

# Updates in Treatment for Advanced Gastroesophageal Cancer

Jon Mizrahi, M.D.

Department of Hematology and Oncology  
Ochsner Cancer Institute

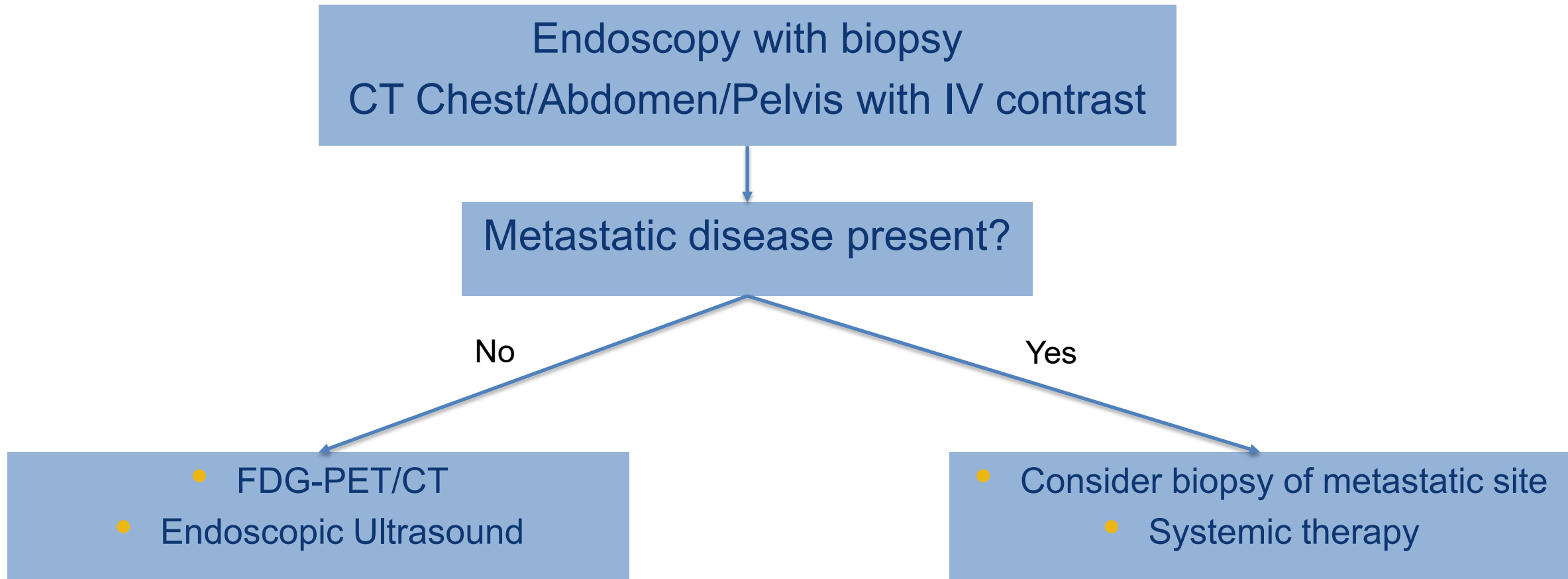
# Disclosures

- Speaking and Advisory Board: Exelixis, AstraZeneca
- Advisory Board: Seagen

# Outline

- Updates for Localized GE Cancers
- Immune Checkpoint Inhibitors in Advanced GE Cancers
- Targeted Therapies for Advanced GE Cancers
- Future Directions

# Diagnosis and Staging



# Treatment – Early Stage Esophageal

- cT1b-cT2 with positive LNs
- cT3-cT4 +/- LNs

Surgical Candidate (medical or anatomical reasons)?

No

Yes

- Definitive chemoradiation

Histology

SCC

Adenocarcinoma

Neoadjuvant chemoradiation  
followed by surgery

Neoadjuvant chemoradiation  
followed by surgery OR  
perioperative chemotherapy

# Treatment – Early Stage **Gastric**

- cT1b-cT2 with positive LNs
- cT3-cT4 +/- LNs

Surgical Candidate (medical or anatomical reasons)?

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Yes

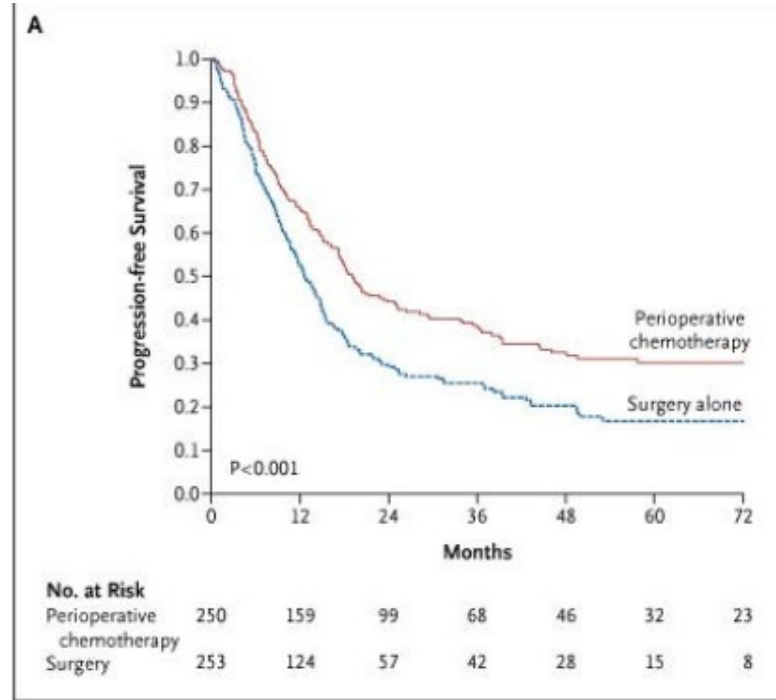
- Definitive chemoradiation (for fit patients) OR
  - Best supportive care

Perioperative chemotherapy

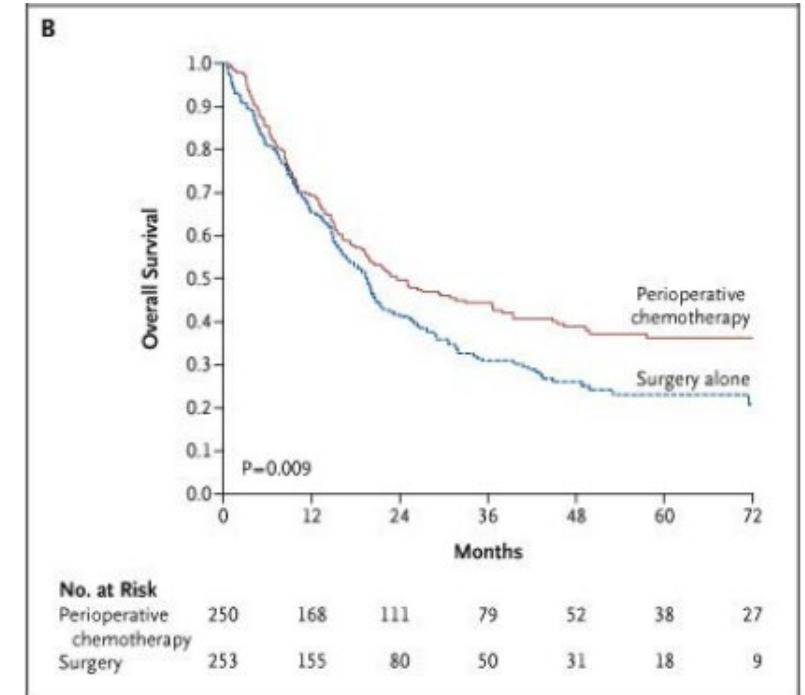
# Early Stage - Gastric/GEJ/Distal Esophageal

- MAGIC Trial – Perioperative ECF

PFS



OS



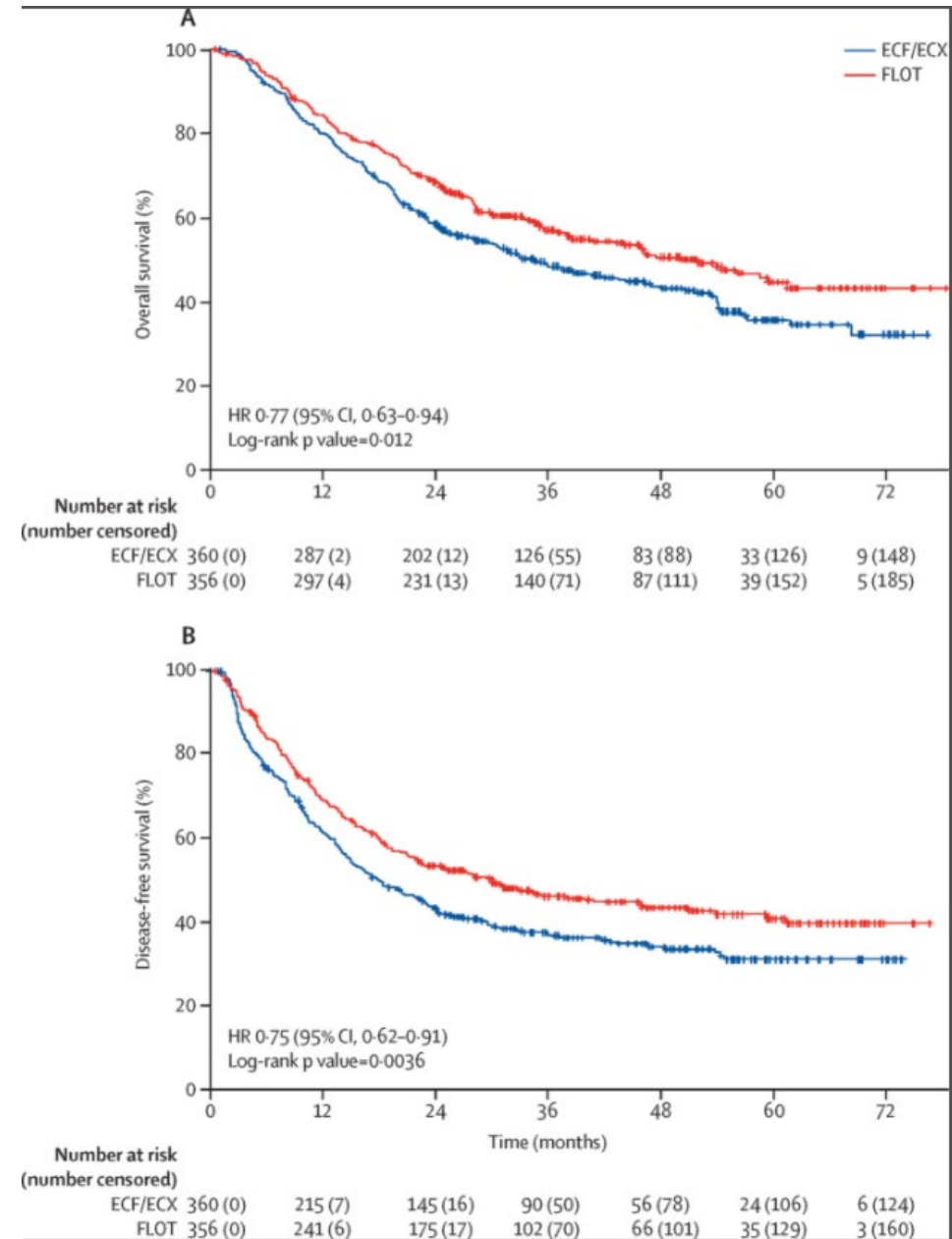
# Treatment – Early Stage Gastric/GEJ

- FLOT4-AIO Trial
  - FLOT vs ECF
  - Docetaxel 50 mg/m<sup>2</sup> + oxaliplatin 85 mg/m<sup>2</sup> + leucovorin 200 mg/m<sup>2</sup> + infusional 5-FU 2600 mg/m<sup>2</sup> over 24 hours administered every 2 weeks
  - Studied FLOT x 4 cycle → Surgery → FLOT x 4 cycles
  - FLOT compared to ECF:
    - ⊙ Higher pCR (16% vs 8%) in phase II portion
    - ⊙ mOS 50m vs 35m (HR 0.77)
    - ⊙ 3-year OS: 57% vs 48%



# Treatment – Early Stage

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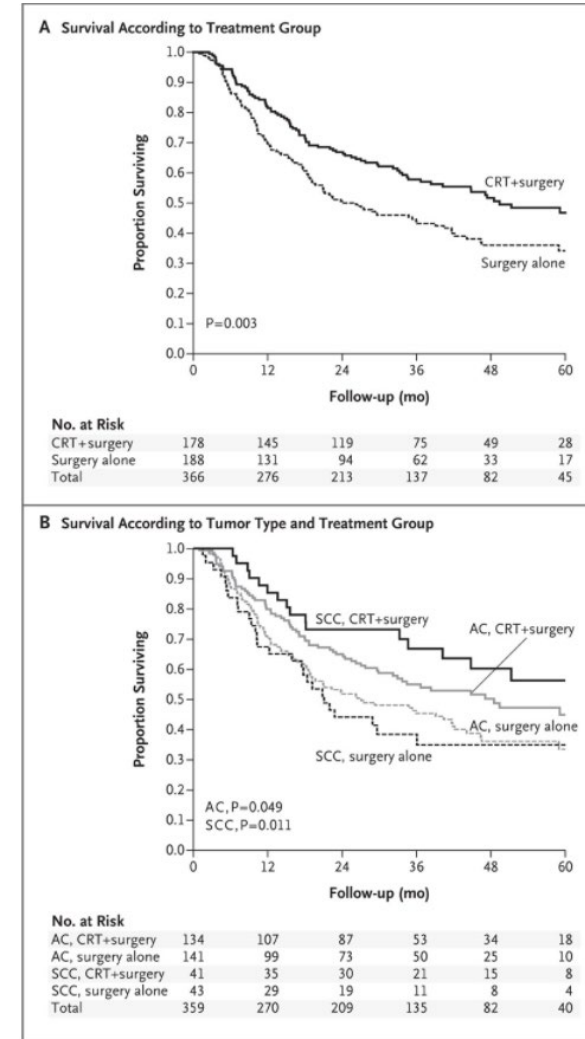


# Treatment – Early Stage - Esophageal

- CROSS Trial
  - Randomized resectable esophageal and GEJ patients to surgery alone or chemoradiation
  - Used carboplatin AUC 2 + paclitaxel 50 mg/m<sup>2</sup> weekly x 5 weeks with 41.4 Gy XRT
  - 75% adenocarcinoma
  - R0 resection 92% vs 69% (P<0.001)
  - pCR 29% of neoadjuvant CRT group

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  - 75% adenocarcinoma
  - R0 resection 92% vs 69% (P<0.001)
  - pCR 29% of neoadjuvant CRT group
  - mOS: 49.4 m vs 24.0 m (HR: 0.657, P=0.003)



Van Hagen et al. NEJM 2012.

# Treatment – Early Stage

**Standard of care for early stage ( $\geq$  T2 or N+, M0) gastric or GEJ (Siewart 3 +/- 2) adenocarcinoma is:**

**FLOT x 4 → SURGERY → FLOT x 4**

\*\* Only for most fit patients

\*\* For less fit patients, consider perioperative FOLFOX or CAPOX based on CLASSIC trial  
- Data extrapolated from adjuvant CLASSIC trial

**Standard of care for early stage esophageal ( $\geq$  T2 or N+, M0) or GEJ (Siewart 1 +/-2) SCC or adenocarcinoma is:**

**Chemoradiation (carboplatin + paclitaxel) → SURGERY → NIVOLUMAB**

\*\* For patients who do not achieve pCR

# CheckMate 577 study design

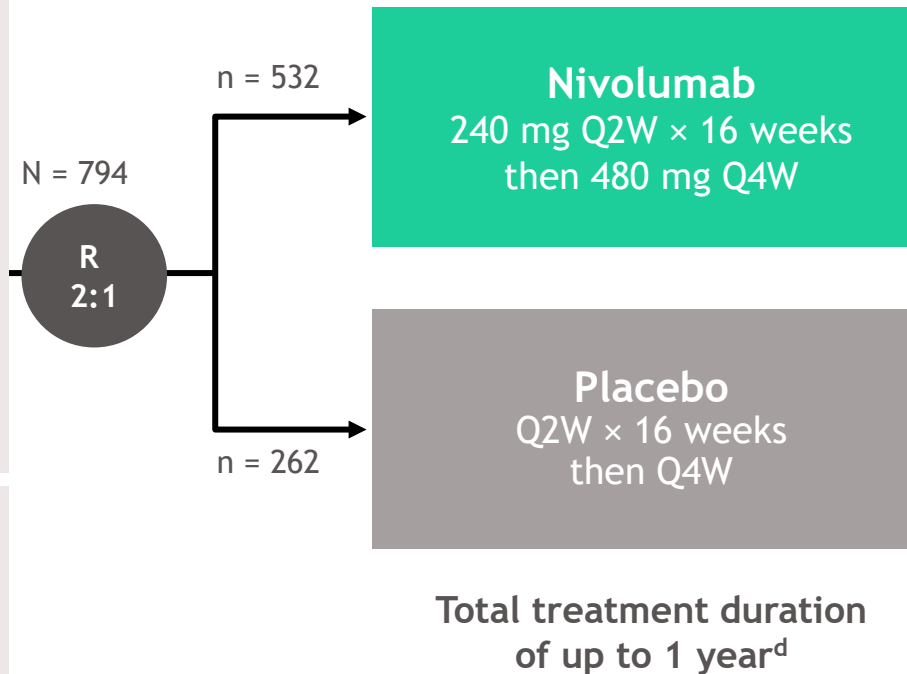
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial<sup>a</sup>

## Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,<sup>b</sup> performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

## Stratification factors

- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%)<sup>c</sup>



## Primary endpoint:

- DFS<sup>e</sup>

## Secondary endpoints:

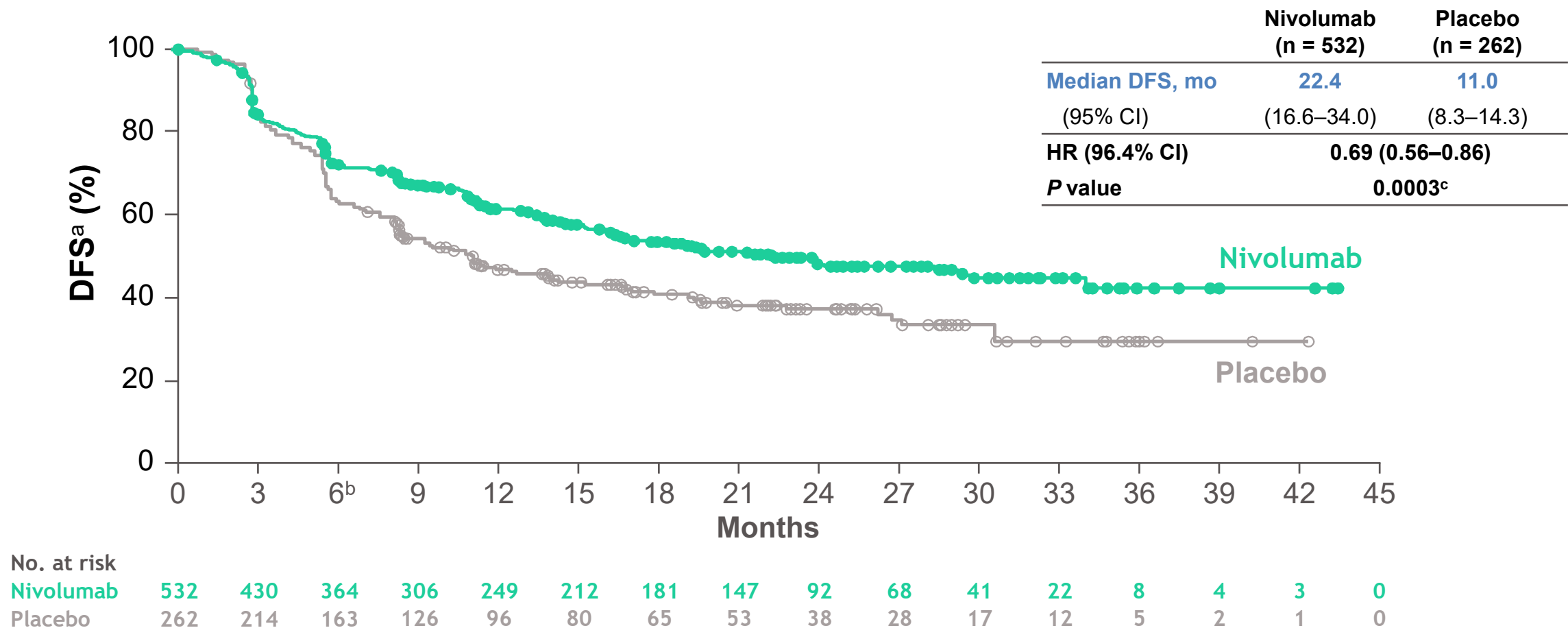
- OS<sup>f</sup>
- OS rate at 1, 2, and 3 years

## Exploratory endpoints included:

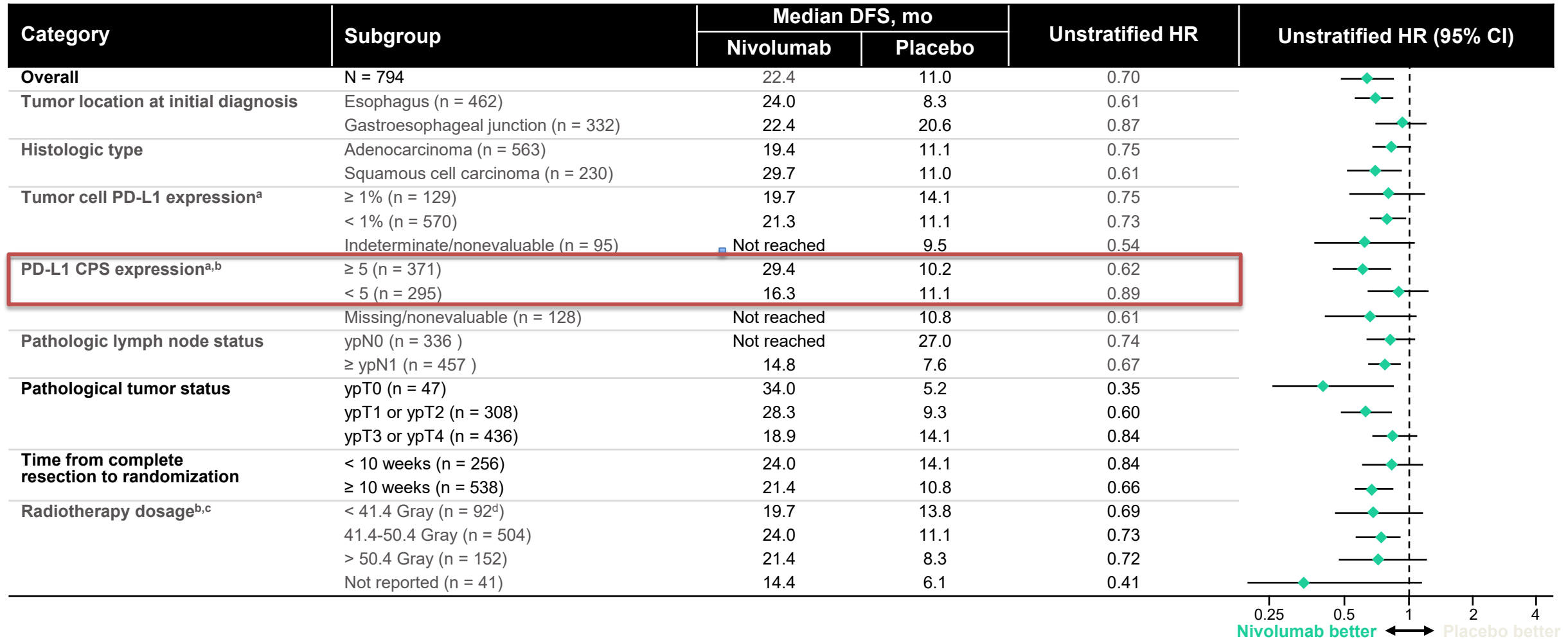
- Safety
- DMFS<sup>g</sup>
- PFS2<sup>h</sup>
- QoL

- Median follow-up was 24.4 months (range, 6.2-44.9)<sup>i</sup>
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

# Disease-free survival (DFS)



# Disease-free survival subgroup analysis



# Treatment – Early Stage

Unanswered question:

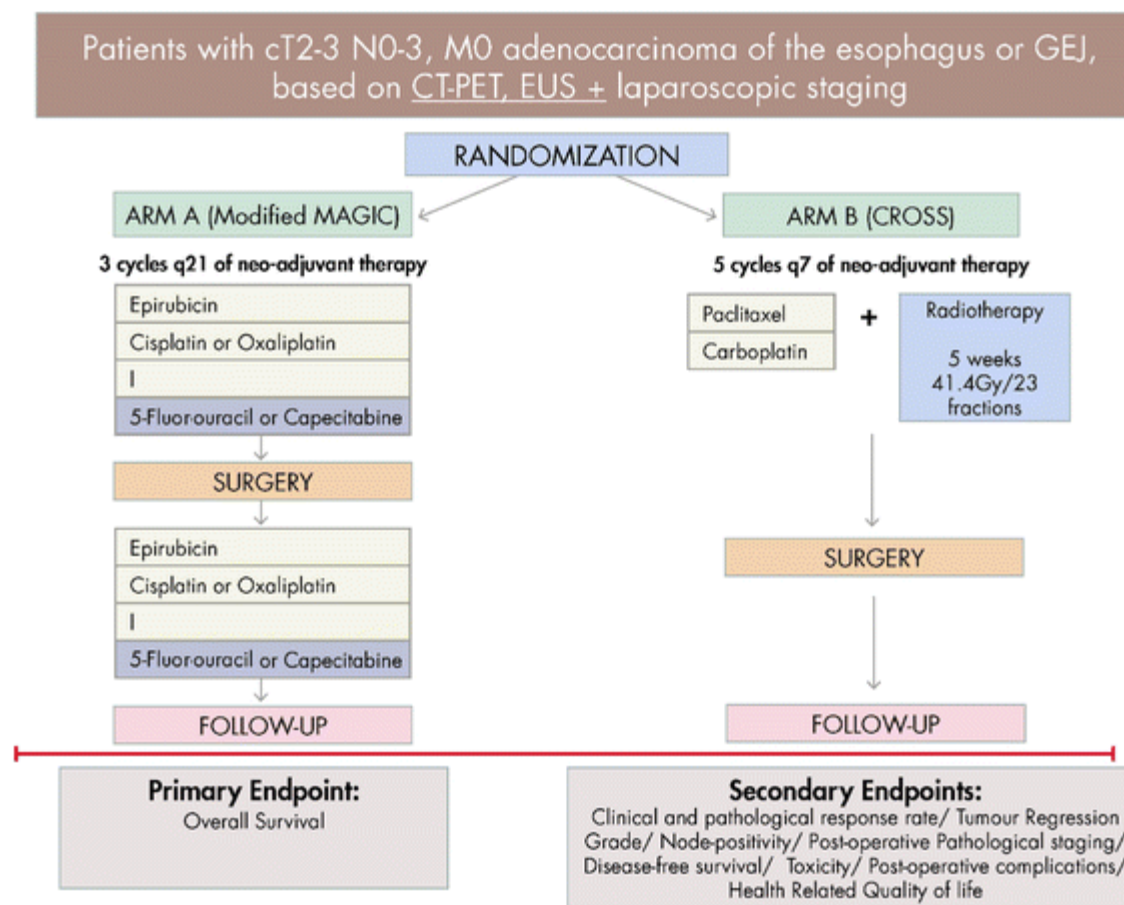
**Is perioperative chemotherapy (i.e. FLOT) superior to neoadjuvant chemoradiation (i.e. CROSS regimen)?**



# Treatment – Early Stage

Neo-AEGIS trial:

- Patients with **adenocarcinoma of esophagus or GEJ**
- Most patients in chemotherapy arm received MAGIC regimen (ECF) vs FLOT (157 vs 27).



# Treatment – Early Stage

## Neo-AEGIS trial:

- Estimated 3 year survival of ChemoRT vs chemo:
  - 56% vs 57%, HR 1.02 (95% CI: 0.74-1.42)
- Authors concluded there was non-inferiority between two approaches

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

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# Treatment – Early Stage

Still unanswered question:

**Is perioperative chemotherapy (i.e. FLOT) superior to neoadjuvant chemoradiation (i.e. CROSS regimen)?**

Well...

If FLOT > MAGIC (FLOT4-AIO)

And MAGIC = CROSS (Neo-Aegis)

Then FLOT > CROSS ??

Treatment

Perhaps. ESO  
esophageal a

But ESOPEC  
So....

S) for

E 577.



## Treatment - M

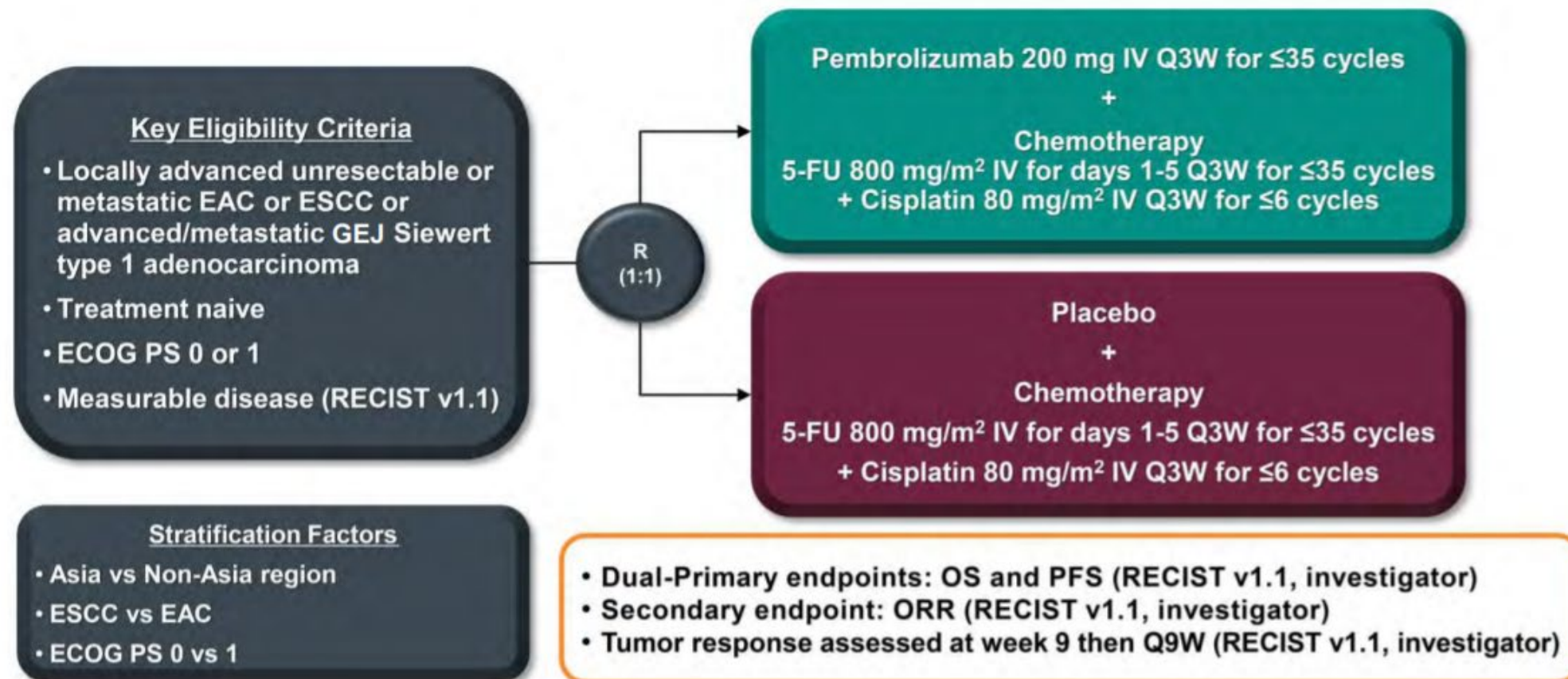
- Two year standard of care first-line therapy: fluoropyrimidine + platinum (i.e. FOLFOX)
- Pembrolizumab was approved as 1<sup>st</sup> line therapy for adenocarcinoma with PD-L1  $\geq 1$
- Nivolumab was approved as 2<sup>nd</sup> line therapy for esophageal SCC independent of PD-L1.

# Treatment - Metastatic

- Immunotherapy Trials:
  - KEYNOTE 590 – Esophageal Cancer (adeno & squamous)
  - CHECKMATE 648 – Esophageal SCC
  - CHECKMATE 649 – Gastric and Esophageal Adenocarcinoma

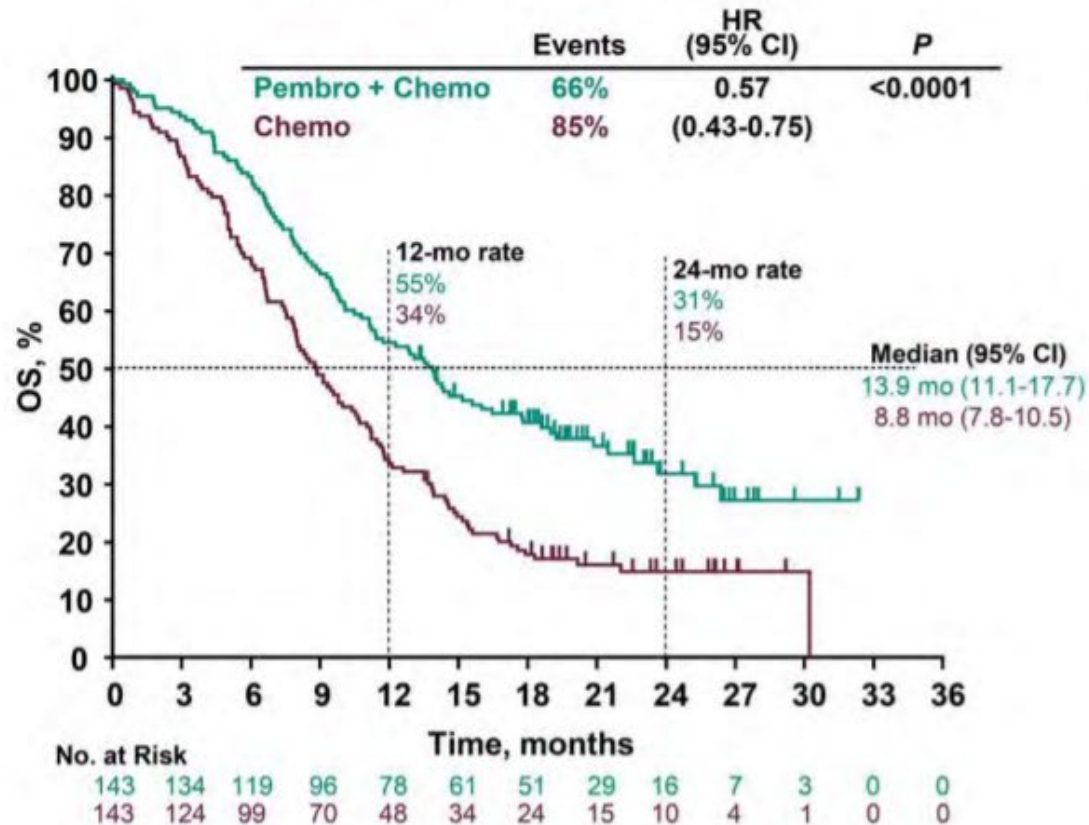


# First-Line Metastatic Esophageal Cancer – KEYNOTE-590

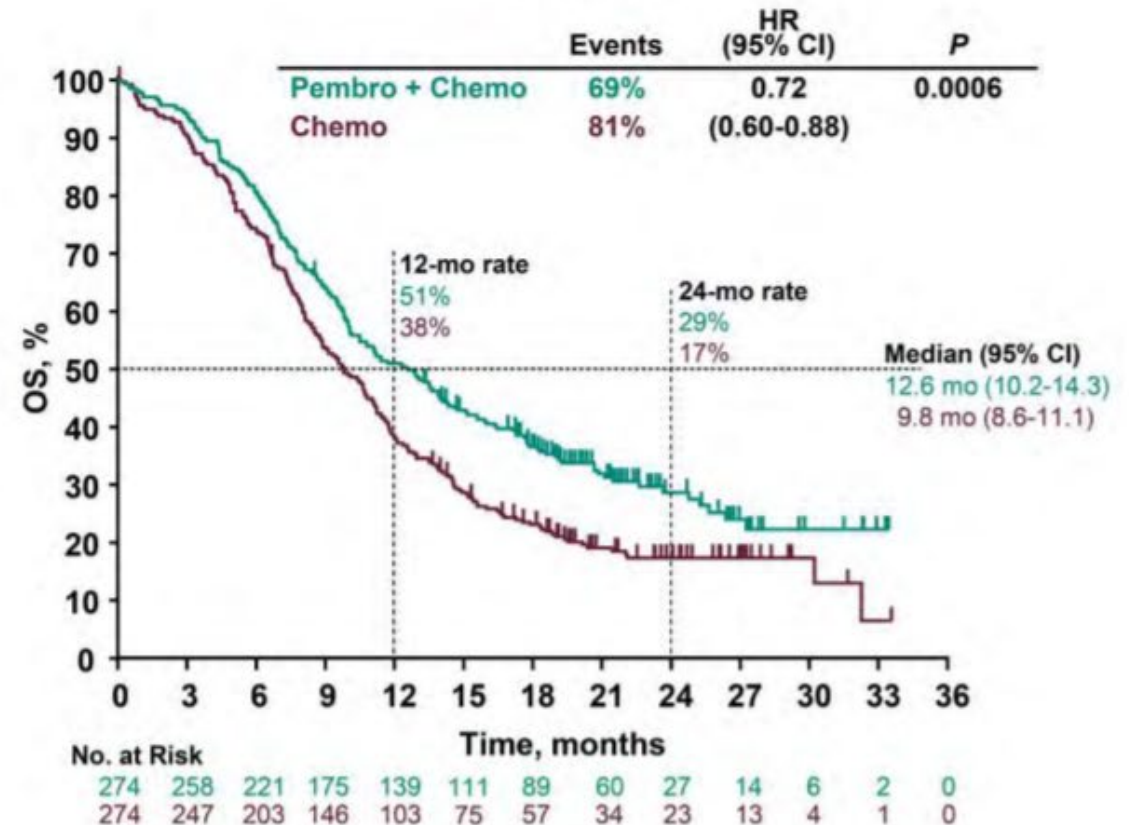


# KEYNOTE-590 – Overall Survival in SCC Patients

## ESCC PD-L1 CPS $\geq 10$

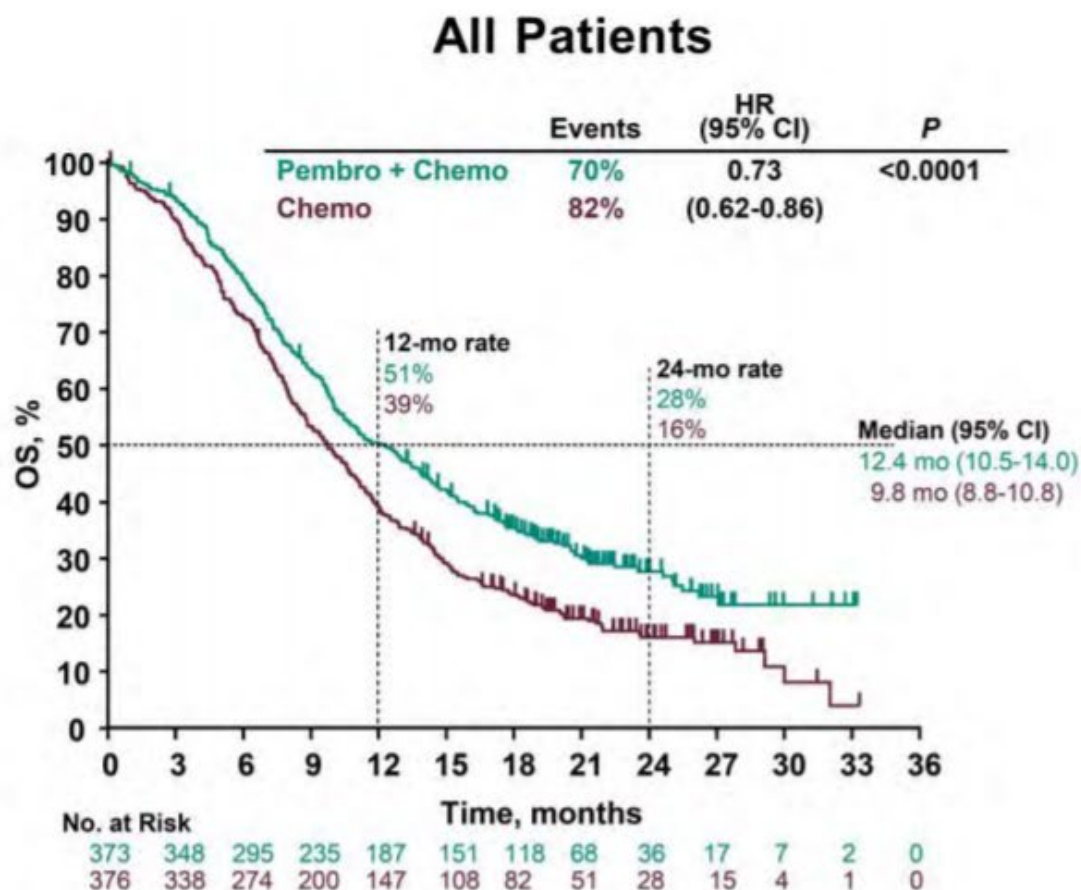
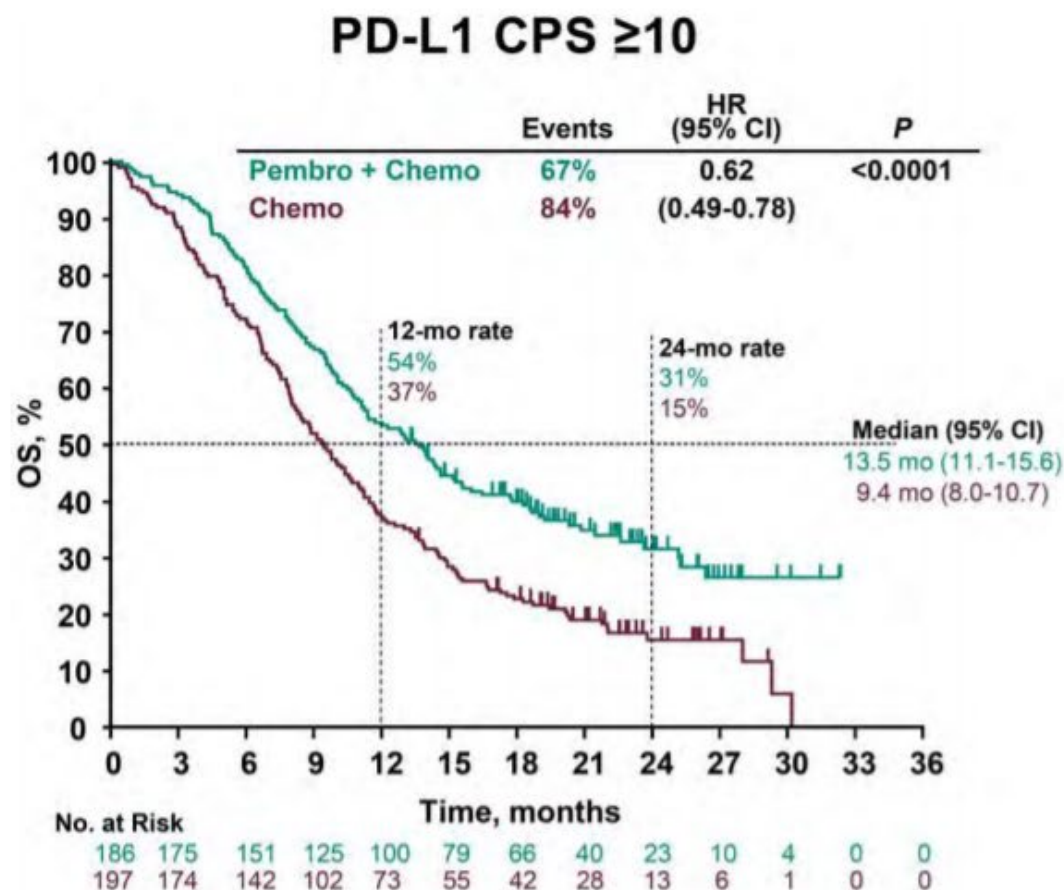


## ESCC

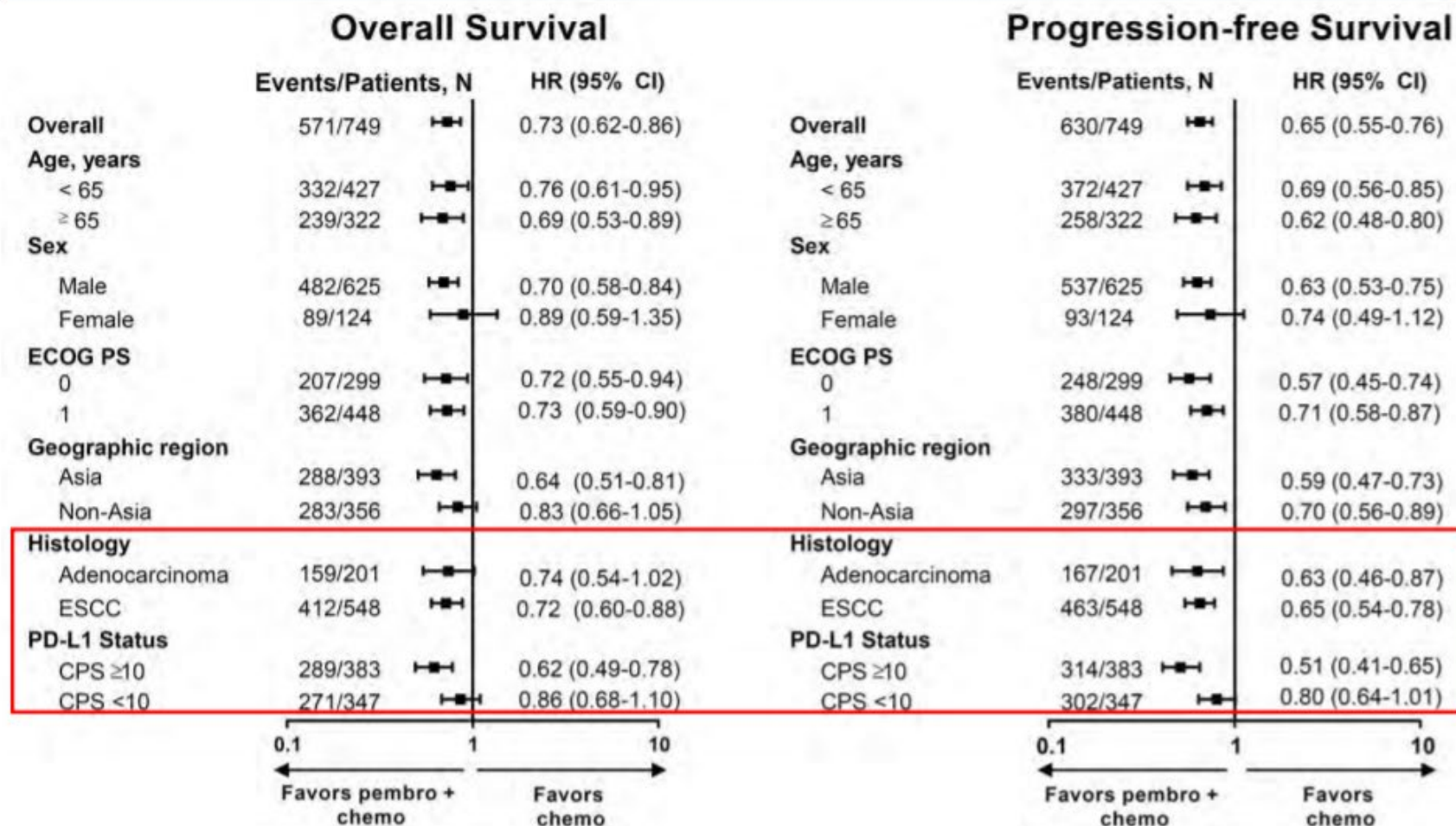




# KEYNOTE-590 – Overall Survival in All Patients



# KEYNOTE-590 – Subgroup Analyses



# CheckMate 648 study design

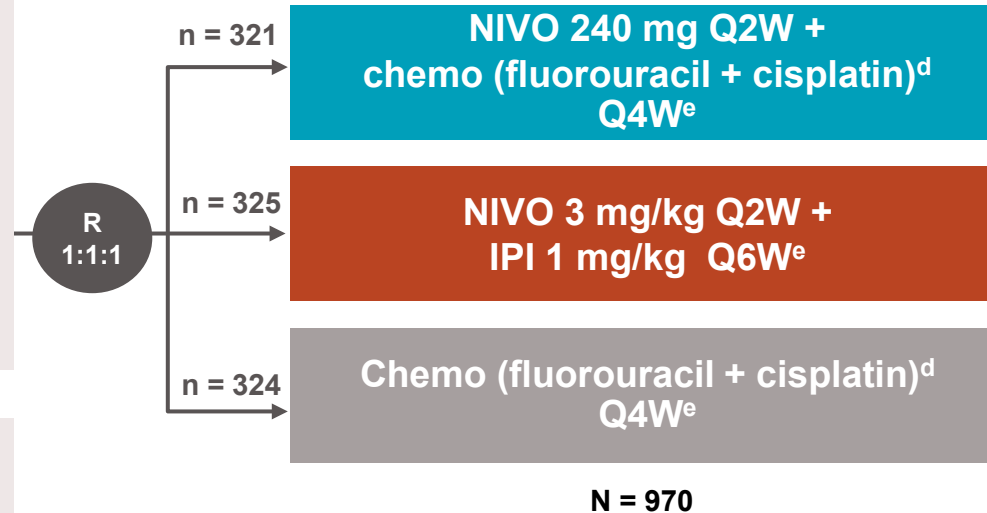
- CheckMate 648 is a global, randomized, open-label phase 3 study<sup>a</sup>

## Key eligibility criteria

- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

## Stratification factors

- Tumor cell PD-L1 expression ( $\geq 1\%$  vs  $< 1\%$ <sup>b</sup>)
- Region (East Asia<sup>c</sup> vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases ( $\leq 1$  vs  $\geq 2$ )



## Primary endpoints:

- OS and PFS<sup>f</sup> (tumor cell PD-L1  $\geq 1\%$ )

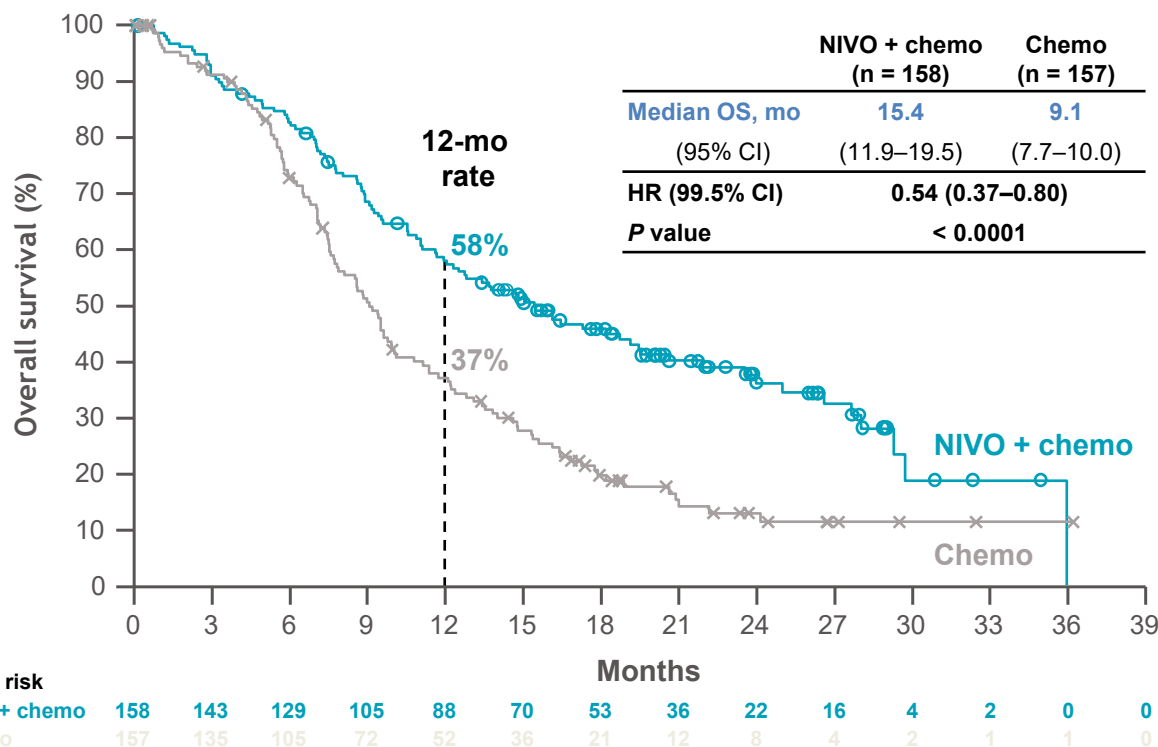
## Secondary endpoints:

- OS and PFS<sup>f</sup> (all randomized)
- ORR<sup>f</sup> (tumor cell PD-L1  $\geq 1\%$  and all randomized)

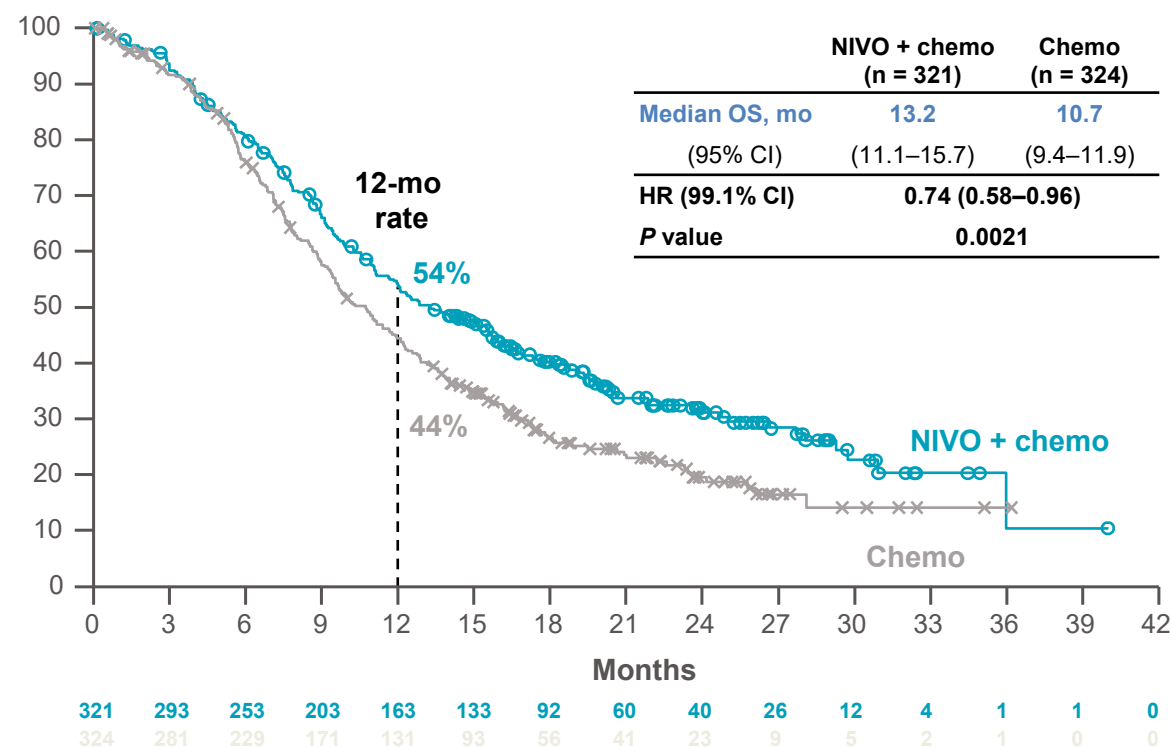
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months<sup>g</sup>

# Overall survival: NIVO + chemo vs chemo

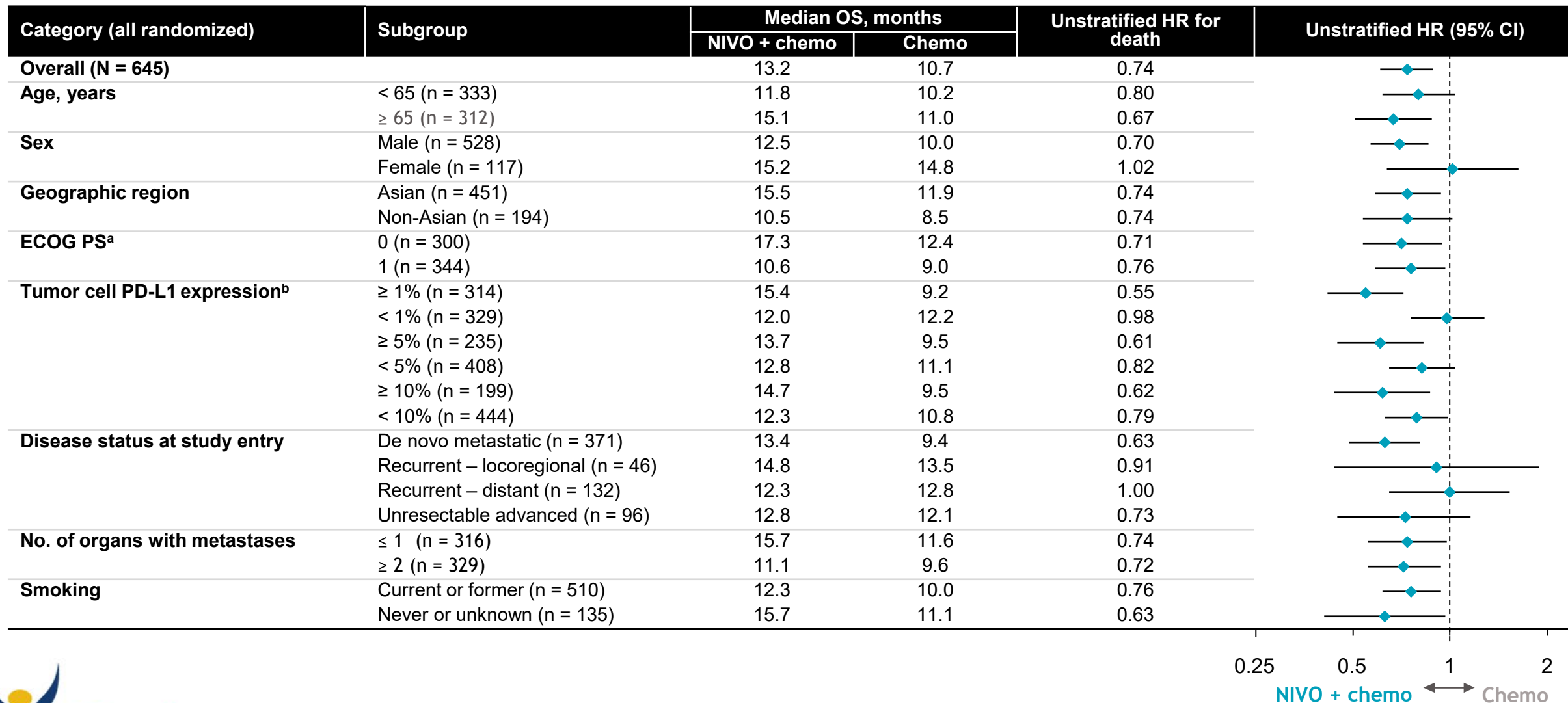
Primary endpoint (tumor cell PD-L1  $\geq 1\%$ )<sup>a</sup>



All randomized<sup>a</sup>



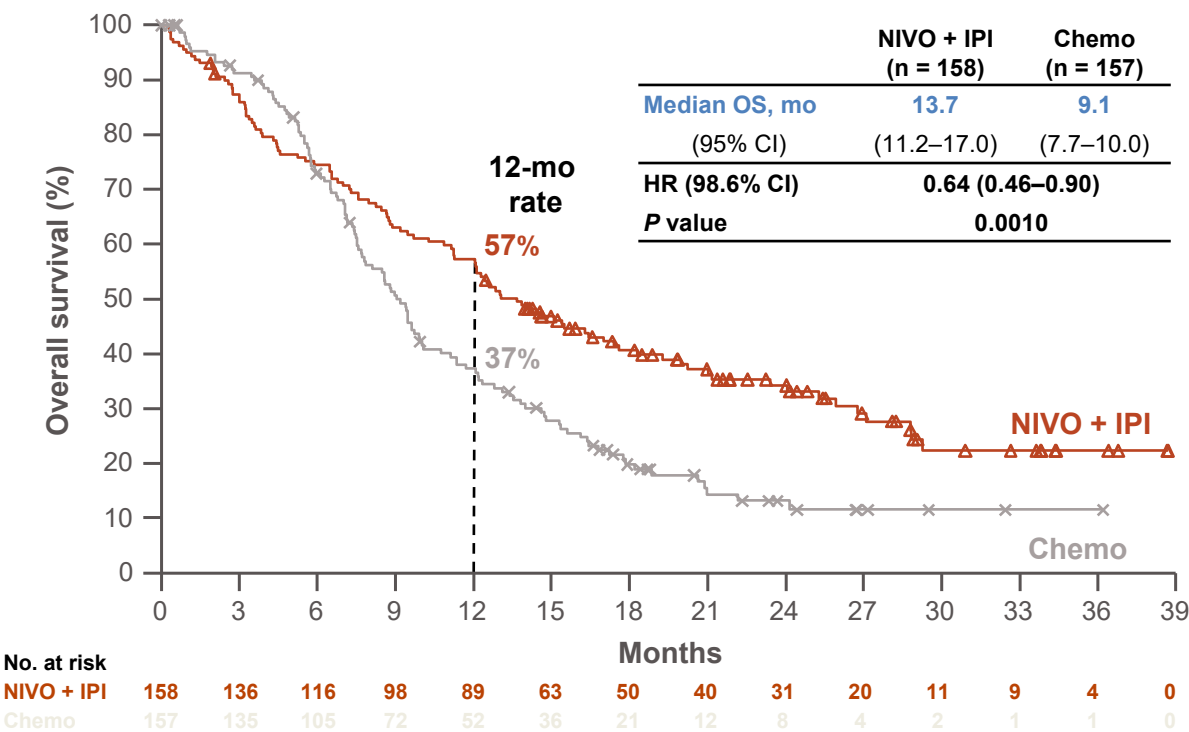
# Overall survival subgroup analysis: NIVO + chemo vs chemo



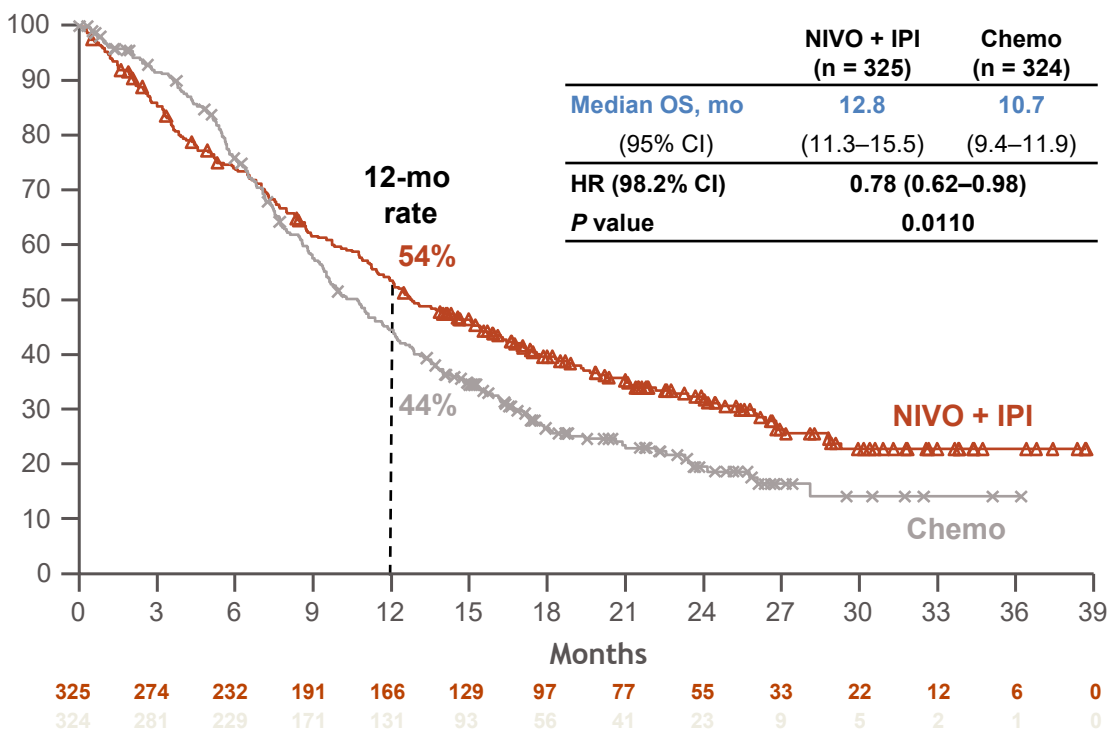


# Overall survival: NIVO + IPI vs chemo

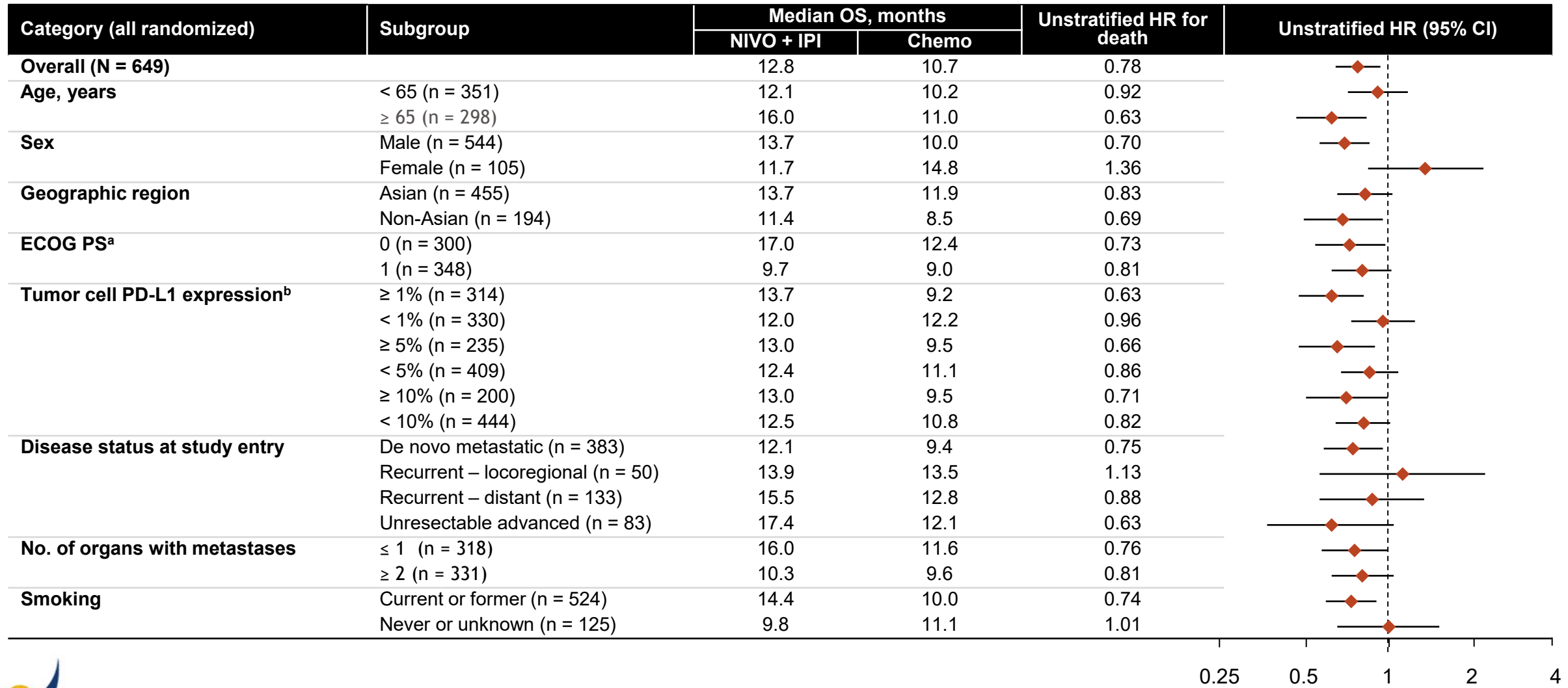
Primary endpoint (tumor cell PD-L1 ≥ 1%)<sup>a</sup>



All randomized<sup>a</sup>



# Overall survival subgroup analysis: NIVO + IPI vs chemo



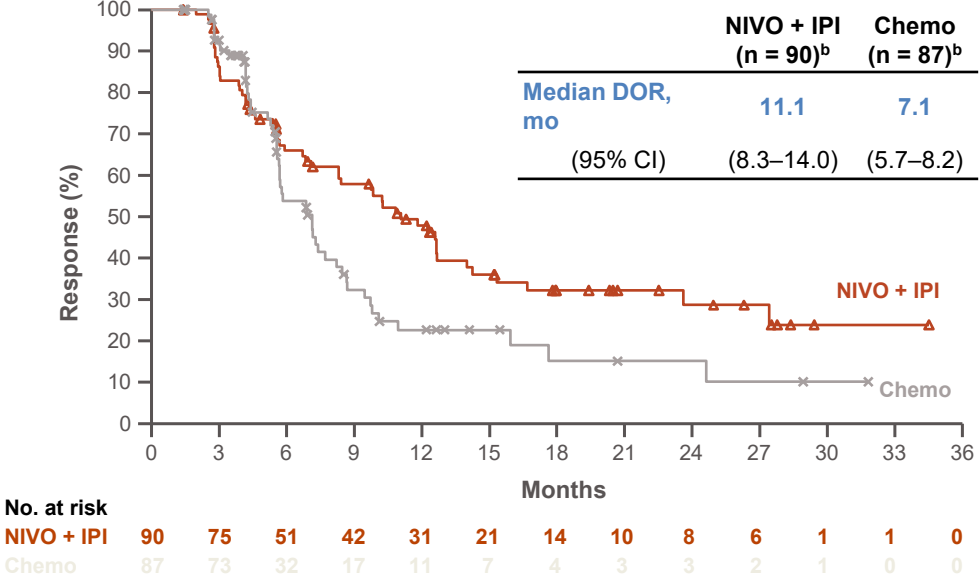
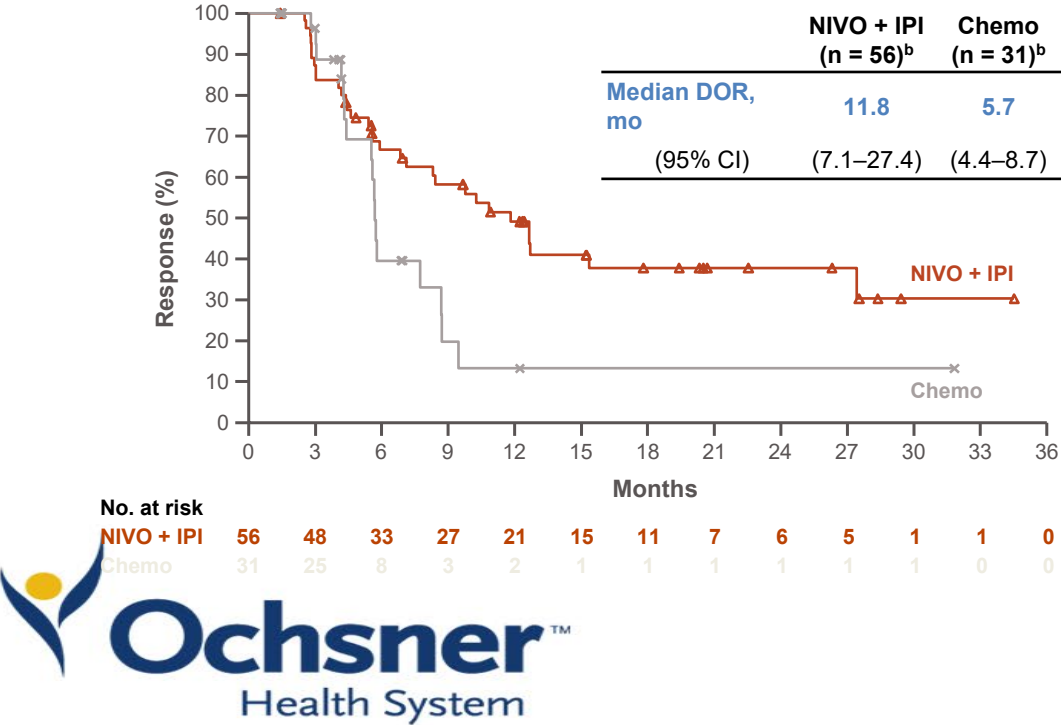
# Response and duration of response: NIVO + IPI vs chemo

Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + IPI (n = 158)	Chemo (n = 157)
<b>ORR, % (95% CI)</b>	35 (28-43)	20 (14-27)
CR <sup>a</sup>	18	5
PR <sup>a</sup>	18	15
SD	27	46
PD	30	15

All randomized

Response per BICR	NIVO + IPI (n = 325)	Chemo (n = 324)
<b>ORR, % (95% CI)</b>	28 (23-33)	27 (22-32)
CR	11	6
PR	17	21
SD	32	46
PD	32	12



Chau et al. ASCO Annual Meeting 2021.



# Treatment – Metastatic

ARTICLES | [VOLUME 398, ISSUE 10294, P27-40, JULY 03, 2021](#)



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## First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

[Yelena Y Janjigian, MD](#) <sup>†</sup> • [Kohei Shitara, MD](#) <sup>†</sup> <sup>†</sup> • [Prof Markus Moehler, MD](#) • [Prof Marcelo Garrido, MD](#)

[Pamela Salman, MD](#) • [Prof Lin Shen, MD](#) • et al. [Show all authors](#) • [Show footnotes](#)

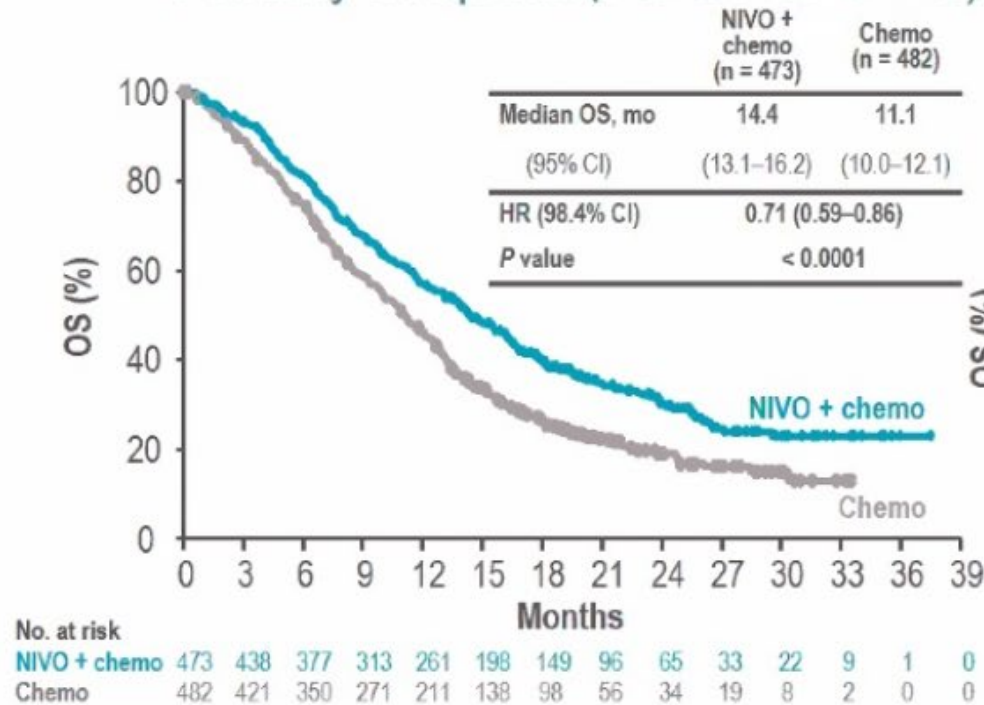
Published: June 05, 2021 • DOI: [https://doi.org/10.1016/S0140-6736\(21\)00797-2](https://doi.org/10.1016/S0140-6736(21)00797-2)



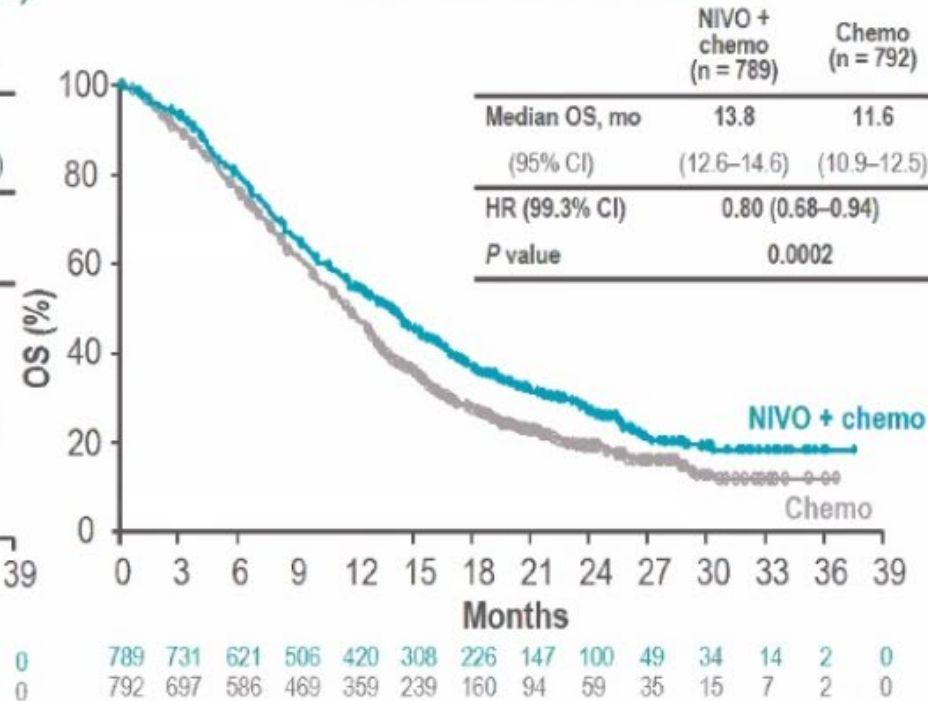
Check for updates

# Overall survival in Checkmate-649

Primary endpoint (PD-L1 CPS  $\geq 5$ )

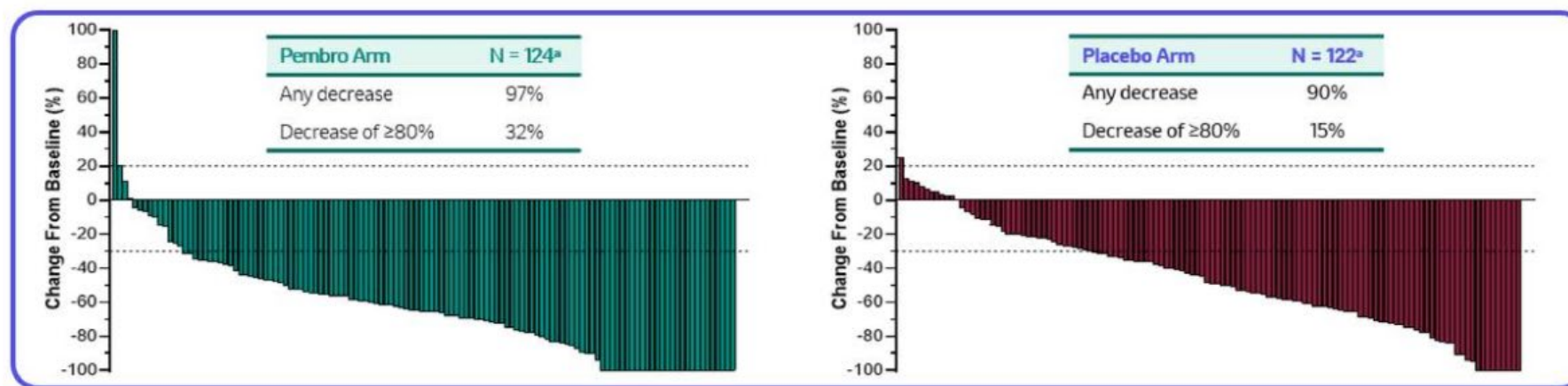


All randomized



# Treatment – Metastatic

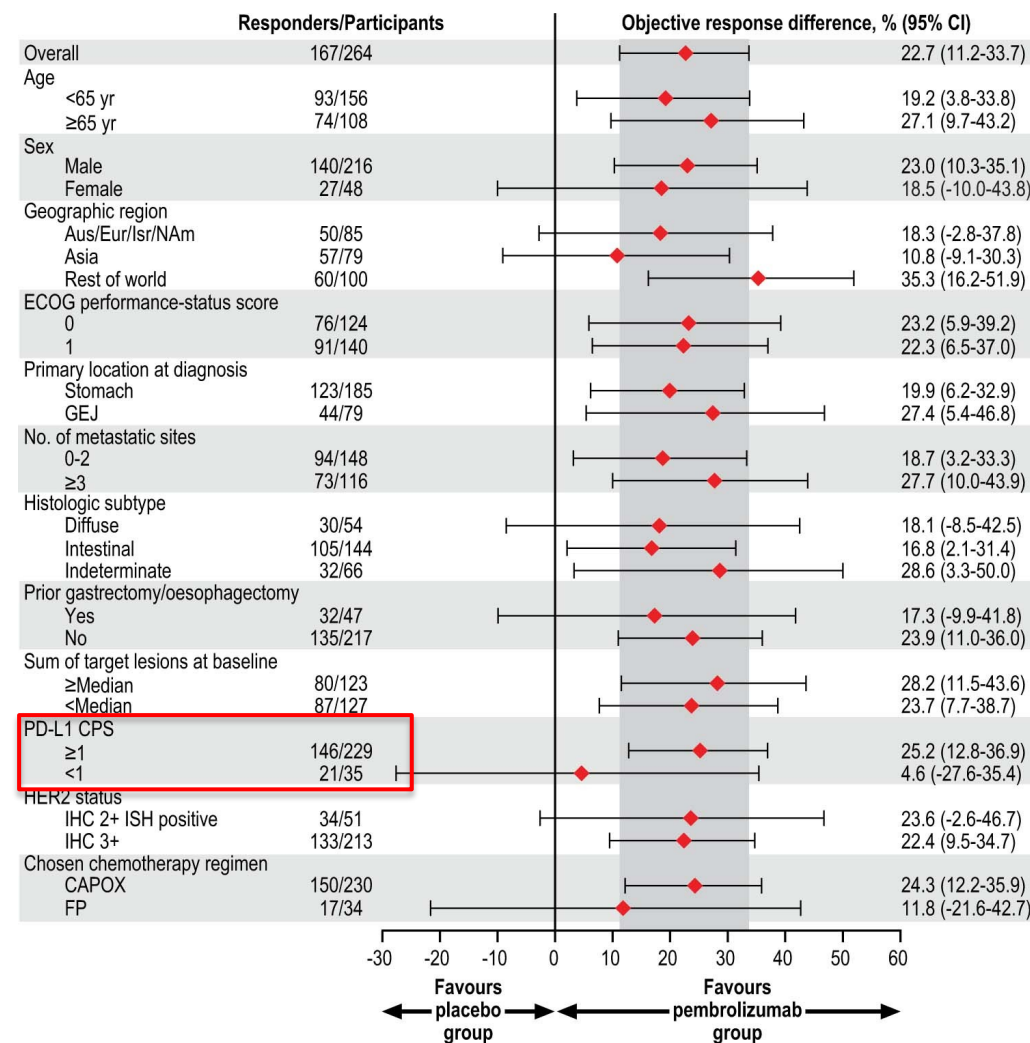
KEYNOTE-811: KEYTRUDA+trastuzumab+chemotherapy becomes new treatment option for HER2+ metastatic gastric/GEJ cancer



- Results support FDA accelerated approval in May 2021
- Pembrolizumab plus trastuzumab and chemotherapy provided a 74.4% ORR that resulted in a statistically significant, clinically meaningful 22.7% improvement in ORR compared with placebo plus trastuzumab and chemotherapy
- Responses to pembrolizumab plus trastuzumab and chemotherapy were deeper and more durable
- Study is continuing as planned, and analyses of OS and PFS will be performed in the future in accordance with the analysis plan

# Treatment – Metastatic

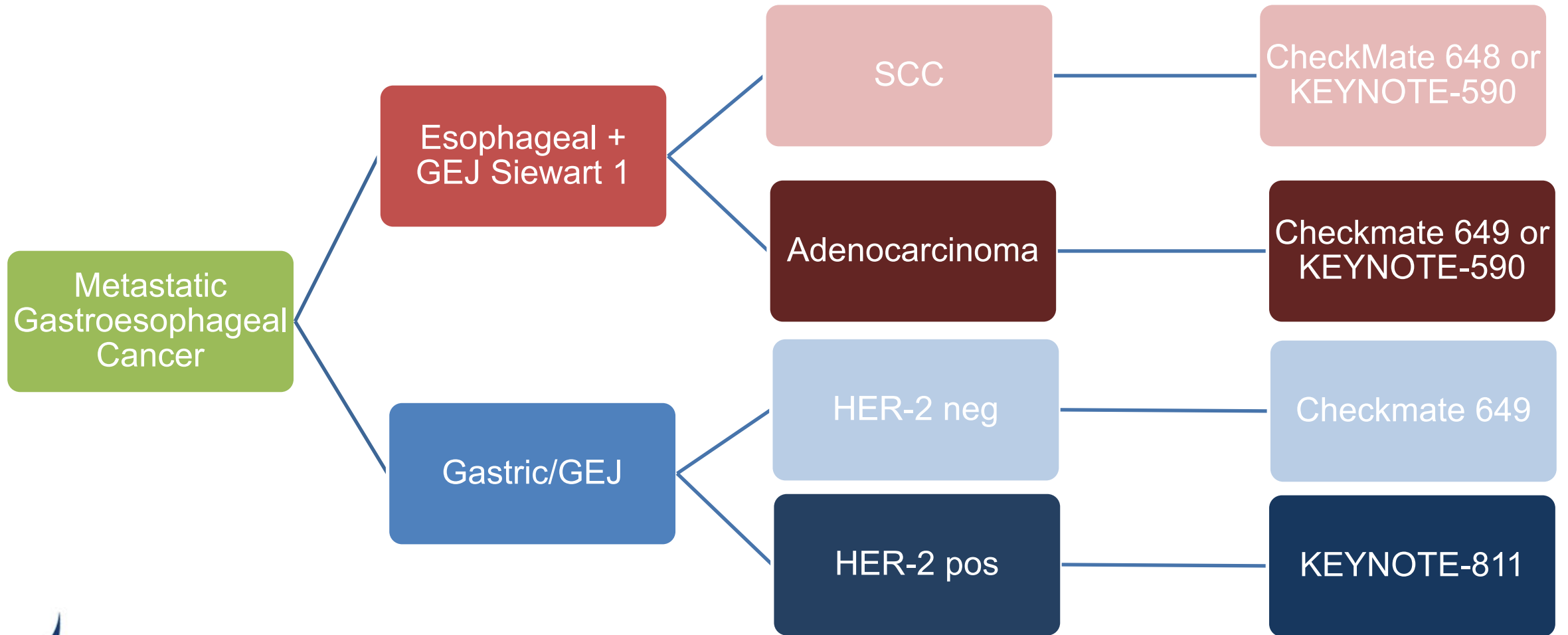
- Complete Response:
  - **11.3%** in pembro arm vs **3.1%** in placebo arm
- Duration of Response:
  - **10.6 months** in pembro arm vs **9.5 months** in placebo arm



Janjigian et al. Nature 2021.



# For visual learners...

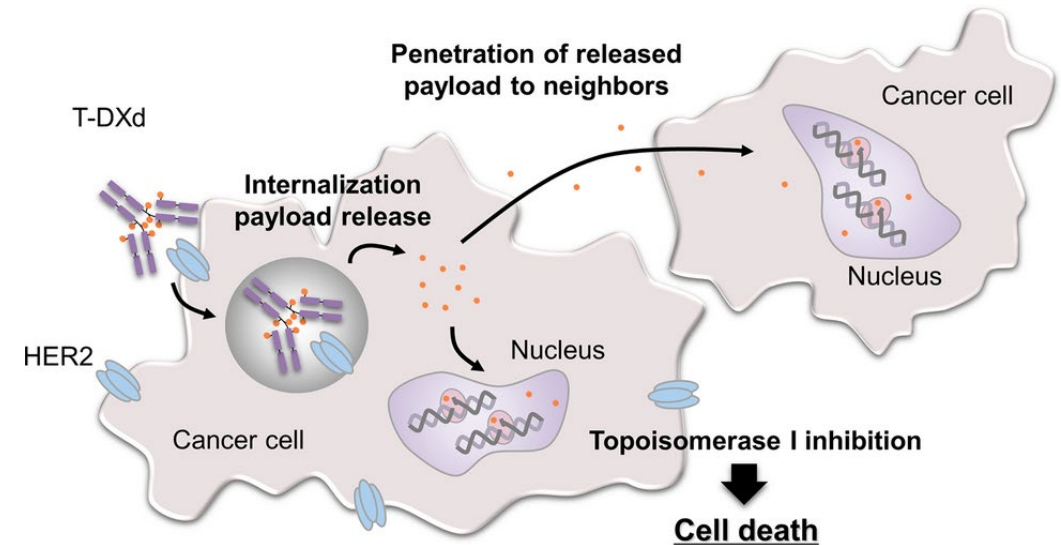


# Treatment - Metastatic

- 2<sup>nd</sup> + line options:
  - Paclitaxel +/- ramucirumab (adenocarcinoma)
  - Docetaxel
  - Irinotecan +/- 5-FU
  - Nivolumab (ESCC)
  - Trastuzumab deruxtecan (HER-2+)
  - TAS-102/Lonsurf

# Pretreated HER-2 Positive Gastric Cancer

- Trastuzumab Deruxtecan
  - Antibody-drug conjugate
  - **HER-2 positive** gastric cancer: DESTINY-Gastric01
  - Randomized phase 2 study of HER-2 positive patients that progressed on  $\geq 2$  prior therapies including trastuzumab.
  - **ORR 51%** in patients treated with trastuzumab deruxtecan vs 14% in control group.
  - Median OS: 12.5 vs 8.4 months ( $P = 0.01$ )



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*January 15, 2021*

**FDA approves fam-trastuzumab deruxtecan-nxki for HER2-positive gastric adenocarcinomas**



# Gastroesophageal Cancer – FGFR2b overexpression

- **Bemarituzumab**

- IgG1 monoclonal antibody to FGFR2b
- **FIGHT** trial: phase 2 trial of first-line HER-2 negative gastric cancer patients randomizing patients to FOLFOX +/- bemarituzumab
  - ⦿ Patients must have FGFR2b overexpression or FGFR2 amplification by ctDNA
  - ⦿ 30% of prescreened patients met above criteria

**TABLE 1:** Outcomes From FIGHT Trial With Bemarituzumab Plus mFOLFOX6 vs Placebo

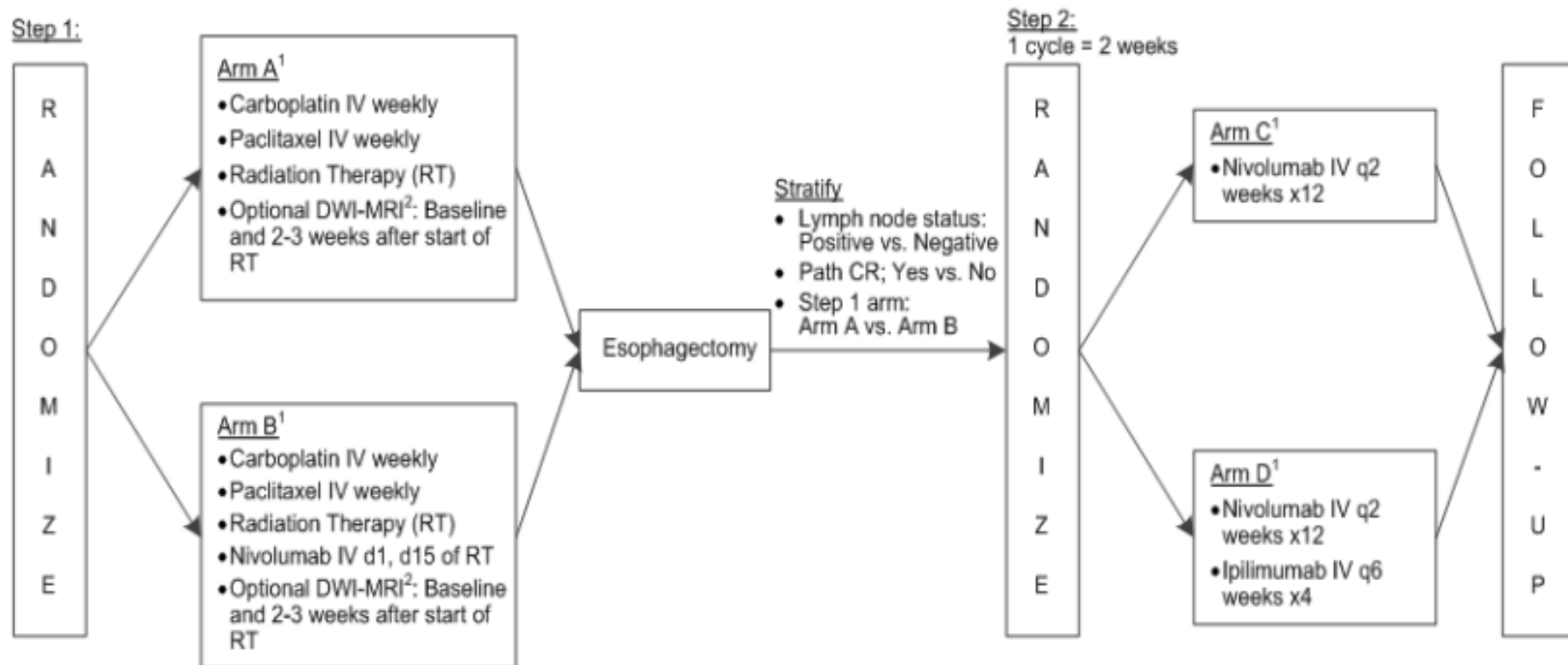
	Intent to Treat (n = 155)		IHC 2+/3+ ≥ 5% (n = 118)		IHC 2+/3+ ≥ 10% (n = 96)	
	Bema	Placebo	Bema	Placebo	Bema	Bema
mPFS	9.5 mo	7.4 mo	10.2 mo	7.3 mo	14.1 mo	7.3 mo
	HR = 0.68		HR = 0.54		HR = 0.44	
mOS	NR	12.9 mo	NR	12.5 mo	NR	11.1 mo
	HR = 0.58		HR = 0.52		HR = 0.41	

Bema = bemarituzumab; HR = hazard ratio; IHC = immunohistochemistry; mFOLFOX6 = modified fluorouracil, leucovorin, oxaliplatin; mOS = median overall survival; mPFS = median progression-free survival; NR = not reached.

# Future Directions

- Moving more targeted therapies into first line
  - Trastuzumab Deruxtecan for HER-2+
  - Bemarituzumab for FGFR2b +
  - Zolbetuximab for CLDN18.2 +
- Optimizing management of locally advanced disease
  - ESOPEC: FLOT vs CROSS regimen for esophageal and GEJ
  - Improving on KEYNOTE-577 – EA2174
- Novel therapies
  - ADCs, BiTE, CAR-T

## Schema



N=278

# Summary and Take-Home Points

- Localized Disease:
  - FLOT is standard of care perioperative therapy for locally advanced gastric
  - CROSS w/ adjuvant nivolumab is standard of care for locally advanced esophageal
  - ESOPEC results should guide whether this will remain the case moving forward
- Metastatic Disease:
  - **Immune checkpoint inhibitors** – nivolumab and pembrolizumab – have made significant changes to first line therapy. Primarily driven by PD-L1 positive tumors.
  - **Targeted therapies** – HER-2 (KEYNOTE 811 in 1<sup>st</sup> line, DESTINY-Gastric01 in pre-treated) approved. FGFR2b, CLDN18.2 may be approved in the near future.
  - Don't forget to check MMR/MSI status!
  - All patients with advanced disease should have HER-2, MSI, PD-L1 status checked upfront.

Thanks!

E-mail me with questions.

[Jonathan.Mizrahi@ochsner.org](mailto:Jonathan.Mizrahi@ochsner.org)