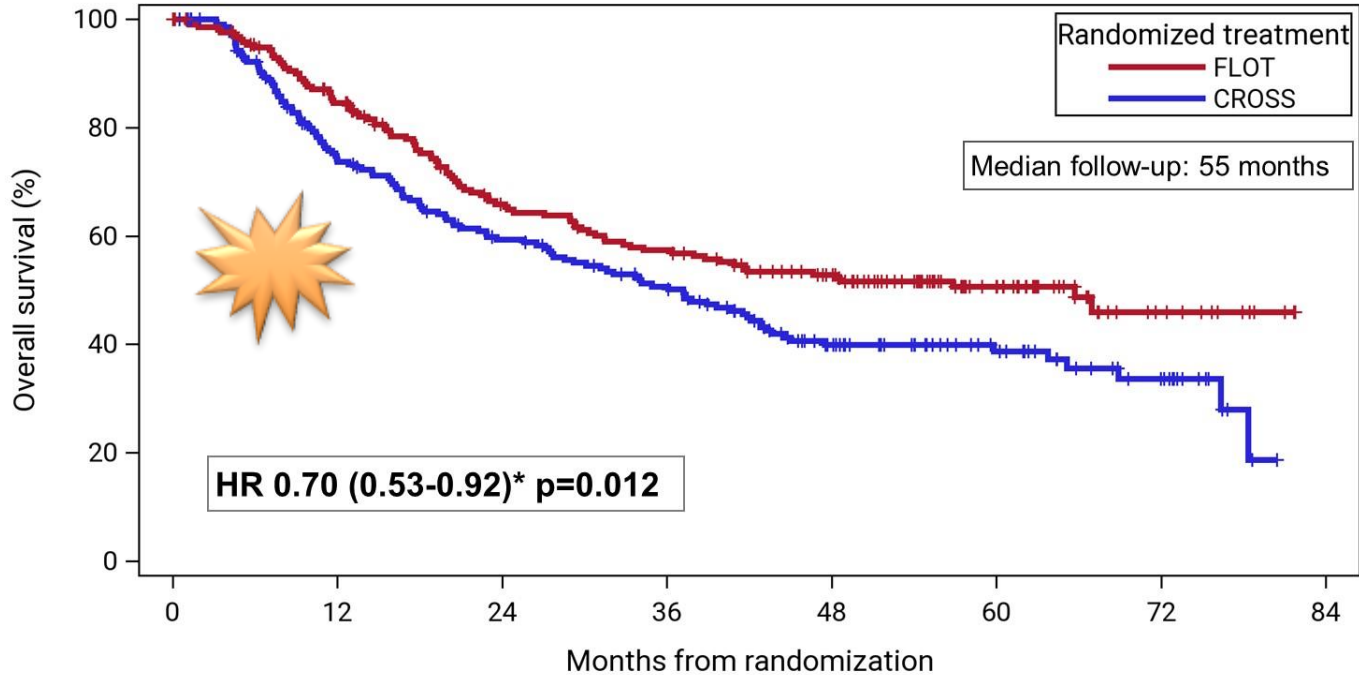
# ESOPEC Trial: Peri-Operative FLOT v. Neoadjuvant Chemoradiation



\*5-FU, Leucovorin, Oxaliplatin, Docetaxel

*Hoepfner J, Proc ASCO, 2024*


# Overall Survival - ITT Population



FLOT	221	172	124	107	84	44	11	0
CROSS	217	146	113	92	54	32	15	0

	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

# Pathology Results – Surgery Population

	FLOT Group	CROSS Group
<b>N</b>	<b>191</b>	<b>180</b>
<b>Resection status</b>		
<b>No resection</b>	<b>0.5%</b>	<b>1.1%</b>
<b>R0</b>	<b>94.2%</b>	<b>95.0%</b>
<b>R1</b>	<b>5.2%</b>	<b>3.9%</b>
<b>Postoperative N-Stage</b>		
<b>ypN-</b>	<b>50.8%</b>	<b>54.4%</b>
<b>ypN+</b>	<b>48.7%</b>	<b>44.4%</b>
<b>Pathological complete remission</b>		
<b>ypT0 ypN0</b>	<b>16.8%</b>	<b>10.0%</b> 
<b>Tumor regression grade (Becker<sup>1</sup>)</b>		
<b>Complete regression</b>	<b>18.3%</b>	<b>13.3%</b>
<b>Near complete regression (&lt;10% vital tumor)</b>	<b>25.1%</b>	<b>39.4%</b>

per local pathology assessment

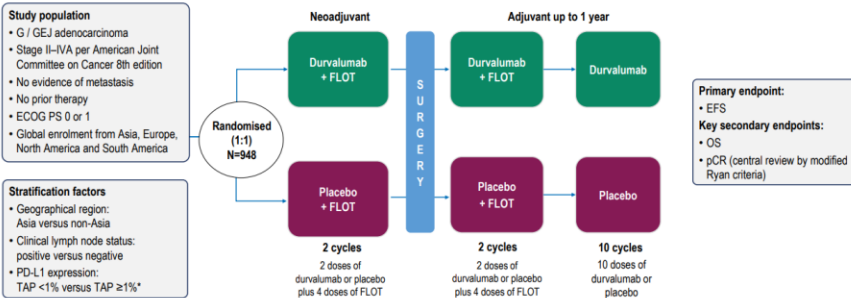
What about immune checkpoint  
inhibitors?

## Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer

Y.Y. Janjigian,<sup>1</sup> S.-E. Al-Batran,<sup>2</sup> Z.A. Wainberg,<sup>3</sup> K. Muro,<sup>4</sup> D. Molena,<sup>5</sup> E. Van Cutsem,<sup>6</sup> W.J. Hyung,<sup>7</sup> L. Wyrwicz,<sup>8</sup> D.-Y. Oh,<sup>9</sup> T. Omori,<sup>10</sup> M. Moehler,<sup>11</sup> M. Garrido,<sup>12</sup> S.C.S. Oliveira,<sup>13</sup> M. Liberman,<sup>14</sup> V.C. Oriden,<sup>15</sup> E.C. Smyth,<sup>16</sup> A. Stein,<sup>17</sup> M. Bilici,<sup>18</sup> M.L. Alvarenga,<sup>19</sup> V. Kozlov,<sup>20</sup> F. Rivera,<sup>21</sup> A. Kawazoe,<sup>22</sup> O. Serrano,<sup>23</sup> E. Heilbron,<sup>24</sup> A. Negro,<sup>24</sup> J.F. Kurland,<sup>24</sup> and J. Taberero,<sup>25</sup> for the MATTERHORN Investigators\*

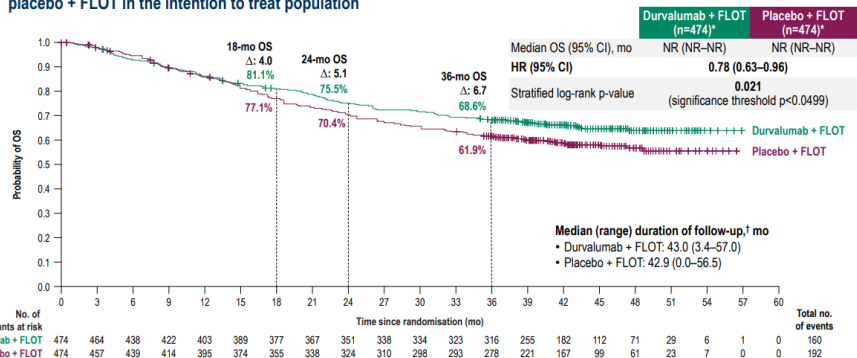
## MATTERHORN study design<sup>1,2</sup>

MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study



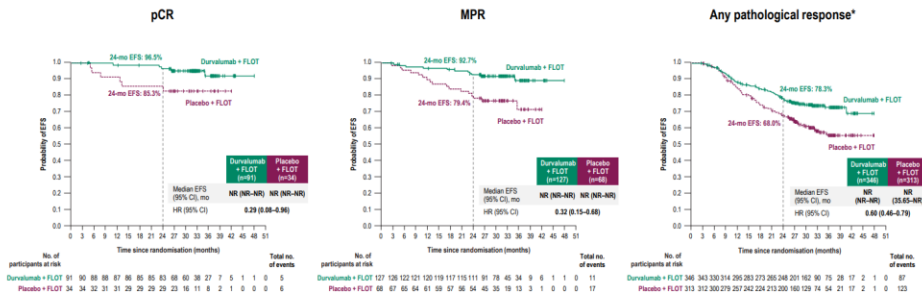
## Final OS

Durvalumab + FLOT demonstrated a statistically significant and clinically meaningful improvement in OS versus placebo + FLOT in the intention to treat population



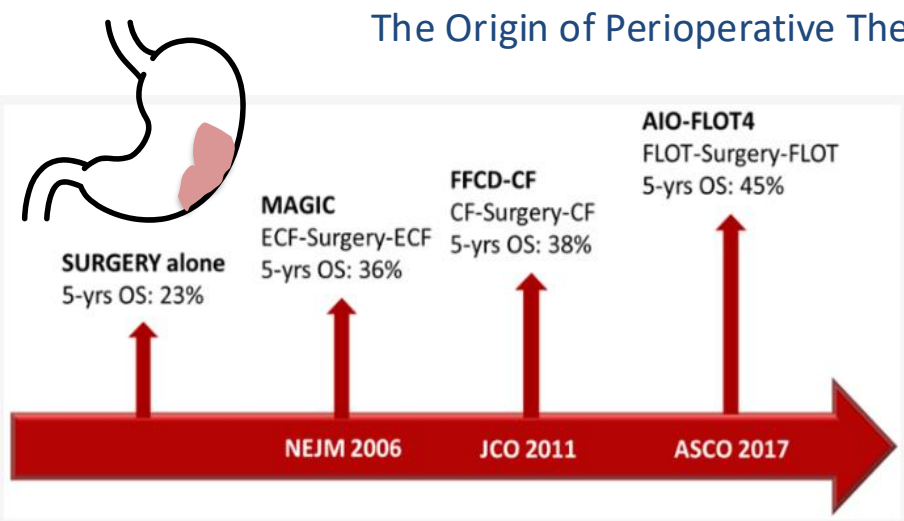
## Pathological response and EFS

EFS was improved with durvalumab + FLOT versus placebo + FLOT among participants with any degree of pathological response

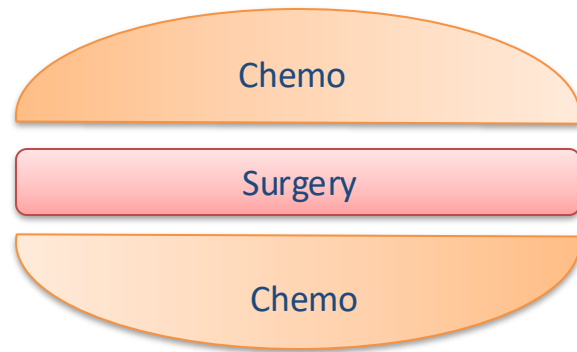


Longer Neoadjuvant Treatment?  
All Neoadjuvant Treatment?  
Total Neoadjuvant Treatment?

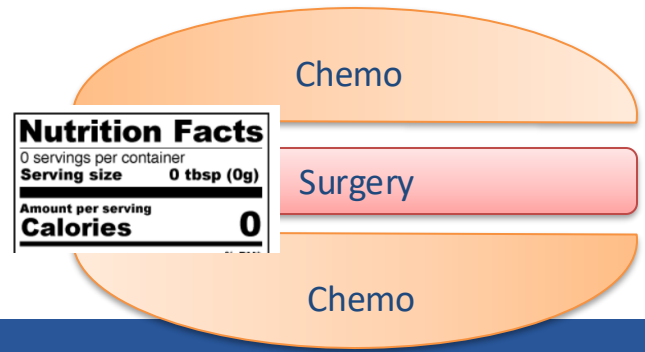
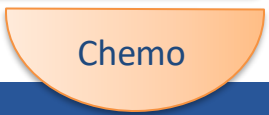
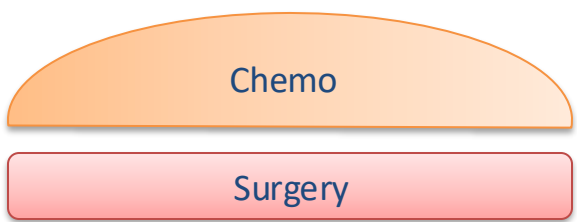
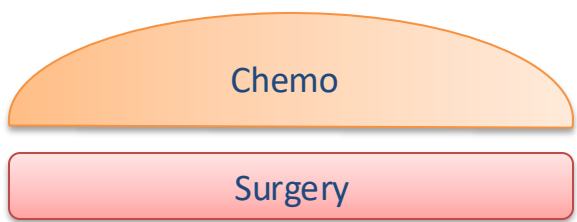
# The Origin of Perioperative Therapy for Gastric Cancer



“Standard”



Reality:



<b>Nutrition Facts</b>	
0 servings per container	
<b>Serving size</b>	<b>0 tbsp (0g)</b>
<b>Amount per serving</b>	<b>0</b>
<b>Calories</b>	<b>0</b>

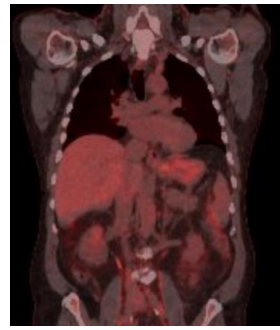
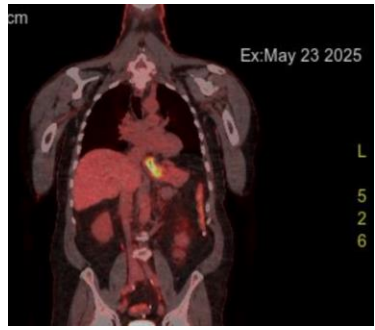
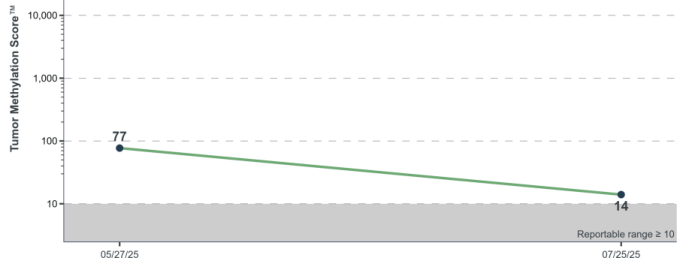
# Response Adapted Neoadjuvant Therapy in Gastroesophageal Cancers (RANT-GC Trial)

## Conditions

Gastroesophageal Adenocarcinoma

## Locations

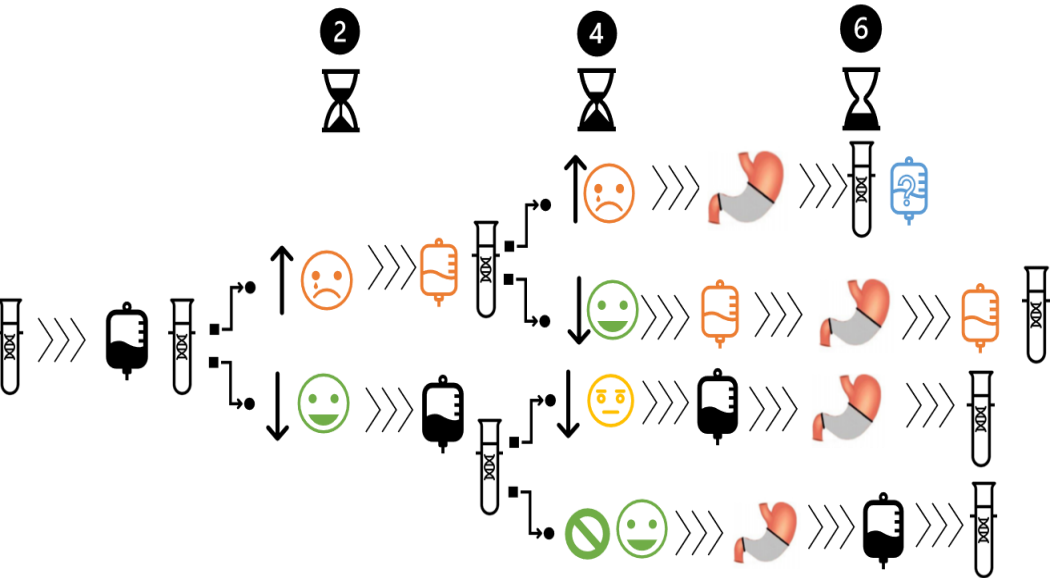
Orange, California, United States



### PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition)

Reporting of pT, pN, and (when applicable) pM categories is the pathologist's responsibility at the time the report is issued. As per the managing physician's responsibility to establish the final pathologic stage, the pathologist should report pertinent information, including but potentially not limited to:

TNM Descriptors: y (post-treatment)  
 pT Category: pT0  
 pN Category: pN0



# Conclusions

- Gastric or esophageal adenocarcinoma: perioperative FLOT > CROSS
- neoadjuvant antiPDL1 + FLOT: EFS, OS, pCR improved
- next Frontier in LAGEC: ? TNT (RANT-GC Trial UCI)
- Targets for Stage IV:
  - Established: MMR, Her-2, PDL1 (CPS), Cldn18.2
- Advanced Esophageal SCC: Tislelizumab+Chemo = 17 months mOS

**Thank you**

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