# Bringing Treatment Into Focus: Biomarker-Driven First-Line Therapy for Metastatic Gastric/GEJ Cancers

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TOTAL CME

# Case 1

# Case Presentation

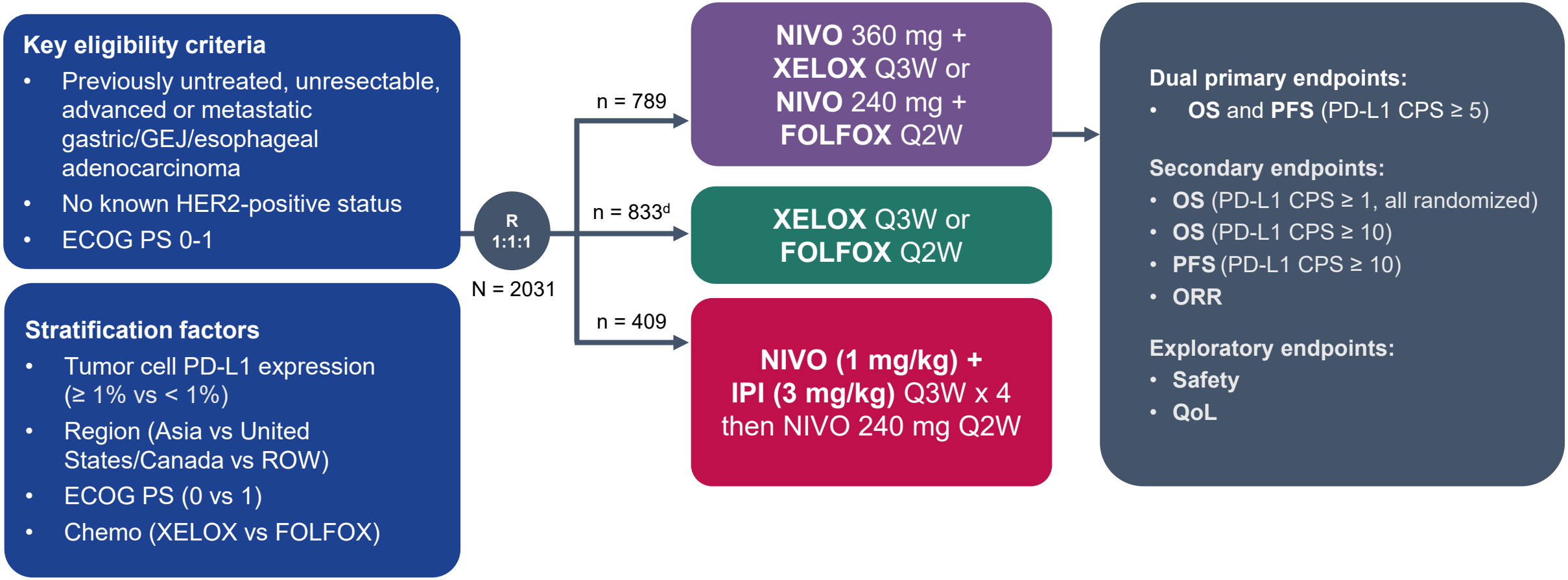
- 62-year-old man with dark stools and reflux symptoms
- Upper endoscopy shows a large infiltrative and ulcerated non-circumferential mass with stigmata of recent bleeding in the lesser curvature of stomach
- Pathology shows invasive adenocarcinoma with signet ring cell features
- CT chest/abdomen/pelvis shows concentric soft tissue density thickening of the gastric antrum

# Case Presentation (cont'd)

- Diagnostic laparoscopy shows peritoneal nodules
- Biopsy confirms signet ring adenocarcinoma
  - Consistent with history of gastric primary
- Biomarker testing performed
  - HER2 IHC: 0
  - **PD-L1 CPS: 6**
  - CLDN 18.2 IHC: 1+, 30%
- Started on FOLFOX + nivolumab
- Repeat CT chest/abdomen/pelvis showing stable disease for 9 months

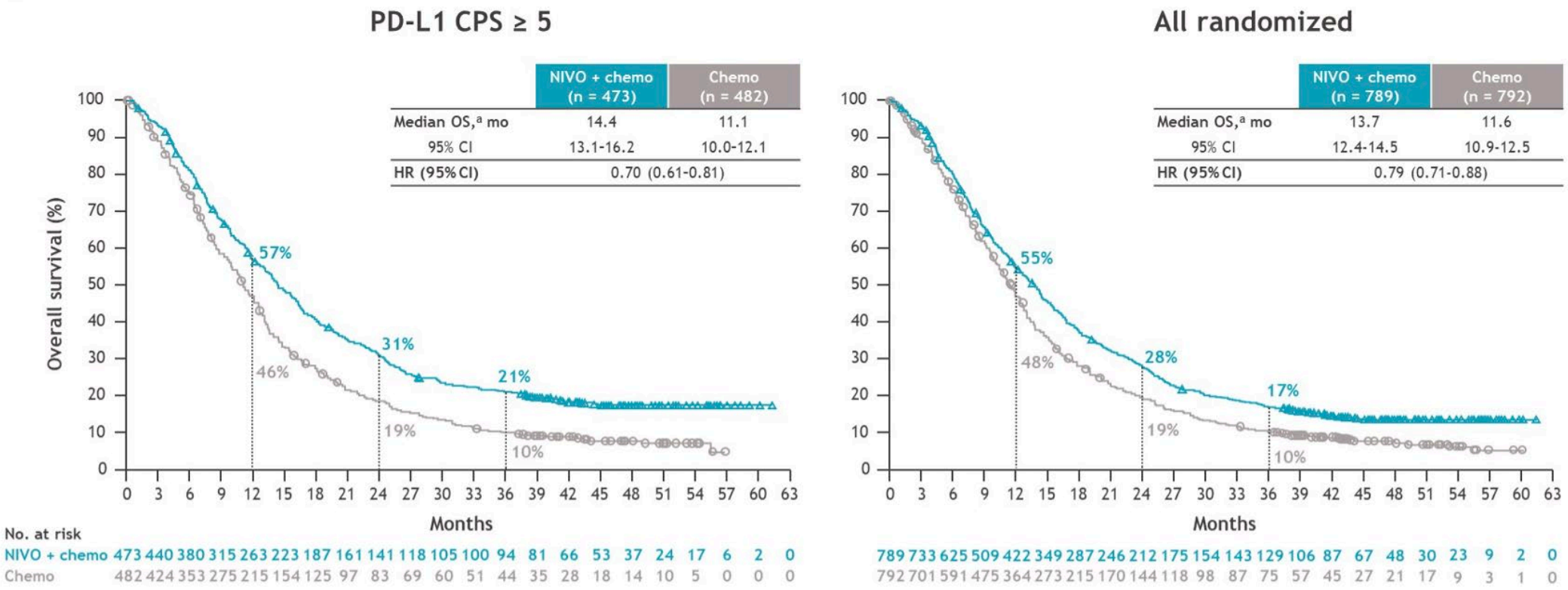
# CheckMate 649: Study Design

- CheckMate 649 is a randomized, open-label, global phase 3 study




Shitara K, et al. ASCO GI 2024. Abstract 306.

# CheckMate 649: Overall Survival



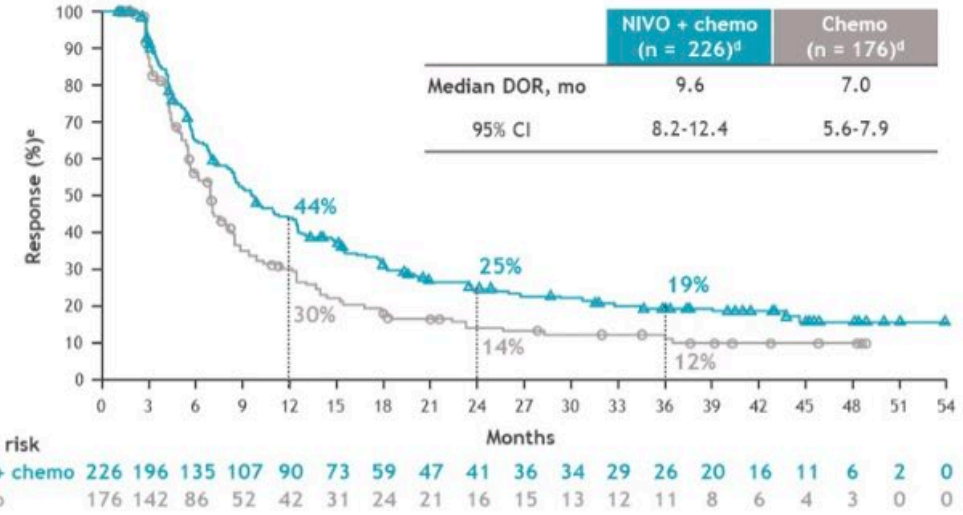

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

Janjigian YY, et al. *J Clin Oncol*. 2024;(17):2012-2020.

# CheckMate 649: Response and Duration of Response

## PD-L1 CPS ≥ 5

| Response per BICR | NIVO + chemo (n = 378)[a] | Chemo (n = 390)[a] |
|---|---|---|
| ORR,[b] % (95% CI) | 60 (55-65) | 45 (40-50) |
| CR | 13 | 7 |
| PR | 47 | 38 |
| SD | 28 | 34 |
| PD | 7 | 11 |



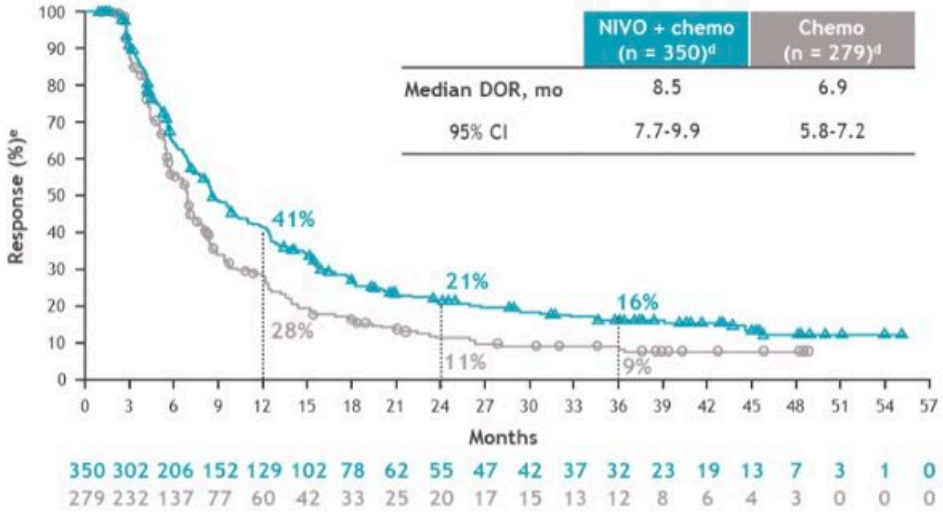

| | NIVO + chemo (n = 226)[d] | Chemo (n = 176)[d] |
|---|---|---|
| Median DOR, mo | 9.6 | 7.0 |
| 95% CI | 8.2-12.4 | 5.6-7.9 |

No. at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO + chemo | 226 | 196 | 135 | 107 | 90 | 73 | 59 | 47 | 41 | 36 | 34 | 29 | 26 | 20 | 16 | 11 | 6 | 2 | 0 |
| Chemo | 176 | 142 | 86 | 52 | 42 | 31 | 24 | 21 | 16 | 15 | 13 | 12 | 11 | 8 | 6 | 4 | 3 | 0 | 0 |

## All randomized

| Response per BICR | NIVO + chemo (n = 602)[a] | Chemo (n = 607)[a] |
|---|---|---|
| ORR,[c] % (95% CI) | 58 (54-62) | 46 (42-50) |
| CR | 11 | 7 |
| PR | 47 | 39 |
| SD | 28 | 33 |
| PD | 7 | 10 |




| | NIVO + chemo (n = 350)[d] | Chemo (n = 279)[d] |
|---|---|---|
| Median DOR, mo | 8.5 | 6.9 |
| 95% CI | 7.7-9.9 | 5.8-7.2 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO + chemo | 350 | 302 | 206 | 152 | 129 | 102 | 78 | 62 | 55 | 47 | 42 | 37 | 32 | 23 | 19 | 13 | 7 | 3 | 1 | 0 |
| Chemo | 279 | 232 | 137 | 77 | 60 | 42 | 33 | 25 | 20 | 17 | 15 | 13 | 12 | 8 | 6 | 4 | 3 | 0 | 0 | 0 |

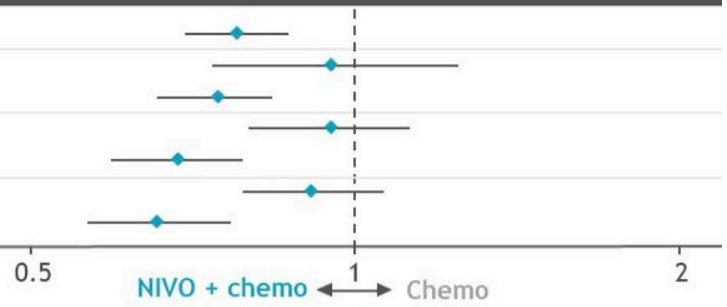
- Higher ORR was maintained, and responses remained more durable with NIVO + chemo vs chemo with longer follow-up

Janjigian YY, et al. *J Clin Oncol*. 2024;(17):2012-2020.

# CheckMate 649: Subgroup Analysis

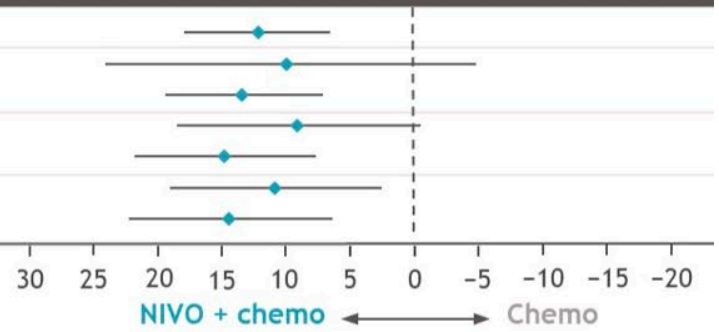
## Overall survival

| PD-L1 CPS[a] | Number of patients | Median OS, months | | Unstratified HR for death | Unstratified HR (95% CI) |
|---|---|---|---|---|---|
| | | NIVO + chemo | Chemo | | |
| Overall (N = 1581) | | 13.7 | 11.6 | 0.78 | |
| < 1 | 265 | 13.1 | 12.5 | 0.95 | |
| ≥ 1 | 1297 | 13.8 | 11.3 | 0.75 | |
| < 5 | 607 | 12.4 | 12.3 | 0.95 | |
| ≥ 5 | 955 | 14.4 | 11.1 | 0.69 | |
| < 10 | 794 | 12.4 | 12.5 | 0.91 | |
| ≥ 10 | 768 | 15.0 | 10.9 | 0.66 | |




## Objective response rate

| PD-L1 CPS[b] | Number of patients | Objective response rate, % | | Unweighted ORR difference,[c] % | Unweighted ORR difference,[c] % (95% CI) |
|---|---|---|---|---|---|
| | | NIVO + chemo | Chemo | | |
| Overall (N = 1209) | | 58 | 46 | 12 | |
| < 1 | 179 | 51 | 41 | 10 | |
| ≥ 1 | 1016 | 60 | 46 | 13 | |
| < 5 | 427 | 56 | 46 | 9 | |
| ≥ 5 | 768 | 60 | 45 | 15 | |
| < 10 | 577 | 58 | 47 | 11 | |
| ≥ 10 | 618 | 59 | 44 | 14 | |



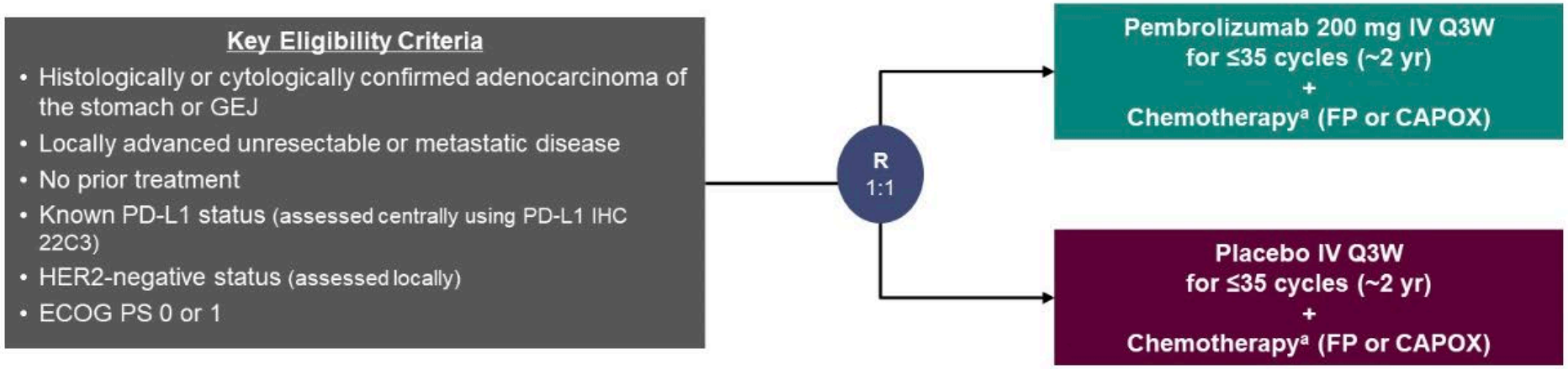

- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs
- ORR was higher vs chemo across all PD-L1 CPS subgroups

[a]PD-L1 CPS expression indeterminate/nonevaluable/not reported, n = 19; [b]Randomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/nonevaluable/not reported, n = 14; [c]Percentages may not reflect an exact difference due to rounding.

Shitara K, et al, ASCO GI 2024. Abstract 306.

# KEYNOTE-859: Study Design

## Randomized, Double-Blind, Phase 3 Trial




**Stratification Factors**
- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

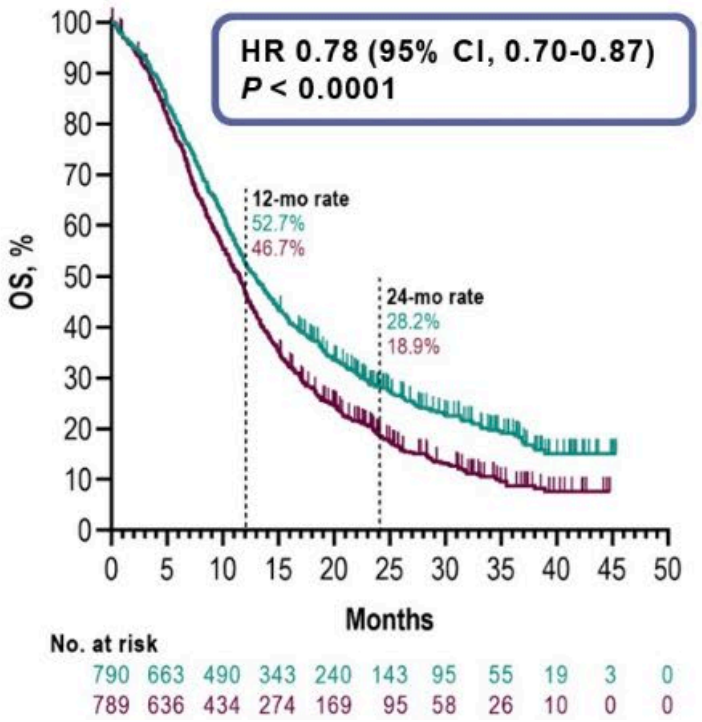
- **Alpha-controlled analyses:** OS, PFS, and ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations

Rha SY, et al. *Lancet Oncol*. 2023;24(11):1181-1195.

# KEYNOTE-859: OS (Primary Endpoint)

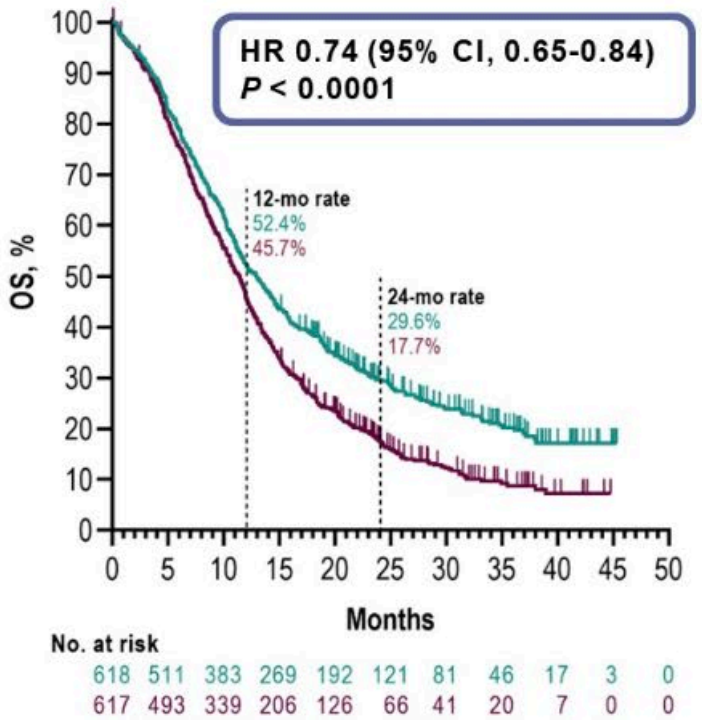
## Overall[1]

| | Pts w/ Event | Median (95% CI), mo |
|---|---|---|
| Pembro + chemo | 76.3% | 12.9 (11.9-14.0) |
| Placebo + chemo | 84.4% | 11.5 (10.6-12.1) |



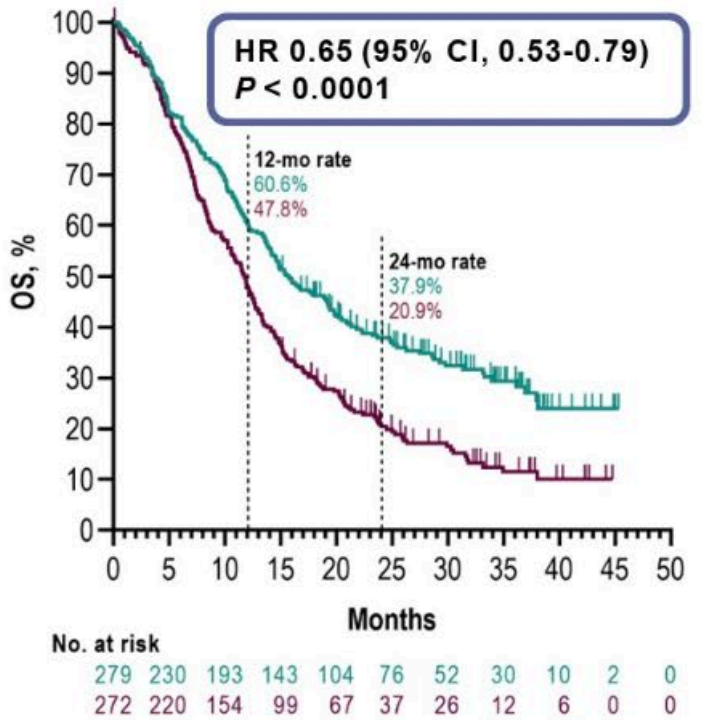

## PD-L1 CPS ≥1

| | Pts w/ Event | Median (95% CI), mo |
|---|---|---|
| Pembro + chemo | 75.1% | 13.0 (11.6-14.2) |
| Placebo + chemo | 85.3% | 11.4 (10.5-12.0) |




## PD-L1 CPS ≥10

| | Pts w/ Event | Median (95% CI), mo |
|---|---|---|
| Pembro + chemo | 67.4% | 15.7 (13.8-19.3) |
| Placebo + chemo | 83.1% | 11.8 (10.3-12.7) |

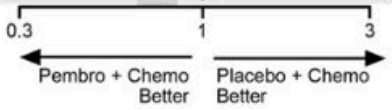



Rha SY, et al. *Lancet Oncol*. 2023;24(11):1181-1195.

# KEYNOTE-859: OS in Subgroups

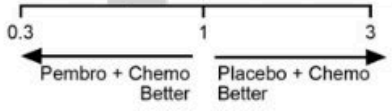
## PD-L1 CPS ≥1

| | No. Events/ No. Participants | Hazard ratio (95% CI) |
|---|---|---|
| **Overall** | 990/1235 | 0.74 (0.652-0.838) |
| **Age** | | |
| <65 years | 612/741 | 0.73 (0.621-0.855) |
| ≥65 years | 378/494 | 0.73 (0.595-0.892) |
| **Sex** | | |
| Female | 309/365 | 0.69 (0.551-0.865) |
| Male | 681/870 | 0.74 (0.638-0.864) |
| **Geographic region** | | |
| Asia | 299/401 | 0.70 (0.556-0.877) |
| W Eur/Isr/N Am/Australia | 272/332 | 0.76 (0.595-0.961) |
| Rest of world | 419/502 | 0.76 (0.624-0.918) |
| **ECOG performance status** | | |
| 0 | 341/451 | 0.66 (0.535-0.823) |
| 1 | 649/784 | 0.77 (0.657-0.894) |
| **Primary tumor location** | | |
| GEJ | 235/287 | 0.71 (0.547-0.927) |
| Stomach | 754/947 | 0.73 (0.634-0.844) |
| **Histologic subtype** | | |
| Diffuse | 391/456 | 0.73 (0.601-0.897) |
| Intestinal | 345/454 | 0.78 (0.635-0.969) |
| Indeterminate | 252/323 | 0.64 (0.494-0.822) |
| **Disease status** | | |
| Metastatic | 951/1184 | 0.73 (0.643-0.831) |
| **Liver metastases** | | |
| No | 572/723 | 0.71 (0.600-0.835) |
| Yes | 417/511 | 0.77 (0.631-0.929) |
| **Prior gastrectomy/esophagectomy** | | |
| No | 839/1014 | 0.77 (0.674-0.885) |
| Yes | 145/214 | 0.59 (0.422-0.816) |
| **PD-L1 CPS** | | |
| ≥10 | 414/551 | 0.64 (0.523-0.772) |
| 1-9 | 574/682 | 0.83 (0.705-0.979) |
| **Chemo choice at randomization** | | |
| CAPOX | 832/1056 | 0.72 (0.626-0.824) |
| FP | 158/179 | 0.82 (0.601-1.125) |




## PD-L1 CPS ≥10

| | No. Events/ No. Participants | Hazard ratio (95% CI) |
|---|---|---|
| **Overall** | 414/551 | 0.65 (0.532-0.787) |
| **Age** | | |
| <65 years | 247/320 | 0.67 (0.522-0.864) |
| ≥65 years | 167/231 | 0.59 (0.437-0.806) |
| **Sex** | | |
| Female | 123/153 | 0.58 (0.405-0.830) |
| Male | 291/398 | 0.65 (0.514-0.818) |
| **Geographic region** | | |
| Asia | 126/184 | 0.63 (0.441-0.889) |
| W Eur/Isr/N Am/Australia | 107/142 | 0.83 (0.565-1.213) |
| Rest of world | 181/225 | 0.58 (0.431-0.784) |
| **ECOG performance status** | | |
| 0 | 141/202 | 0.58 (0.416-0.816) |
| 1 | 273/349 | 0.65 (0.515-0.830) |
| **Primary tumor location** | | |
| GEJ | 103/138 | 0.57 (0.384-0.852) |
| Stomach | 311/413 | 0.65 (0.521-0.815) |
| **Histologic subtype** | | |
| Diffuse | 161/191 | 0.57 (0.415-0.779) |
| Intestinal | 143/210 | 0.77 (0.556-1.073) |
| Indeterminate | 109/149 | 0.49 (0.327-0.724) |
| **Disease status** | | |
| Metastatic | 398/526 | 0.64 (0.524-0.780) |
| **Liver metastases** | | |
| No | 245/322 | 0.60 (0.464-0.769) |
| Yes | 169/229 | 0.69 (0.511-0.940) |
| **Prior gastrectomy/esophagectomy** | | |
| No | 360/462 | 0.65 (0.526-0.800) |
| Yes | 53/88 | 0.62 (0.360-1.060) |
| **Chemo choice at randomization** | | |
| CAPOX | 351/477 | 0.63 (0.512-0.781) |
| FP | 63/74 | 0.62 (0.378-1.029) |

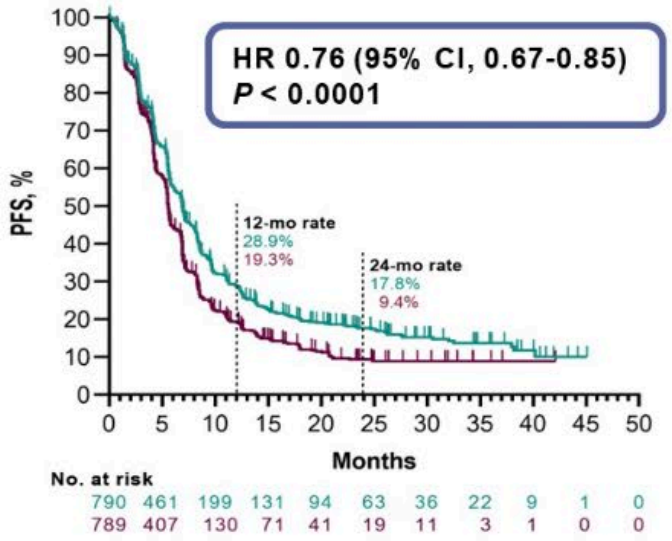



Rha SY, et al. *Lancet Oncol*. 2023;24(11):1181-1195.

# KEYNOTE-859: Secondary Endpoints

## Overall[1]

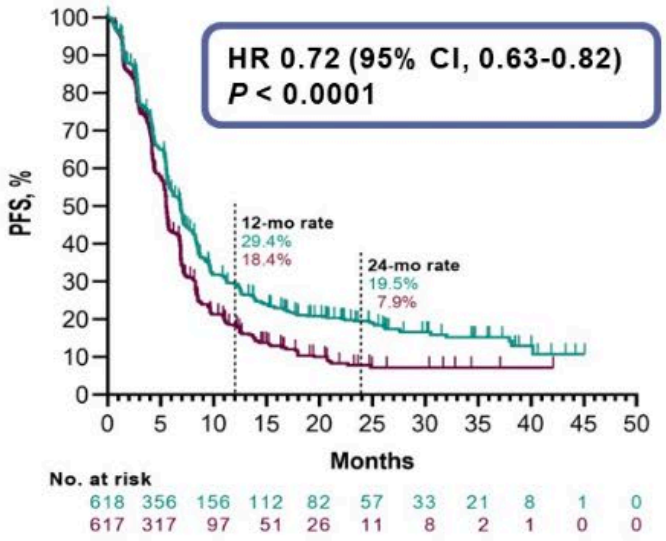
| | Pts w/ Event | Median PFS (95% CI), mo |
|---|---|---|
| Pembro + chemo | 72.4% | 6.9 (6.3-7.2) |
| Placebo + chemo | 77.1% | 5.6 (5.5-5.7) |




| | Pembro + Chemo | Placebo + Chemo |
|---|---|---|
| ORR, % (95% CI) | 51.3% (47.7-54.8) | 42.0% (38.5-45.5) |
| Δ (95% CI) | 9.3 (4.4-14.1); *P* = 0.00009 | |
| mDOR (range) | 8.0 mo (1.2+ - 41.5+) | 5.7 mo (1.3+ - 34.7+) |

## PD-L1 CPS ≥1

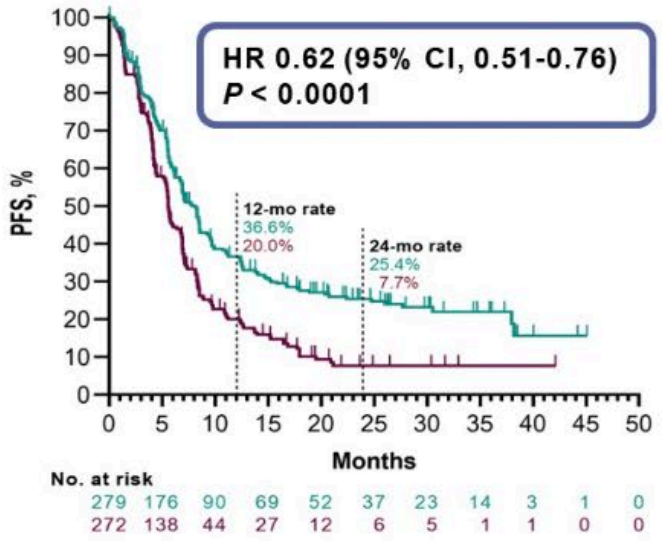
| | Pts w/ Event | Median PFS (95% CI), mo |
|---|---|---|
| Pembro + chemo | 71.7% | 6.9 (6.0-7.2) |
| Placebo + chemo | 78.3% | 5.6 (5.4-5.7) |




| | Pembro + Chemo | Placebo + Chemo |
|---|---|---|
| ORR, % (95% CI) | 52.1% (48.1-56.1) | 42.6% (38.7-46.6) |
| Δ (95% CI) | 9.5 (3.9-15.0); *P* = 0.00041 | |
| mDOR (range) | 8.3 mo (1.2+ - 41.5+) | 5.6 mo (1.3+ - 34.2+) |

## PD-L1 CPS ≥10

| | Pts w/ Event | Median PFS (95% CI), mo |
|---|---|---|
| Pembro + chemo | 68.1% | 8.1 (6.8-8.5) |
| Placebo + chemo | 77.2% | 5.6 (5.4-6.7) |




| | Pembro + Chemo | Placebo + Chemo |
|---|---|---|
| ORR, % (95% CI) | 60.6% (54.6-66.3) | 43.0% (37.1-49.1) |
| Δ (95% CI) | 17.5 (9.3-23.5); *P* = 0.00002 | |
| mDOR (range) | 10.9 mo (1.2+ - 41.5+) | 5.8 mo (1.4+ - 31.2+) |

Rha SY, et al. *Lancet Oncol*. 2023;24(11):1181-1195.

# ASCO Guidelines Recommendations

| Recommendation | Type | Evidence Quality | Strength |
|---|---|---|---|
| **1.1.** For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS ≥ 5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended. | EB | M | S |
| *Qualifying statements:*<br>*For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 1-5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy may be considered on a case-by-case basis.*<br>*For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 0, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy, without the addition of nivolumab, is recommended.* | | | |
| **1.2.** For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L I CPS ≥ 5, or pembrolizumab for PD-L1 CPS ≥ 10, in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended. | EB | L | S |
| *Qualifying statements:*<br>*For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS 1-5, or pembrolizumab for patients with PD-L1 CPS 1-10, in combination with fluoropyrimidine-and platinum-based chemotherapy, may be recommended on a case-by-case basis.*<br>*For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 0 or PD-L1 TPS 0%, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy, without the addition of PD-1 inhibitors, is recommended.* | | | |

Rajdev L, et al. *JCO Oncol Pract*. 2023;19(4):197-200.

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DOCTOR NAME, CREDS

# Case 2

# Gastric/GEJ Adenocarcinoma: HER2-/PD-L1-/CLDN 18.2+

- 60-year-old man with a history of *Helicobacter pylori*+ gastritis 5 years ago, treated and monitored for clearance
- Presents with anemia, epigastric pain with eating, and a 25-pound weight loss
- EGD: Fungating mass in the gastric antrum, biopsy shows poorly differentiated adenocarcinoma
- CT scan: 3-5 cm bilobar hepatic metastases, gastric wall mass, perigastric and retroperitoneal lymph node metastases
- PMH: HTN, elevated cholesterol
- ECOG 1, lab evaluation within normal limits

# Gastric/GEJ Adenocarcinoma: HER2-/PD-L1-/CLDN 18.2+ (cont'd)

- Tumor testing is HER2- by IHC, MMRp, PD-L1 CPS < 1%, claudin 18.2 90%
- NGS: p53 mutation, MSS, HER2 non-amplified
- What is optimal chemotherapy and targeted agent?
  - FOLFOX + pembro or nivo
  - FOLFOX + zolbetuximab

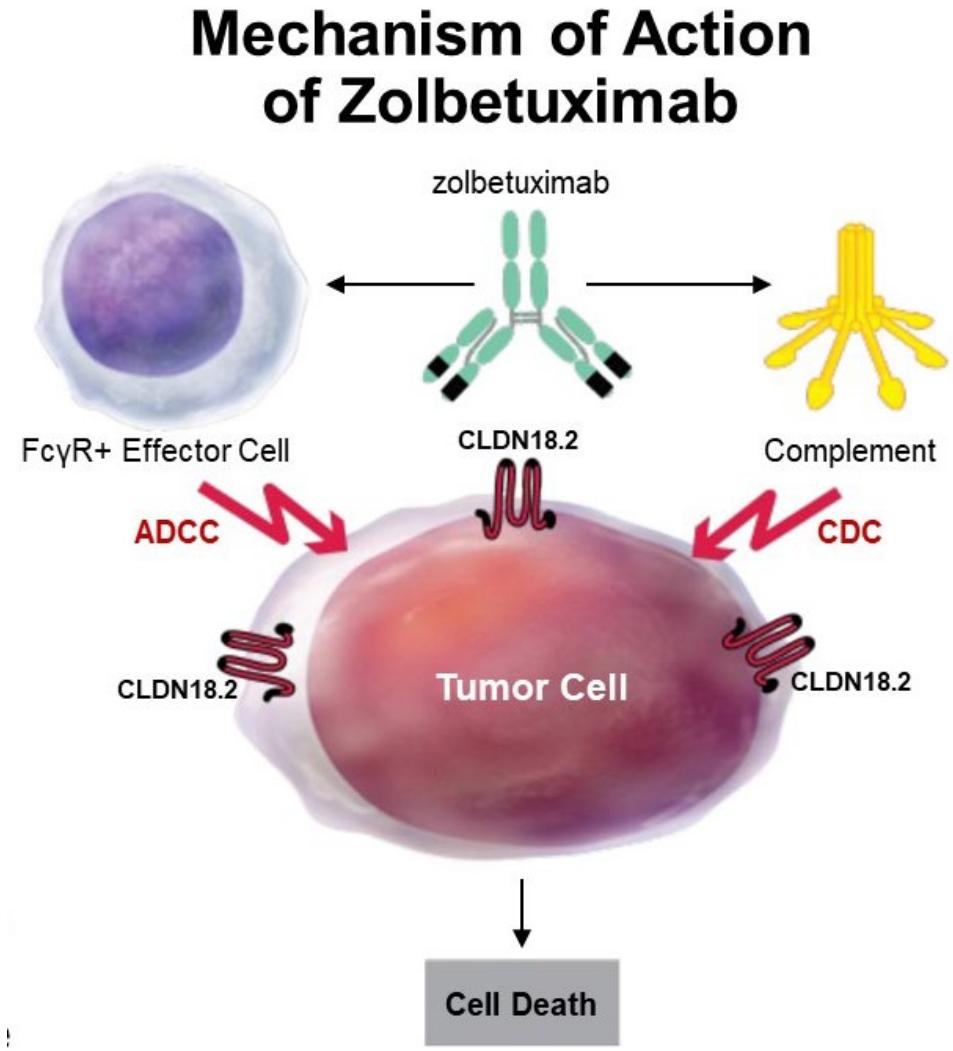
# Minimum Biomarker Testing in a Newly Diagnosed M1 Esophagogastric Cancer

1) IHC for HER2
2) IHC for DNA mismatch repair protein deficiency
   - Gastric cancer: 7%
   - Esophageal cancer: < 1%
3) IHC for PD-L1, combined positive score

- IHC for claudin 18.2 will become standard, positive if 75% of cells +
- NGS
  - Covers HER2 and other gene amplification
  - Validate MSI MSS
  - Tests for rare but targetable genes
    - NTRK gene fusion, BRAF V600E, RET gene fusion
  - Blood-based genomic testing if tissue unavailable

# Zolbetuximab and Claudin 18.2

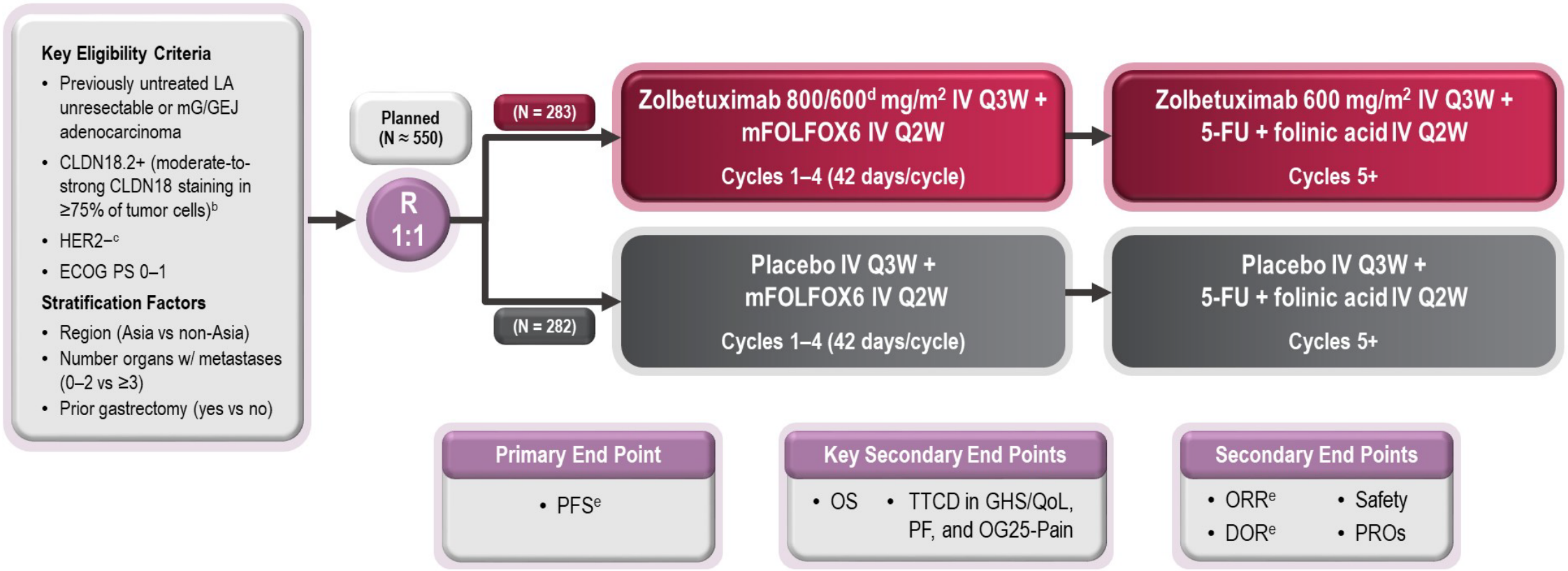
- CLDN 18.2 is a tight junction protein that is normally expressed in gastric cells and retained in gastric/GEJ adenocarcinoma
- CLDN 18.2 may become exposed on the surface of gastric/GEJ adenocarcinoma cells, making it a promising target
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody targeting CLDN 18.2 and inducing ADCC/CDC




Shitara K, et al. ASCO GI 2023. Abstract LBA292.

# SPOTLIGHT: Study Design

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



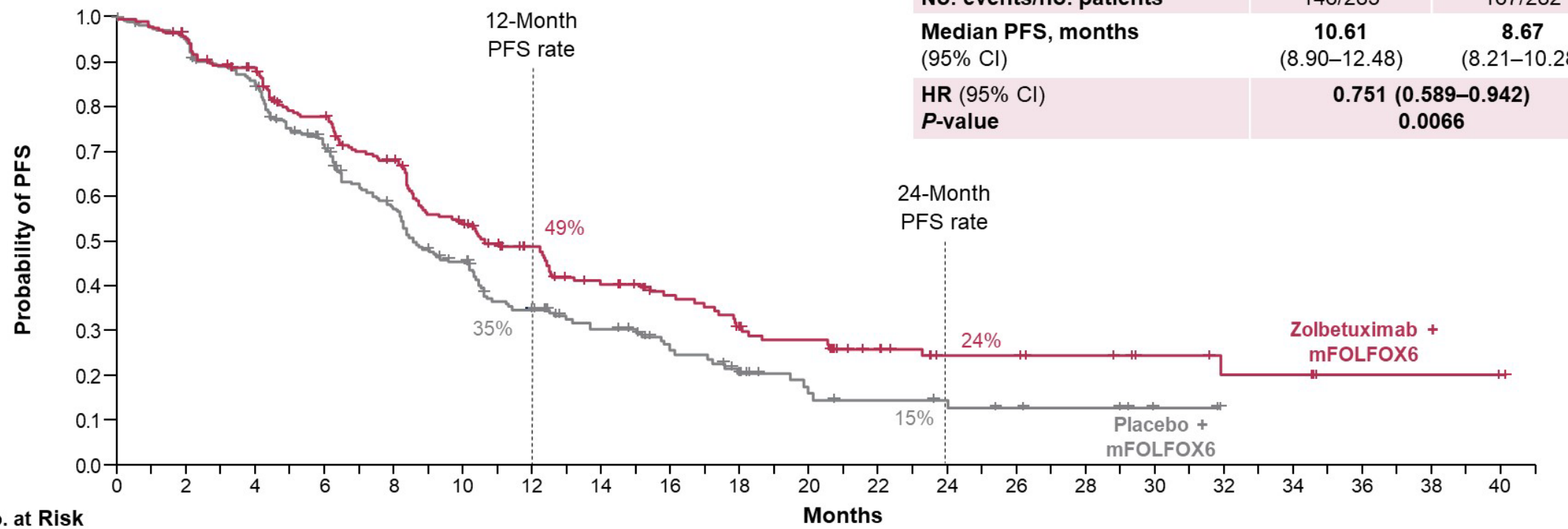

[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: PFS (Primary Endpoint)

Primary Endpoint: PFS by Independent Review Committee

| | Zolbetuximab + mFOLFOX6 | Placebo + mFOLFOX6 |
|---|---|---|
| **No. events/no. patients** | 146/283 | 167/282 |
| **Median PFS, months** (95% CI) | **10.61** (8.90–12.48) | **8.67** (8.21–10.28) |
| **HR** (95% CI) | **0.751 (0.589–0.942)** | |
| ***P*-value** | **0.0066** | |




| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + mFOLFOX6 | 283 | 263 | 254 | 232 | 226 | 190 | 187 | 148 | 143 | 108 | 102 | 84 | 78 | 59 | 56 | 53 | 43 | 40 | 33 | 28 | 28 | 21 | 19 | 17 | 12 | 12 | 12 | 10 | 10 | 9 | 7 | 7 | 5 | 5 | 5 | 2 | 2 | 2 | 2 | 2 | 1 | 0 |
| Placebo + mFOLFOX6 | 282 | 273 | 260 | 237 | 226 | 183 | 168 | 136 | 122 | 91 | 83 | 60 | 56 | 43 | 40 | 38 | 26 | 25 | 19 | 14 | 12 | 9 | 9 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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

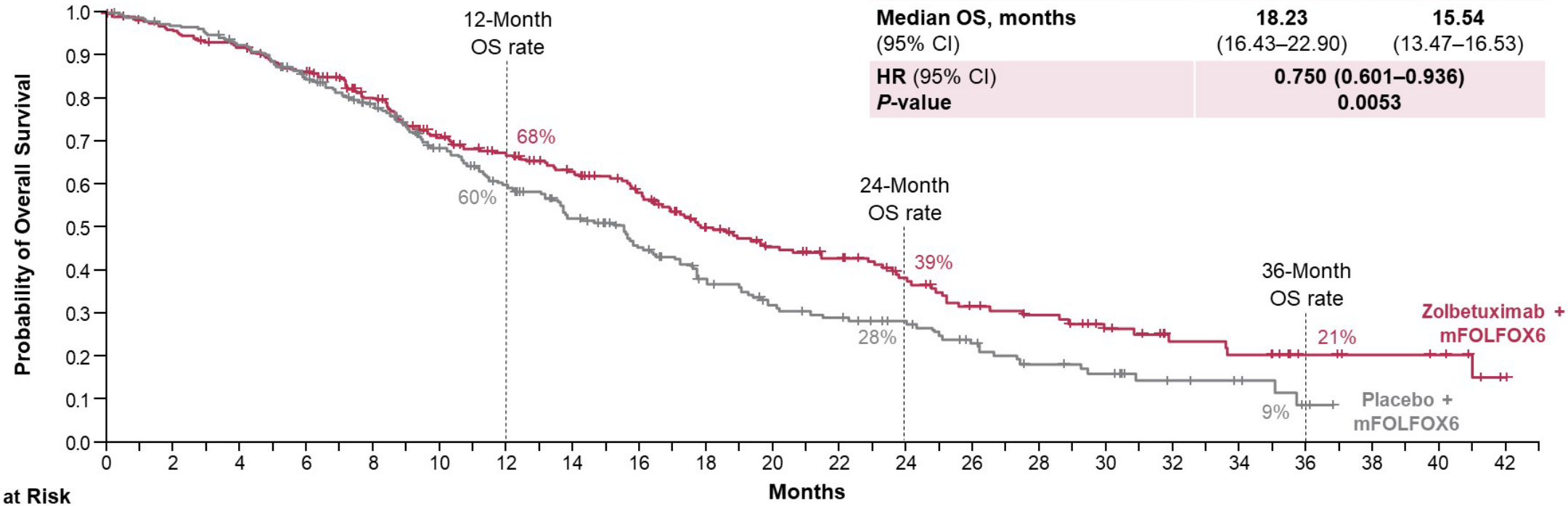
Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: OS

Key Secondary Endpoint: OS

| | Zolbetuximab + mFOLFOX6 | Placebo + mFOLFOX6 |
|---|---|---|
| **No. events/no. patients** | 149/283 | 177/282 |
| **Median OS, months** (95% CI) | **18.23** (16.43–22.90) | **15.54** (13.47–16.53) |
| **HR** (95% CI) | **0.750 (0.601–0.936)** | |
| ***P*-value** | **0.0053** | |




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + mFOLFOX6 | 283 | 270 | 264 | 255 | 251 | 241 | 233 | 217 | 196 | 178 | 164 | 152 | 146 | 135 | 125 | 117 | 107 | 93 | 83 | 75 | 70 | 67 | 62 | 58 | 49 | 42 | 34 | 32 | 30 | 27 | 23 | 20 | 15 | 15 | 13 | 13 | 9 | 8 | 7 | 7 | 6 | 4 | 1 | 0 |
| Placebo + mFOLFOX6 | 282 | 277 | 271 | 266 | 253 | 242 | 224 | 210 | 197 | 183 | 164 | 152 | 139 | 129 | 108 | 101 | 85 | 77 | 64 | 60 | 49 | 42 | 40 | 36 | 34 | 30 | 25 | 21 | 18 | 17 | 15 | 9 | 8 | 7 | 6 | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: Response

Secondary Endpoints

| | Zolbetuximab + mFOLFOX6 (N = 211) | Placebo + mFOLFOX6 (N = 211) |
|---|---|---|
| **Patients[a], n** | 128 | 131 |
| **ORR[b], % (95% CI)** | 60.7 (53.72–67.30) | 62.1 (55.17–68.66) |
| **BOR[c,d], n (%)** | | |
| CR | 12 (5.7) | 7 (3.3) |
| PR | 116 (55.0) | 124 (58.8) |
| SD | 45 (21.3) | 52 (24.6) |
| PD | 14 (6.6) | 14 (6.6) |
| **Median DOR[b], months, (95% CI)** | 8.51 (6.80–10.25) | 8.11 (6.47–11.37) |
| 3rd quartile, months (95% CI) | 29.9 (10.41–NE) | 15.5 (13.27–NE) |

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a]Patients with measurable disease. [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no post-baseline imaging assessment.

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# GLOW: Study Design

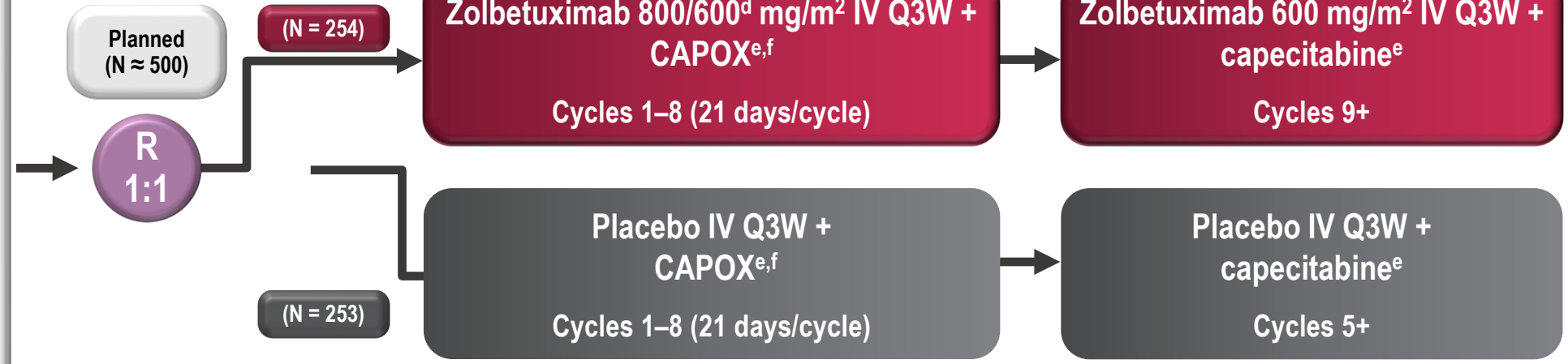
## Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

**Key Eligibility Criteria**

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN 18.2+ (moderate to strong CLDN 18 staining in ≥75% of tumor cells)[b]
- HER2−[c]
- 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 Endpoint**

- PFS[g]

**Key Secondary Endpoints**

- OS
- TTCD in GHS/QoL, PF, and OG25-Pain

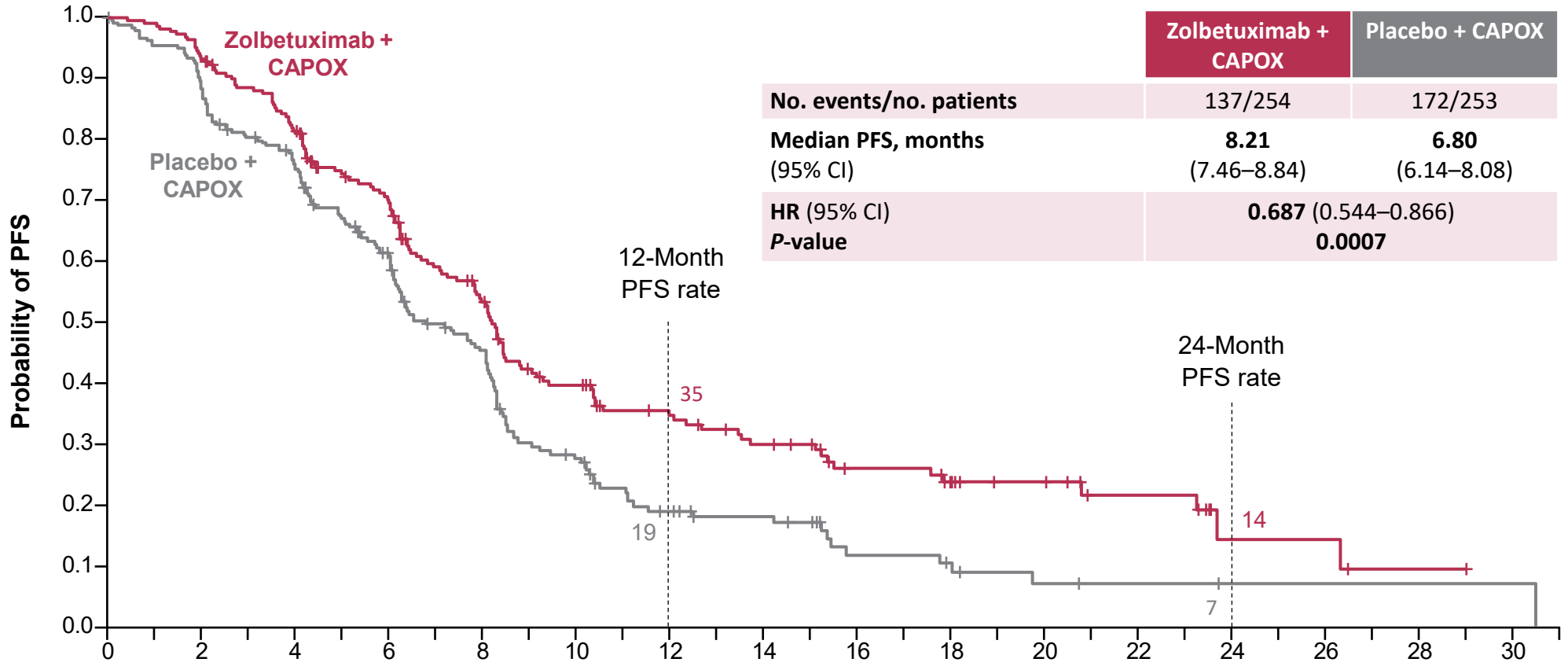
**Secondary Endpoints**

- ORR[g]
- DOR[g]
- Safety
- PROs

[a] Study was conducted at 131 sites in 18 countries across Asia, Europe, N. America, and S. America. [b] By central IHC using the analytically validated VENTANA CLDN 18 (43-14A) RxDx Assay. [c] By central or local HER2 testing. [d] 800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on day 1 of subsequent cycles. [e] 1000 mg/m² capecitabine TID on days 1 and 14 of each cycle. [f] 130 mg/m² oxaliplatin IV on day 1 of each cycle. [g] Per RECIST v1.1 by independent review committee.

Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: PFS by Independent Review Committee




| | Zolbetuximab + CAPOX | Placebo + CAPOX |
|---|---|---|
| **No. events/no. patients** | 137/254 | 172/253 |
| **Median PFS, months** (95% CI) | **8.21** (7.46–8.84) | **6.80** (6.14–8.08) |
| **HR** (95% CI) | **0.687** (0.544–0.866) | |
| ***P*-value** | **0.0007** | |

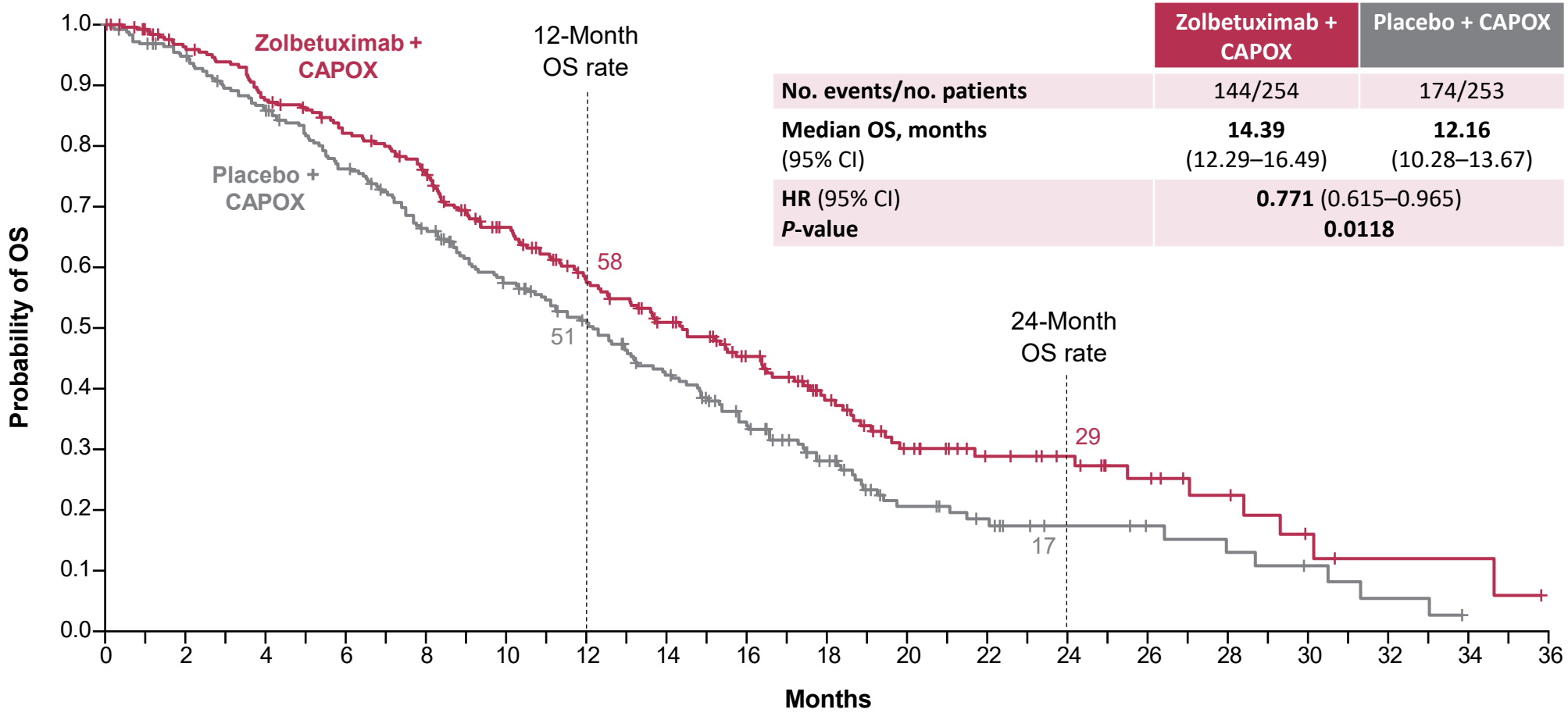
**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 223 | 205 | 187 | 171 | 141 | 132 | 104 | 91 | 66 | 61 | 47 | 45 | 41 | 37 | 35 | 24 | 24 | 19 | 14 | 14 | 9 | 9 | 9 | 3 | 3 | 3 | 1 | 1 | 1 | 0 | 0 |
| Placebo + CAPOX | 253 | 233 | 215 | 188 | 175 | 146 | 127 | 93 | 84 | 48 | 43 | 30 | 24 | 19 | 19 | 17 | 9 | 9 | 7 | 5 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

- PFS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX

Data cutoff: October 7, 2022; Median follow-up = 12.62 months (zolbetuximab + CAPOX) vs 12.09 months (placebo + CAPOX).
Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: OS




| | Zolbetuximab + CAPOX | Placebo + CAPOX |
|---|---|---|
| **No. events/no. patients** | 144/254 | 174/253 |
| **Median OS, months** (95% CI) | **14.39** (12.29–16.49) | **12.16** (10.28–13.67) |
| **HR** (95% CI) | **0.771** (0.615–0.965) | |
| ***P*-value** | **0.0118** | |

**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 243 | 233 | 226 | 211 | 203 | 193 | 187 | 171 | 150 | 138 | 125 | 108 | 100 | 87 | 80 | 68 | 61 | 47 | 38 | 31 | 27 | 22 | 21 | 18 | 13 | 12 | 9 | 8 | 6 | 4 | 2 | 2 | 2 | 2 | 1 | 0 |
| Placebo + CAPOX | 253 | 243 | 235 | 220 | 210 | 197 | 181 | 168 | 152 | 136 | 125 | 115 | 104 | 92 | 82 | 70 | 59 | 49 | 40 | 27 | 22 | 20 | 16 | 12 | 10 | 10 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 2 | 0 | 0 | 0 |

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

Data cutoff: October 7, 2022; Median follow-up = 17.71 months (zolbetuximab + CAPOX) vs 18.43 months (placebo + CAPOX).

Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: Response

| | Zolbetuximab + CAPOX (N = 195) | Placebo + CAPOX (N = 205) |
|---|---|---|
| **Patients[a], n** | 105 | 100 |
| **ORR[b], % (95% CI)** | 53.8 (46.58–60.99) | 48.8 (41.76–55.84) |
| **BOR[c,d], n (%)** | 163 (83.6) | 188 (91.7) |
| CR | 6 (3.1) | 3 (1.5) |
| PR | 99 (50.8) | 97 (47.3) |
| SD | 46 (23.6) | 57 (27.8) |
| PD | 10 (5.1) | 25 (12.2) |
| **Median DOR[b], months, (range)** | 6.28 (5.39-8.28) | 6.18 (4.53-6.41) |

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a] Patients with measurable disease. [b] Per RECIST version 1.1 by independent review committee. [c] Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown. [d] Patients with missing data had no post-baseline imaging assessment.
Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

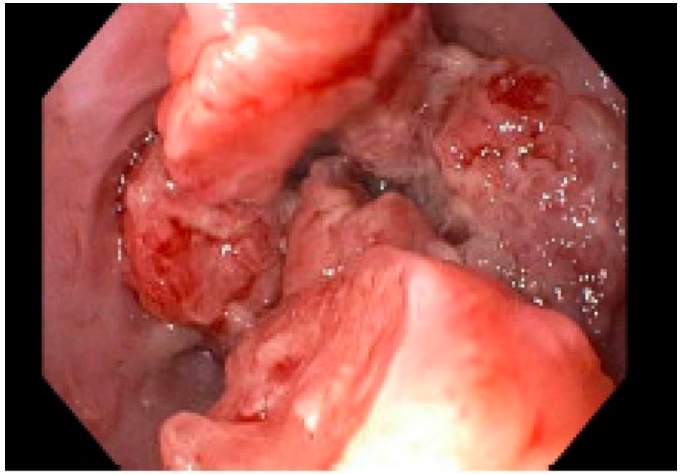
*Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi.*

DOCTOR NAME, CREDS

# Case 3

# Case Presentation

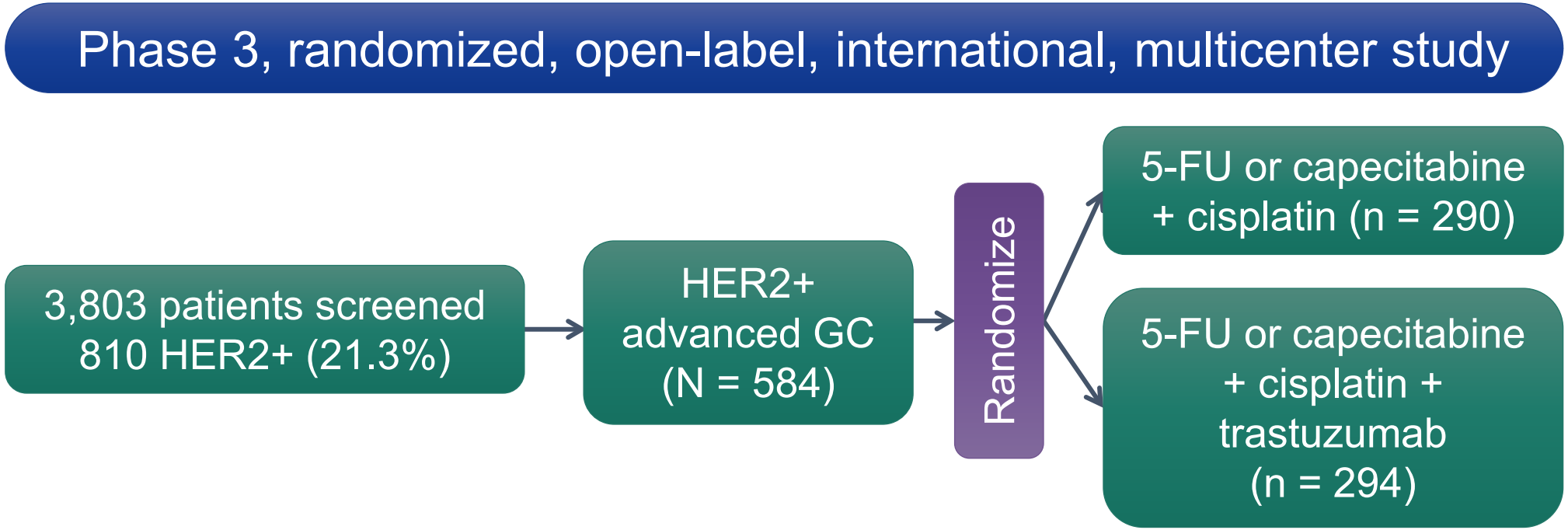
- 71-year-old man with new dysphagia, found to have iron deficiency, Hb: 8.1
- **EGD:** large fungating mass with bleeding in the lower third of the esophagus at 35 cm
- **Pathology:** well-differentiated adenocarcinoma
- **CT chest/abdomen/pelvis** showing
  - GE junction lesion extending to the gastric fundus and body
  - Multiple enlarged mediastinal and upper abdominal lymphadenopathy
  - Hepatic metastases



# Case Presentation (cont'd)

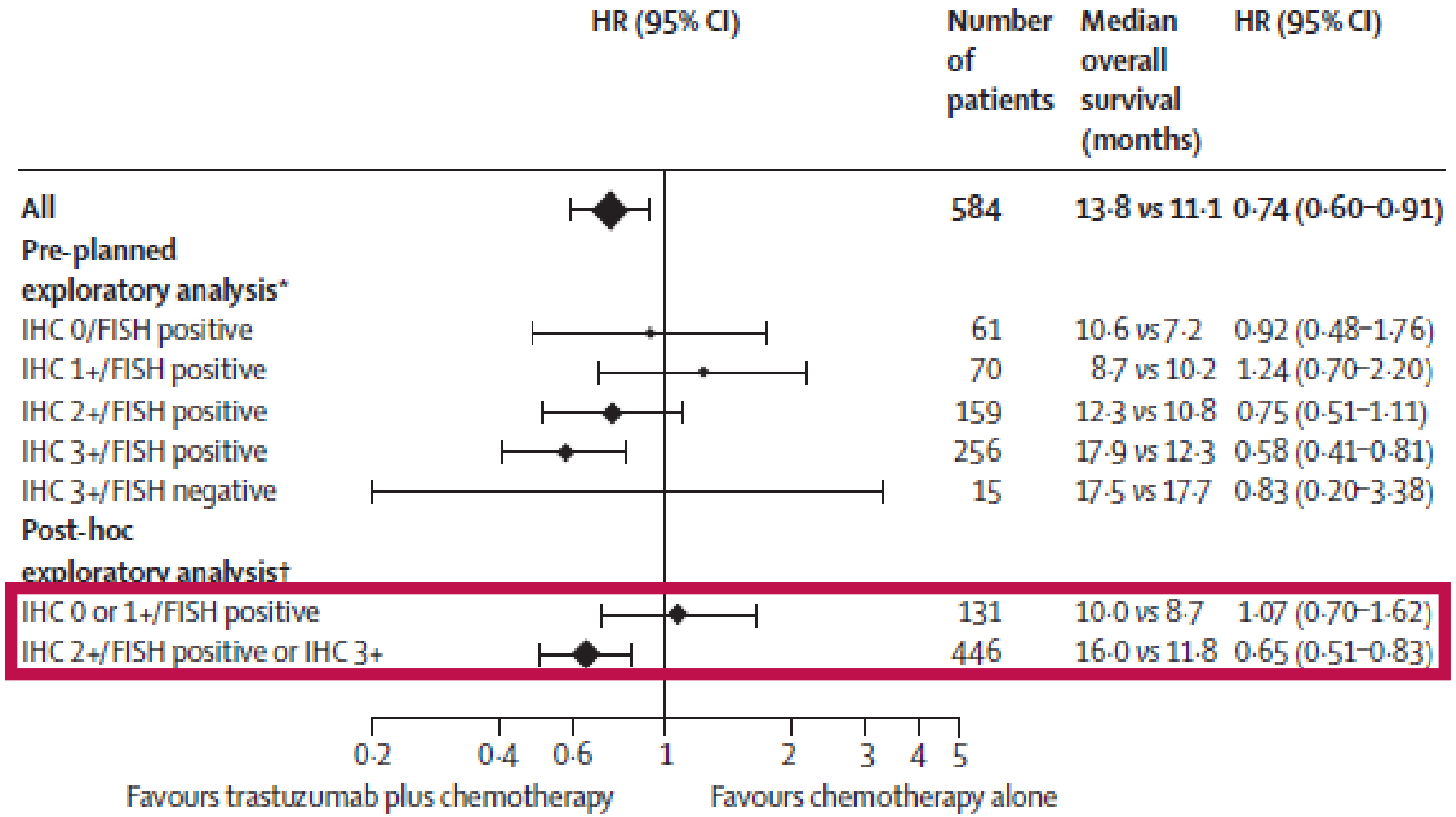
- **Biomarker testing**
  - HER2 IHC: 3+
  - PD-L1 CPS: 2
- Started FOLFOX + trastuzumab + pembrolizumab
- Improvement in dysphagia after first cycle
- CT chest/abdomen/pelvis after 3 months showed a partial response with decrease in size of hepatic mets

# ToGA study: Targeting HER2 With Trastuzumab



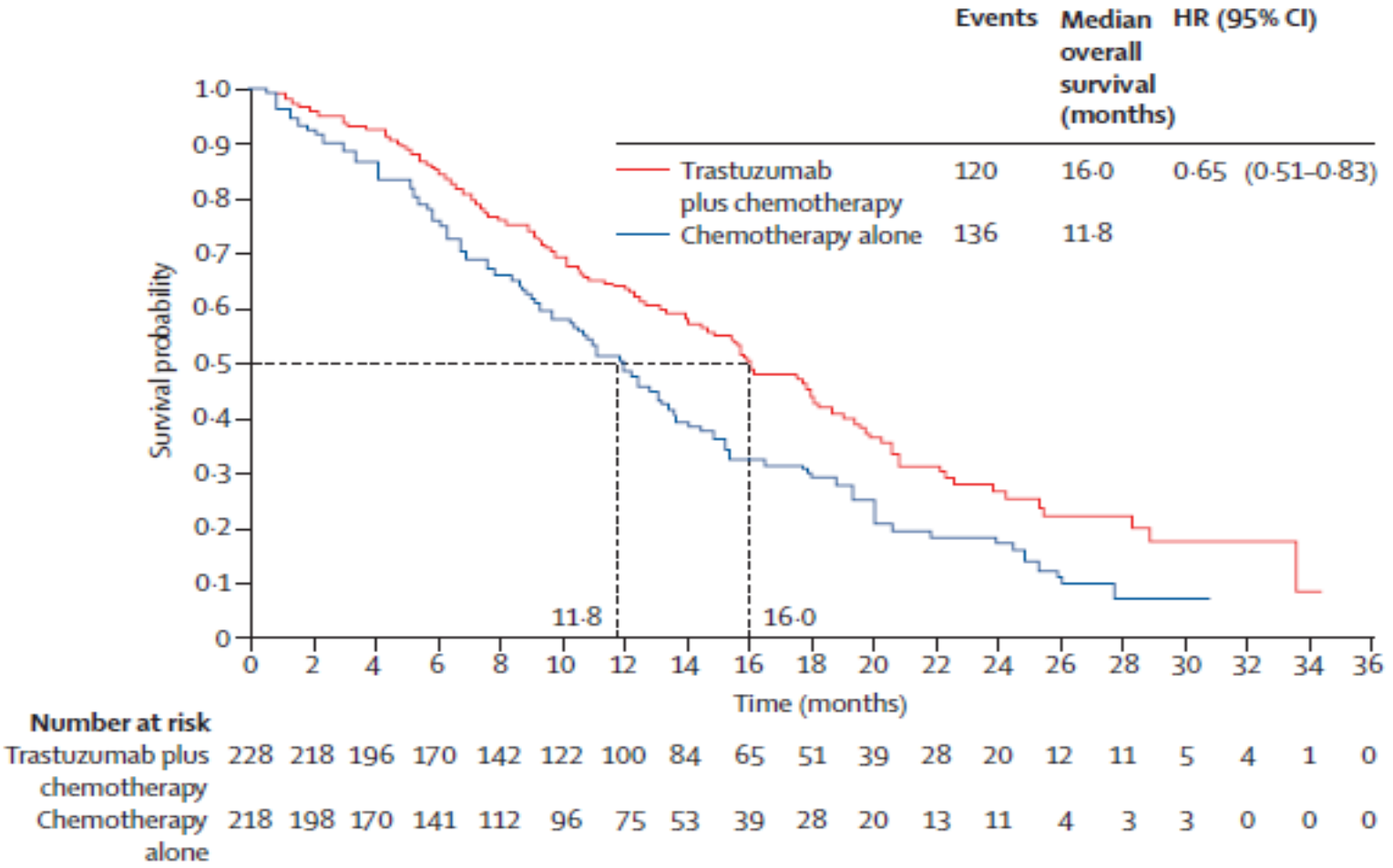

Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

# OS Was Improved in Patients With High HER2 Expression



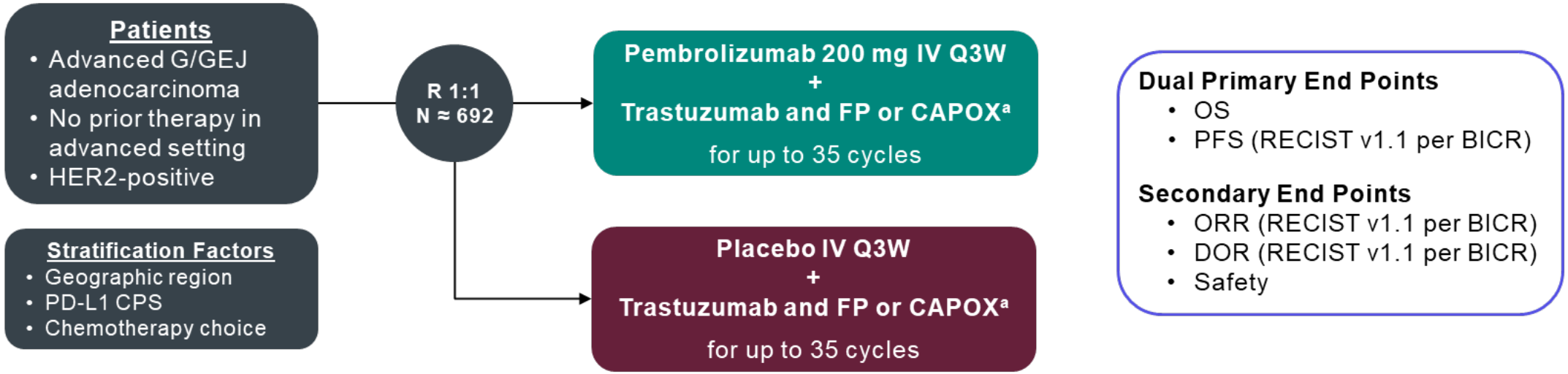

Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

# Improved OS With High HER2 Expression




Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

# KEYNOTE-811: Study Design




[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).

Presented by Janjigian YY, et al. ASCO 2021. Abstract 4013.
Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.

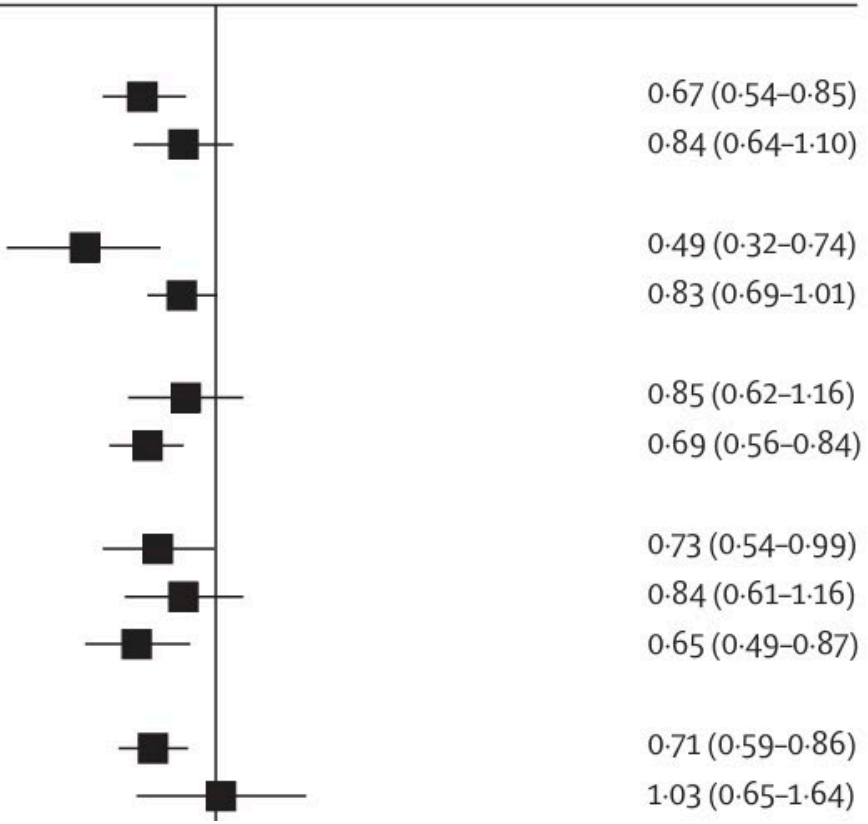
# KEYNOTE-811: First Interim Results

| Variable | Pembrolizumab group (*n* = 133) | Placebo group (*n* = 131) |
|---|---|---|
| Objective response (% (95% confidence interval))[a] | 74.4 (66.2–81.6) | 51.9 (43.0–60.7) |
| Disease control (% (95% confidence interval))[b] | 96.2 (91.4–98.8) | 89.3 (82.7–94.0) |
| Best overall response (number (%)) | | |
| Complete response | 15 (11.3) | 4 (3.1) |
| Partial response | 84 (63.2) | 64 (48.9) |
| Stable disease | 29 (21.8) | 49 (37.4) |
| Progressive disease | 5 (3.8) | 7 (5.3) |
| Not evaluable[c] | 0 (0.0) | 2 (1.5) |
| Not assessed[c] | 0 (0.0) | 5 (3.8) |

Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.

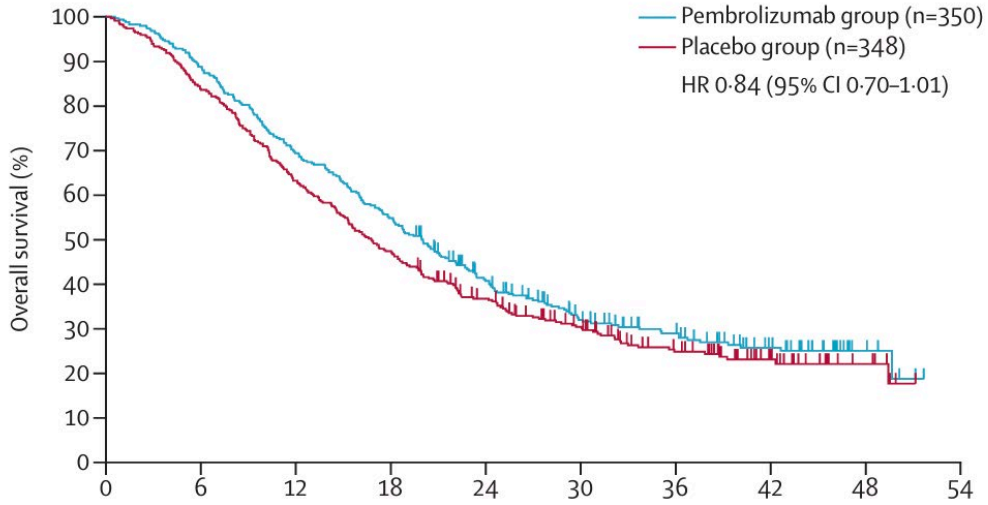
# KEYNOTE-811: PFS in Subgroups

| | Events/patients, n/N | | HR (95% CI) |
|---|---|---|---|
| | Pembrolizumab group | Placebo group | |
| **Age, years** | | | |
| <65 | 152/205 | 153/192 | 0·67 (0·54–0·85) |
| ≥65 | 101/145 | 108/156 | 0·84 (0·64–1·10) |
| **Sex** | | | |
| Female | 42/66 | 55/68 | 0·49 (0·32–0·74) |
| Male | 211/284 | 206/280 | 0·83 (0·69–1·01) |
| **Race** | | | |
| Asian | 76/119 | 80/121 | 0·85 (0·62–1·16) |
| Non-Asian | 177/231 | 179/225 | 0·69 (0·56–0·84) |
| **Geographical region** | | | |
| Europe, North America, and Australia | 84/113 | 88/111 | 0·73 (0·54–0·99) |
| Asia | 75/118 | 78/119 | 0·84 (0·61–1·16) |
| Rest of world | 94/119 | 95/118 | 0·65 (0·49–0·87) |
| **PD-L1 status** | | | |
| CPS≥1 | 217/298 | 225/296 | 0·71 (0·59–0·86) |
| CPS<1 | 36/52 | 36/52 | 1·03 (0·65–1·64) |



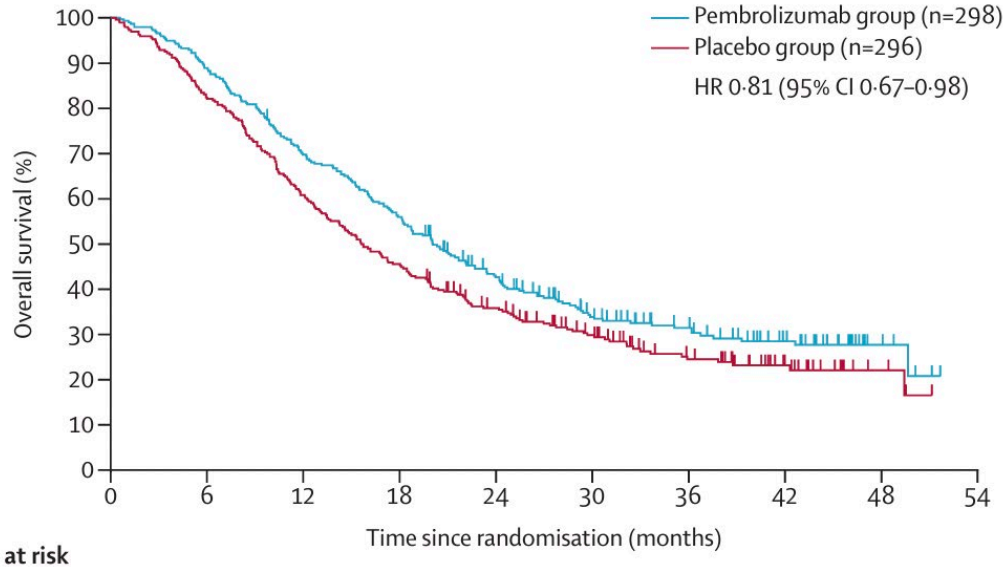
Janjigian YY, et al. *Lancet.* 2023;402(10418):2197-2208.

# KEYNOTE-811: Third Interim Results




| Number at risk (number censored) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 350 (0) | 311 (0) | 243 (0) | 192 (0) | 126 (19) | 84 (36) | 61 (52) | 37 (70) | 7 (99) | 0 (105) |
| Placebo group | 348 (0) | 292 (0) | 220 (0) | 165 (0) | 116 (13) | 83 (27) | 51 (46) | 25 (69) | 8 (85) | 0 (92) |

**All patients**




| Number at risk (number censored) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 298 (0) | 265 (0) | 207 (0) | 166 (0) | 115 (13) | 78 (28) | 58 (43) | 37 (59) | 7 (88) | 0 (94) |
| Placebo group | 296 (0) | 244 (0) | 180 (0) | 135 (0) | 96 (11) | 67 (25) | 41 (41) | 21 (59) | 5 (74) | 0 (78) |

**PD-L1 CPS ≥1**

On May 1, 2024, Merck announced that KEYNOTE-811 met the dual primary endpoint of overall survival.

Janjigian YY, et al. *Lancet.* 2023;402(10418):2197-2208.

# Summary

- ToGA established doublet chemotherapy and trastuzumab as standard first-line therapy for HER2+ gastroesophageal adenocarcinoma
- KEYNOTE-811 showed a PFS and OS benefit with the addition of pembrolizumab with doublet chemotherapy and trastuzumab for PD-L1 CPS ≥1 disease

# Case 4

# Gastric/GEJ Adenocarcinoma: HER2-/PD-L1+/CLDN 18.2+, Prior Peri-Op CPI

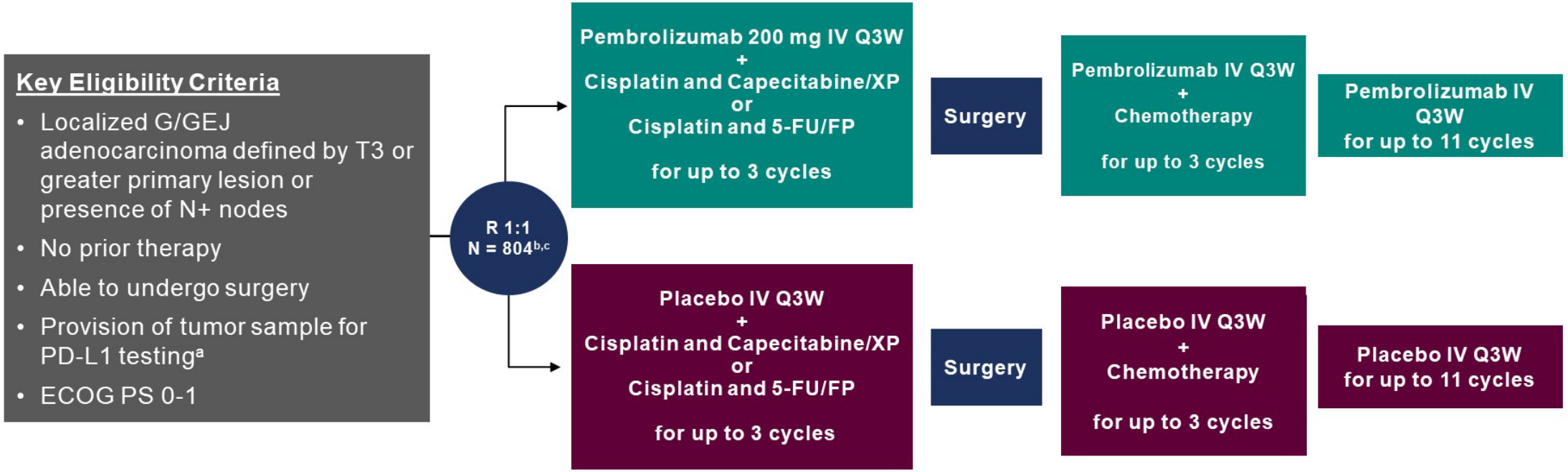
- 55-year-old man presents with fatigue, anemia, epigastric pain, and weight loss
- History of AODM, HTN, elevated cholesterol
- Endoscopy: proximal gastric mass, biopsy adenocarcinoma, MMRp, HER2-, PD-L1+
- CT scan: gastric mass with no metastases
- EUS: T3 N1
- Laparoscopy: no metastases
- Enrolled on KEYNOTE-585: perioperative 5-FU/cisplatin + placebo or pembrolizumab, 3 pre/3 post-op cycles + 11 cycles placebo/pembro
  - Complicated by a skin rash, hypothyroidism
- Resection: T2N0 disease

# Gastric/GEJ Adenocarcinoma: HER2-/PD-L1+/CLDN 18.2+ (cont'd)

- 7 months after treatment, abdominal pain, weight loss
- CT scan: bilobar hepatic metastases, ascites
- Liver biopsy: recurrent adenocarcinoma, HER2-, PD-L1+ CPS 5%, MMRp, claudin 18.2+ at 80%
- Exam is normal, ECOG 1, lab values within normal limits
- NGS: p53 mutation, MSS, HER2 non-amplified
- What is optimal chemotherapy and targeted agent?
  - FOLFOX + pembro or nivo
  - FOLFOX + zolbetuximab

# KEYNOTE-585: Study Design (Main Cohort)

KEYNOTE-585 Study Design
Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (**Main Cohort**)




**Stratification factors**
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

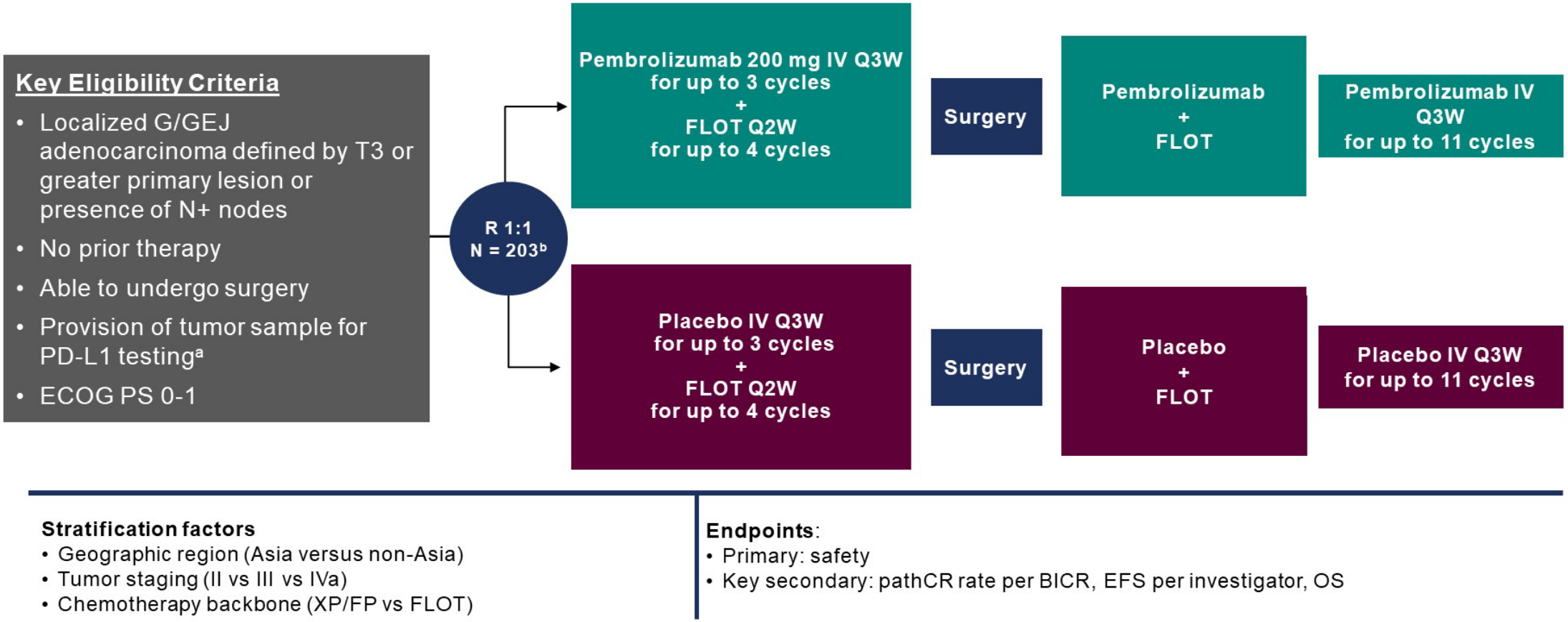
**Endpoints**:
- Primary: pathCR rate per BICR, EFS per investigator, OS (main cohort), safety (FLOT)
- Key secondary: safety (main cohort), safety, OS, EFS (main plus FLOT cohort)

[a]PD-L1 status was centrally assessed; [b]Main cohort. [c]An additional 203 patients were randomized 1:1 to a separate FLOT cohort evaluating pembrolizumab + FLOT vs placebo + FLOT (5-FU 2600 mg/m$^2$, leucovorin 200 mg/m$^2$, oxaliplatin 85 mg/m$^2$, docetaxel 50 mg/m$^2$) Q2W for up to 4 cycles in the neoadjuvant and adjuvant phases. XP: cisplatin 80 mg/m$^2$ IV on d1 and capecitabine 1000 mg/m$^2$ orally BID from d1 – d14. FP: cisplatin 80 mg/m$^2$ IV on d1 and 5-FU 800 mg/m$^2$ IV from d1 – d5 up to 4000 mg/m$^2$.

Shitara K, et al. *Lancet Oncol.* 2024;25(2):212-224.

# KEYNOTE-585: Study Design (FLOT Cohort)

KEYNOTE-585 Study Design
Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (**FLOT Cohort**)



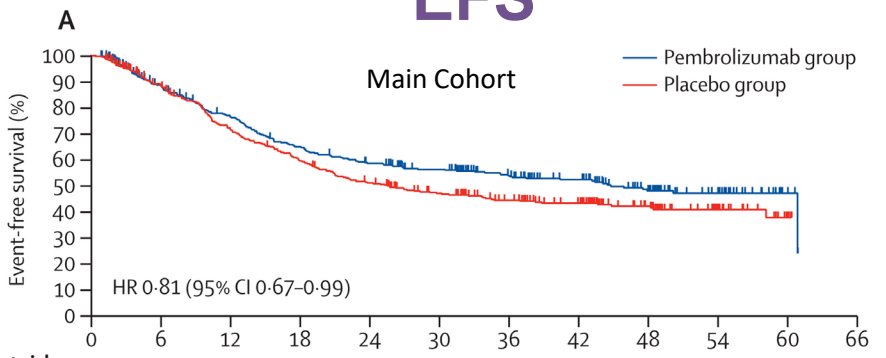

[a]PD-L1 status was centrally assessed; [b]203 patients were randomized 1:1 to a separate FLOT cohort evaluating pembrolizumab + FLOT vs placebo + FLOT (5-FU 2600 mg/m$^2$, leucovorin 200 mg/m$^2$, oxaliplatin 85 mg/m$^2$, docetaxel 50 mg/m$^2$) Q2W for up to 4 cycles in the neoadjuvant and adjuvant phases.

Shitara K, et al. *Lancet Oncol.* 2024;25(2):212-224.

# KEYNOTE-585: EFS and OS

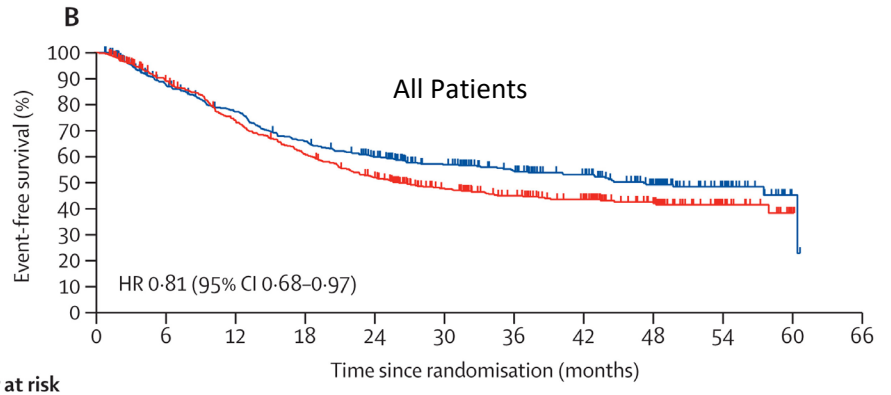
## EFS

### CF



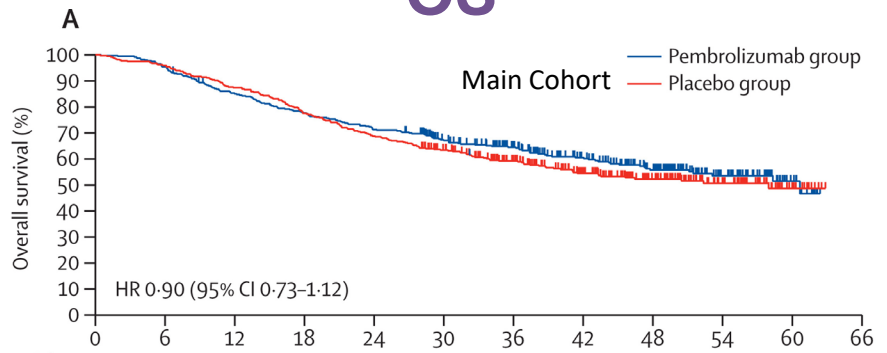

| Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 402 | 326 | 276 | 233 | 207 | 182 | 147 | 118 | 77 | 36 | 3 | 0 |
| | (0) | (33) | (38) | (39) | (42) | (59) | (87) | (112) | (145) | (185) | (217) | (219) |
| Placebo group | 402 | 332 | 265 | 217 | 183 | 154 | 126 | 105 | 63 | 25 | 3 | 0 |
| | (0) | (28) | (32) | (33) | (36) | (51) | (71) | (89) | (129) | (165) | (186) | (189) |

### CF + FLOT

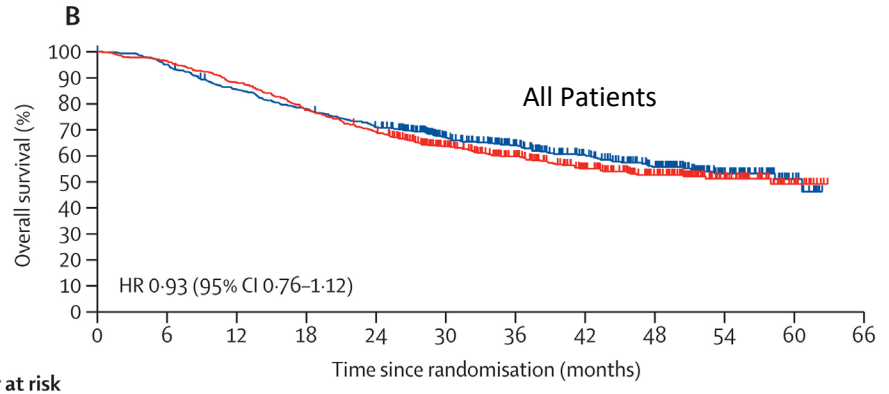



| Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 502 | 410 | 353 | 300 | 261 | 204 | 162 | 132 | 88 | 37 | 3 | 0 |
| | (0) | (39) | (45) | (46) | (56) | (101) | (136) | (161) | (197) | (247) | (280) | (282) |
| Placebo group | 505 | 423 | 345 | 282 | 235 | 176 | 142 | 120 | 77 | 26 | 3 | 0 |
| | (0) | (35) | (40) | (41) | (46) | (87) | (111) | (129) | (170) | (219) | (241) | (244) |

## OS




| Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 402 | 383 | 339 | 310 | 285 | 250 | 211 | 160 | 117 | 60 | 14 | 0 |
| | (0) | (1) | (4) | (4) | (4) | (25) | (54) | (93) | (125) | (179) | (224) | (237) |
| Placebo group | 402 | 386 | 352 | 313 | 278 | 242 | 197 | 147 | 96 | 49 | 13 | 0 |
| | (0) | (0) | (0) | (0) | (0) | (15) | (45) | (81) | (127) | (172) | (207) | (220) |



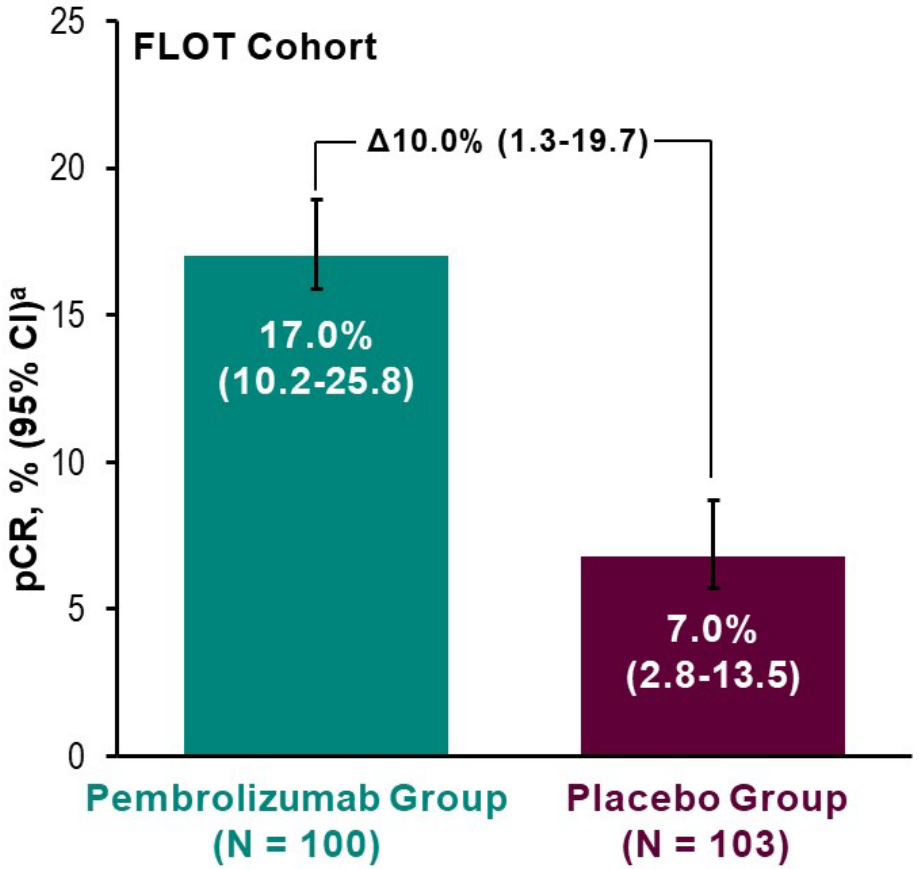

| Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 502 | 477 | 427 | 391 | 355 | 281 | 230 | 179 | 135 | 65 | 14 | 0 |
| | (0) | (1) | (4) | (4) | (6) | (63) | (102) | (141) | (173) | (239) | (289) | (302) |
| Placebo group | 505 | 480 | 447 | 395 | 353 | 275 | 218 | 167 | 115 | 52 | 13 | 0 |
| | (0) | (0) | (0) | (0) | (0) | (51) | (93) | (129) | (175) | (236) | (274) | (287) |

**Path CR rate 2% ➔ 13%**

Shitara K, et al. *Lancet Oncol.* 2024;25(2):212-224.

# KEYNOTE-585: pCR (FLOT Cohort)

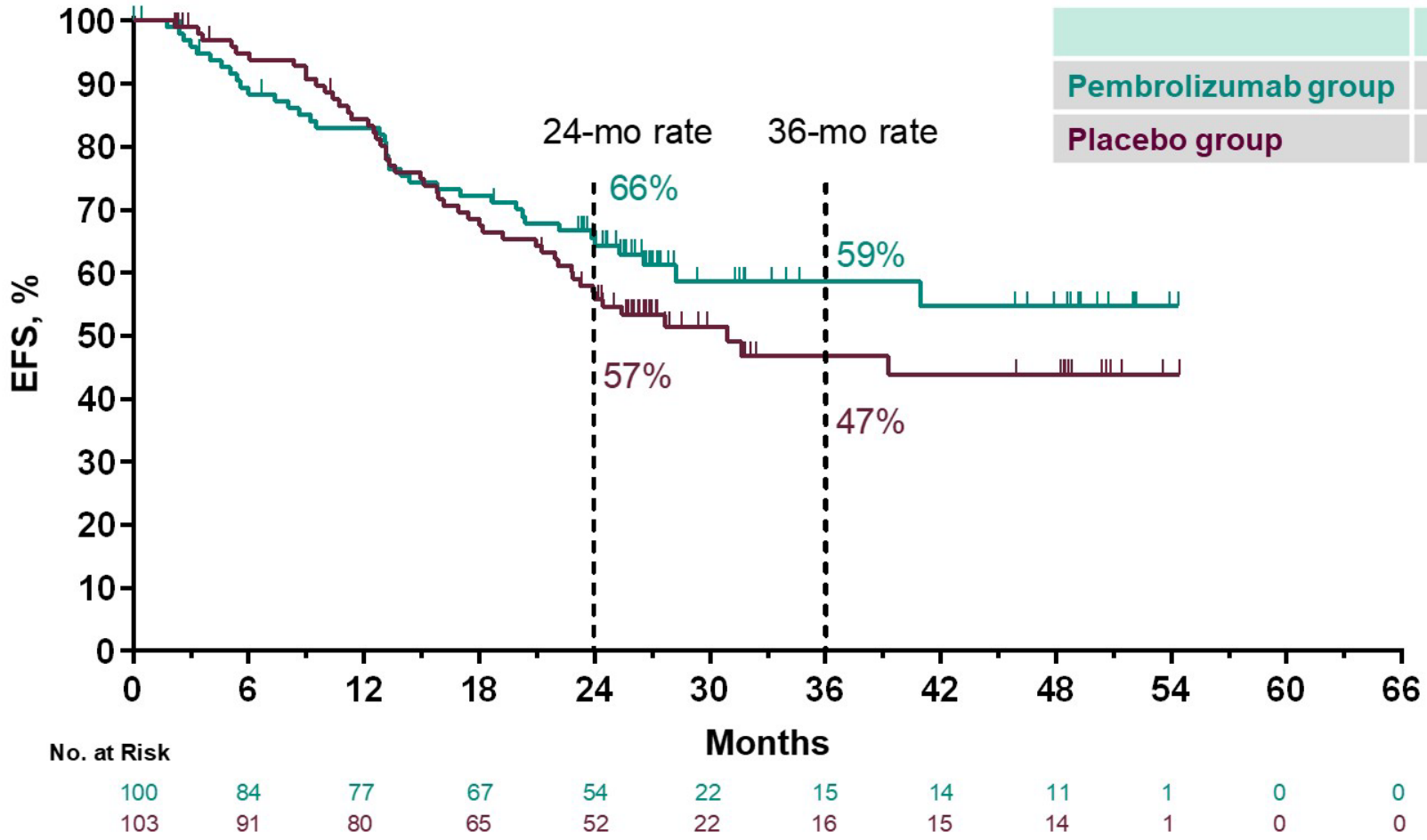
Pathological Complete Responses
Assessed by Blinded, Independent Central Review




Al-Batran SE, et al. ASCO GI 2024. Abstract 247.

# KEYNOTE-585: EFS (FLOT Cohort)

Event-Free Survival: FLOT Cohort



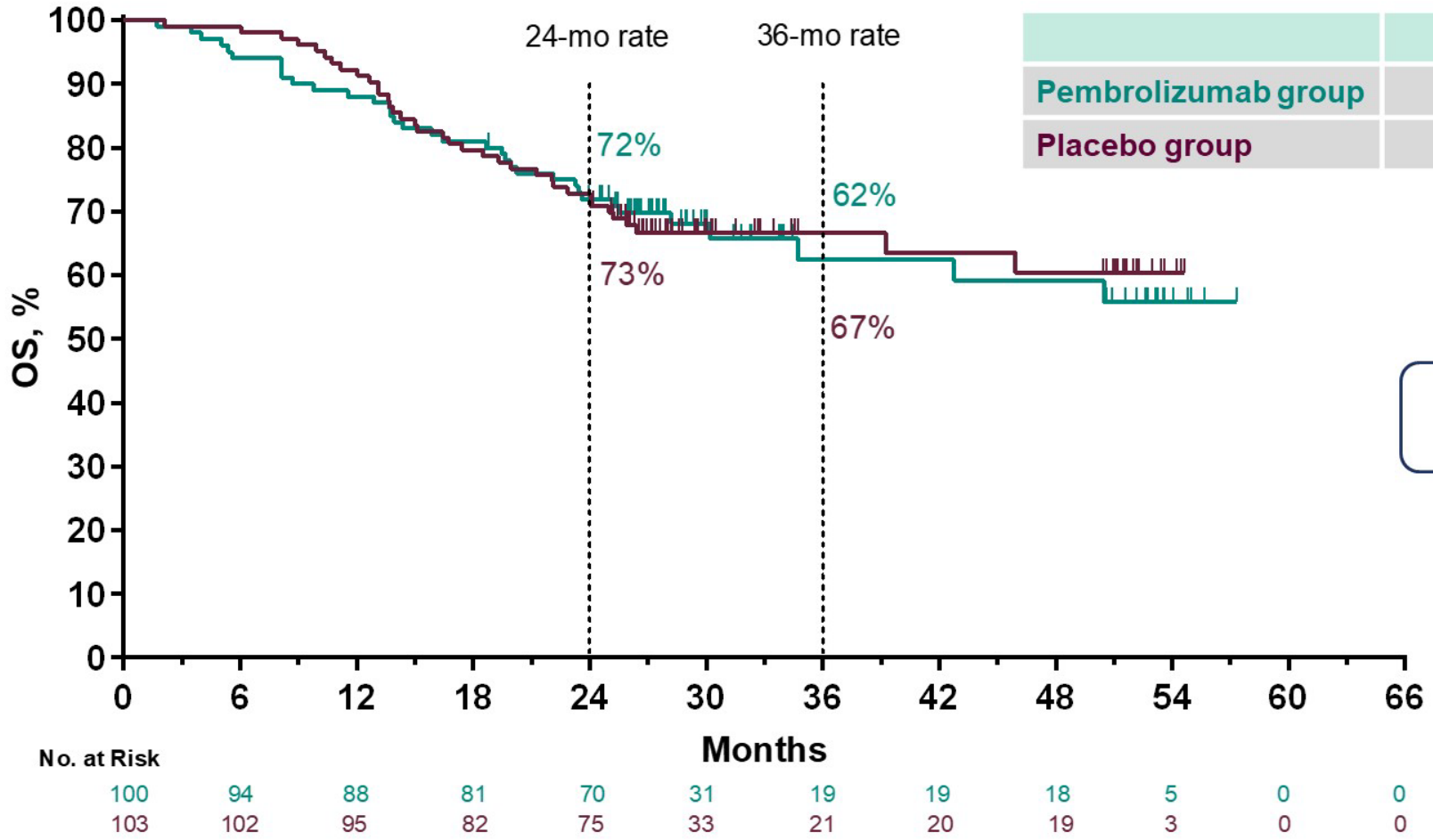

| | Events | Median (95% CI), mo |
|---|---|---|
| Pembrolizumab group | 37% | NR (28.2-NR) |
| Placebo group | 47% | 30.9 (22.8-NR) |

**HR 0.79 (95% CI, 0.52-1.22)**

Al-Batran SE, et al. ASCO GI 2024. Abstract 247.

# KEYNOTE-585: OS (FLOT Cohort)

Overall Survival: FLOT Cohort



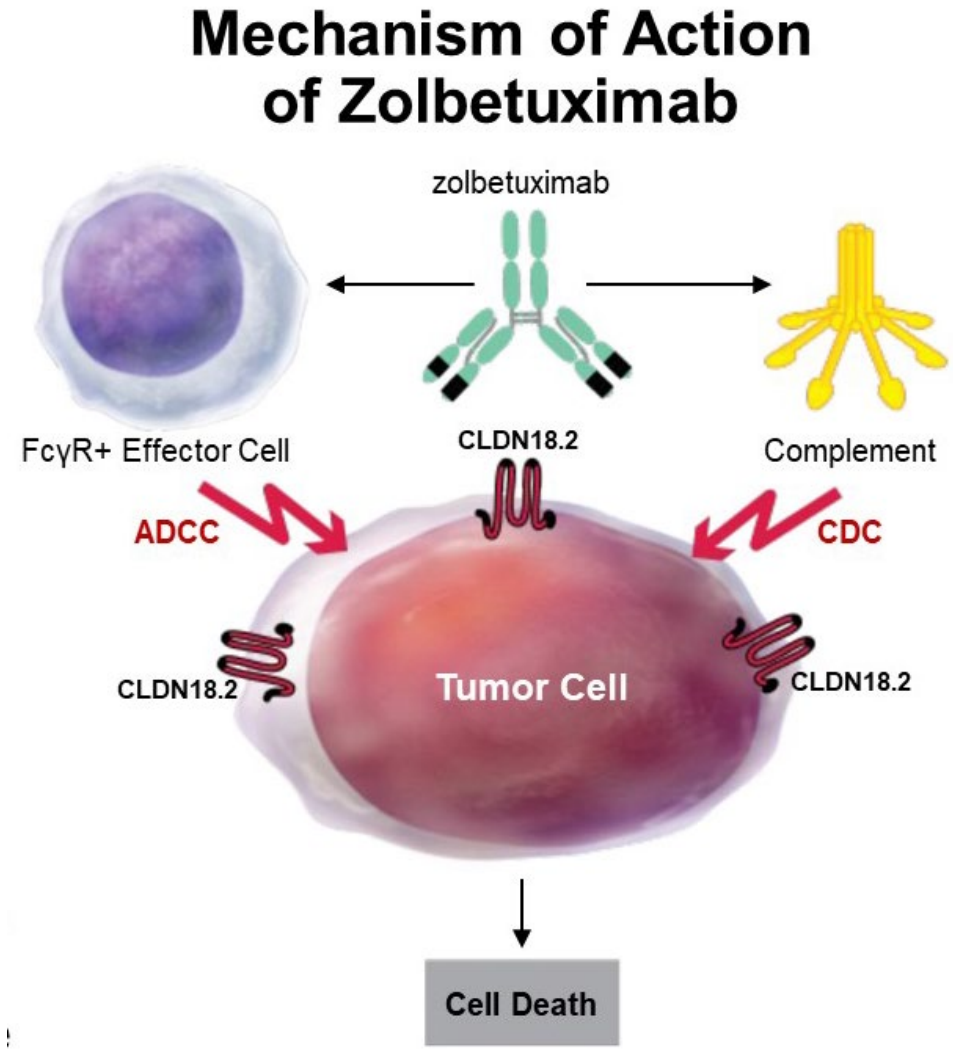

| | Events | Median (95% CI), mo |
|---|---|---|
| Pembrolizumab group | 35% | NR (34.7-NR) |
| Placebo group | 35% | NR (45.9-NR) |

**HR 1.04 (95% CI, 0.66-1.66)**

Al-Batran SE, et al. ASCO GI 2024. Abstract 247.

# Zolbetuximab and Claudin 18.2

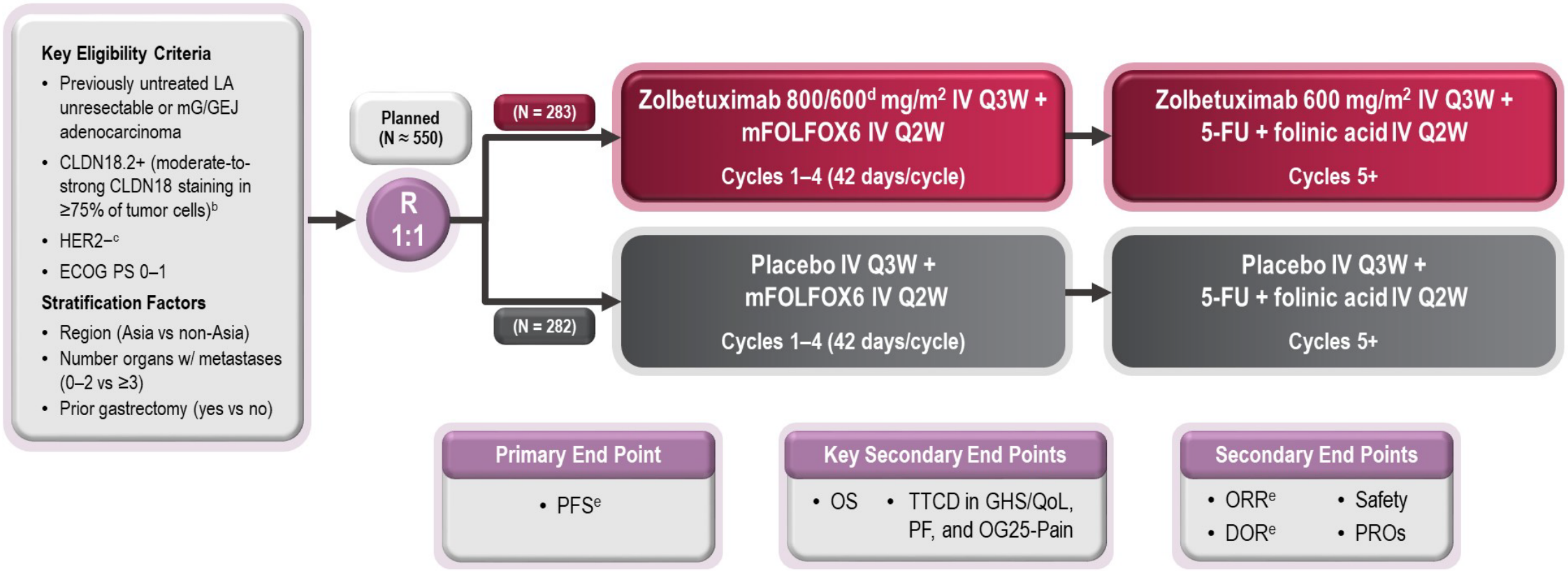
- CLDN 18.2 is a tight junction protein that is normally expressed in gastric cells and retained in gastric/GEJ adenocarcinoma
- CLDN 18.2 may become exposed on the surface of gastric/GEJ adenocarcinoma cells, making it a promising target
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody targeting CLDN 18.2 and inducing ADCC/CDC




Shitara K, et al. ASCO GI 2023. Abstract LBA292.

# SPOTLIGHT: Study Design

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



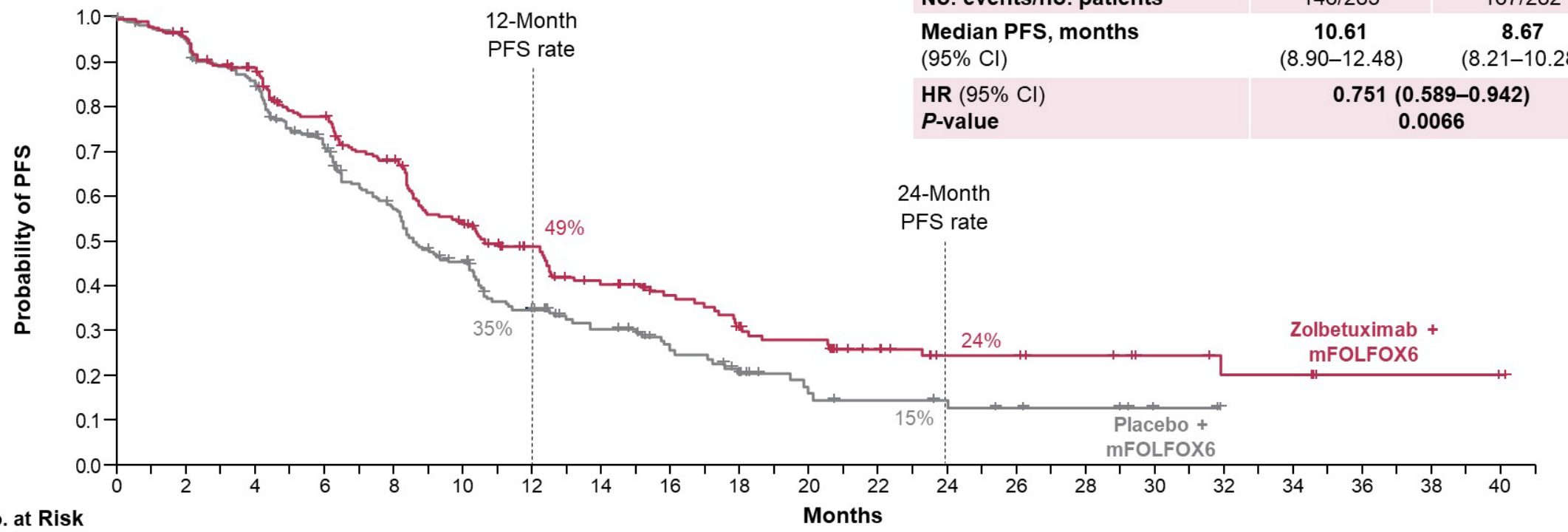

[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: PFS (Primary Endpoint)

Primary Endpoint: PFS by Independent Review Committee

| | Zolbetuximab + mFOLFOX6 | Placebo + mFOLFOX6 |
|---|---|---|
| **No. events/no. patients** | 146/283 | 167/282 |
| **Median PFS, months** (95% CI) | **10.61** (8.90–12.48) | **8.67** (8.21–10.28) |
| **HR** (95% CI) | **0.751 (0.589–0.942)** | |
| ***P*-value** | **0.0066** | |




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + mFOLFOX6 | 283 | 263 | 254 | 232 | 226 | 190 | 187 | 148 | 143 | 108 | 102 | 84 | 78 | 59 | 56 | 53 | 43 | 40 | 33 | 28 | 28 | 21 | 19 | 17 | 12 | 12 | 12 | 10 | 10 | 9 | 7 | 7 | 5 | 5 | 5 | 2 | 2 | 2 | 2 | 2 | 1 | 0 |
| Placebo + mFOLFOX6 | 282 | 273 | 260 | 237 | 226 | 183 | 168 | 136 | 122 | 91 | 83 | 60 | 56 | 43 | 40 | 38 | 26 | 25 | 19 | 14 | 12 | 9 | 9 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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

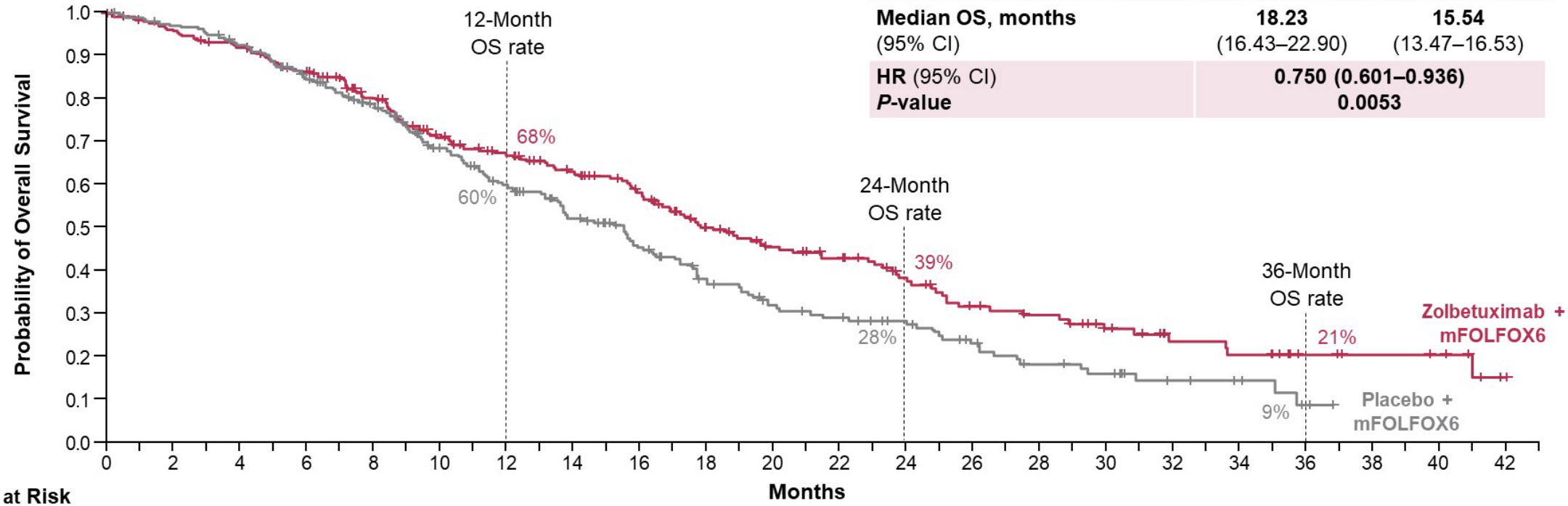
Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: OS

Key Secondary Endpoint: OS

| | Zolbetuximab + mFOLFOX6 | Placebo + mFOLFOX6 |
|---|---|---|
| **No. events/no. patients** | 149/283 | 177/282 |
| **Median OS, months** (95% CI) | **18.23** (16.43–22.90) | **15.54** (13.47–16.53) |
| **HR** (95% CI) | **0.750 (0.601–0.936)** | |
| ***P*-value** | **0.0053** | |




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + mFOLFOX6 | 283 | 270 | 264 | 255 | 251 | 241 | 233 | 217 | 196 | 178 | 164 | 152 | 146 | 135 | 125 | 117 | 107 | 93 | 83 | 75 | 70 | 67 | 62 | 58 | 49 | 42 | 34 | 32 | 30 | 27 | 23 | 20 | 15 | 15 | 13 | 13 | 9 | 8 | 7 | 7 | 6 | 4 | 1 | 0 |
| Placebo + mFOLFOX6 | 282 | 277 | 271 | 266 | 253 | 242 | 224 | 210 | 197 | 183 | 164 | 152 | 139 | 129 | 108 | 101 | 85 | 77 | 64 | 60 | 49 | 42 | 40 | 36 | 34 | 30 | 25 | 21 | 18 | 17 | 15 | 9 | 8 | 7 | 6 | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# SPOTLIGHT: Response

Secondary Endpoints

| | Zolbetuximab + mFOLFOX6 (N = 211) | Placebo + mFOLFOX6 (N = 211) |
|---|---|---|
| **Patients[a], n** | 128 | 131 |
| **ORR[b], % (95% CI)** | 60.7 (53.72–67.30) | 62.1 (55.17–68.66) |
| **BOR[c,d], n (%)** | | |
| CR | 12 (5.7) | 7 (3.3) |
| PR | 116 (55.0) | 124 (58.8) |
| SD | 45 (21.3) | 52 (24.6) |
| PD | 14 (6.6) | 14 (6.6) |
| **Median DOR[b], months, (95% CI)** | 8.51 (6.80–10.25) | 8.11 (6.47–11.37) |
| 3rd quartile, months (95% CI) | 29.9 (10.41–NE) | 15.5 (13.27–NE) |

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a]Patients with measurable disease. [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no post-baseline imaging assessment.

Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

# GLOW: Study Design

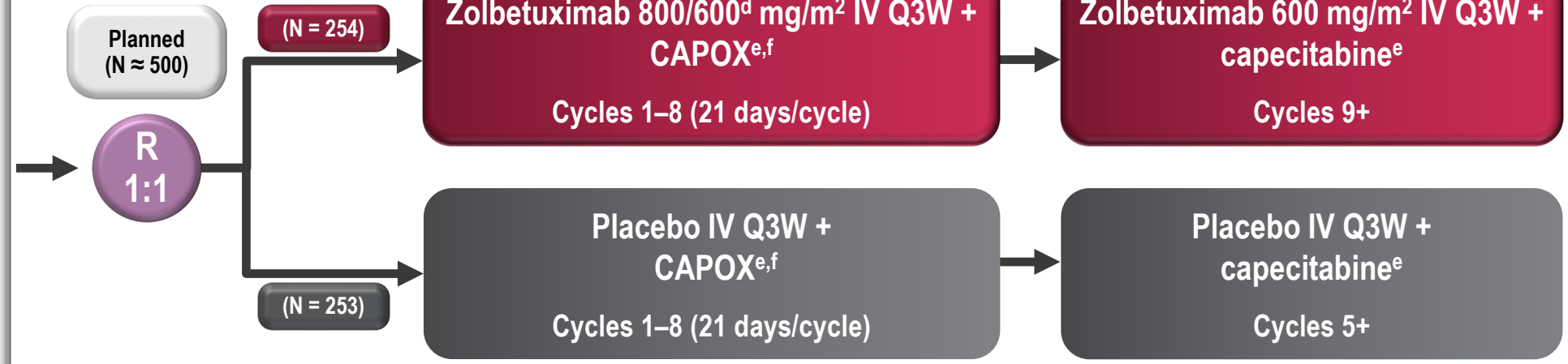
## Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

**Key Eligibility Criteria**

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN 18.2+ (moderate to strong CLDN 18 staining in ≥75% of tumor cells)[b]
- HER2−[c]
- 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 Endpoint**

- PFS[g]

**Key Secondary Endpoints**

- OS
- TTCD in GHS/QoL, PF, and OG25-Pain

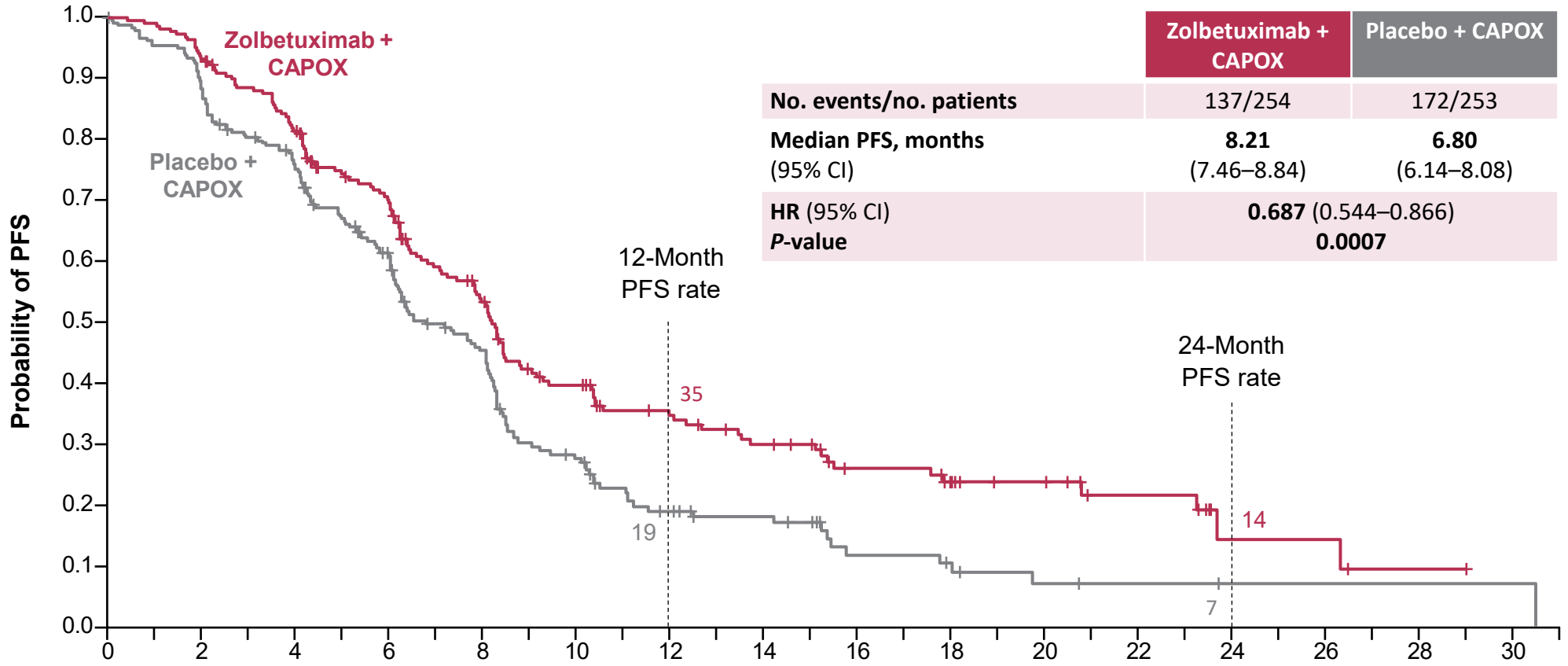
**Secondary Endpoints**

- ORR[g]
- DOR[g]
- Safety
- PROs

[a] Study was conducted at 131 sites in 18 countries across Asia, Europe, N. America, and S. America. [b] By central IHC using the analytically validated VENTANA CLDN 18 (43-14A) RxDx Assay. [c] By central or local HER2 testing. [d] 800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on day 1 of subsequent cycles. [e] 1000 mg/m² capecitabine TID on days 1 and 14 of each cycle. [f] 130 mg/m² oxaliplatin IV on day 1 of each cycle. [g] Per RECIST v1.1 by independent review committee.

Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: PFS by Independent Review Committee




| | Zolbetuximab + CAPOX | Placebo + CAPOX |
|---|---|---|
| **No. events/no. patients** | 137/254 | 172/253 |
| **Median PFS, months** (95% CI) | **8.21** (7.46–8.84) | **6.80** (6.14–8.08) |
| **HR** (95% CI) | **0.687** (0.544–0.866) | |
| ***P*-value** | **0.0007** | |

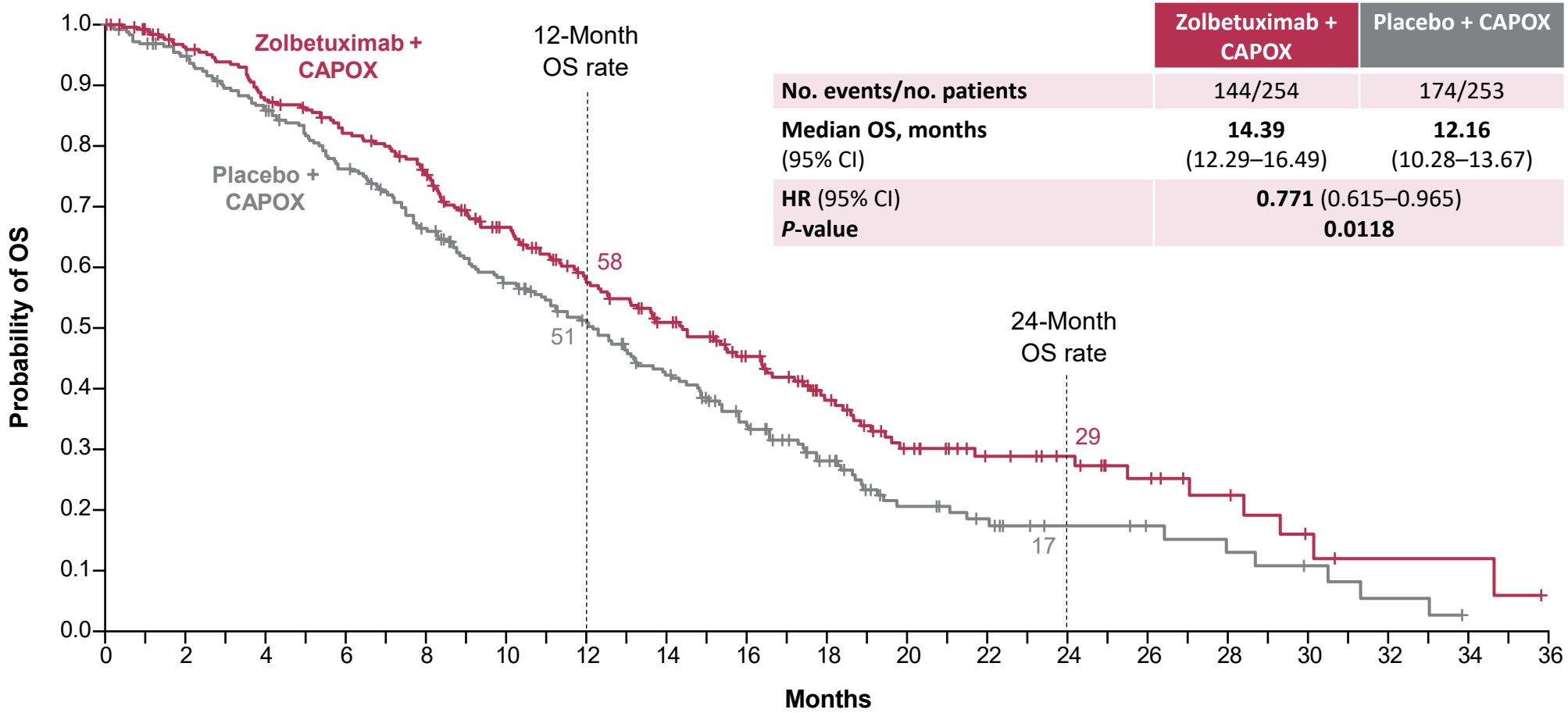
**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 223 | 205 | 187 | 171 | 141 | 132 | 104 | 91 | 66 | 61 | 47 | 45 | 41 | 37 | 35 | 24 | 24 | 19 | 14 | 14 | 9 | 9 | 9 | 3 | 3 | 3 | 1 | 1 | 1 | 0 | 0 |
| Placebo + CAPOX | 253 | 233 | 215 | 188 | 175 | 146 | 127 | 93 | 84 | 48 | 43 | 30 | 24 | 19 | 19 | 17 | 9 | 9 | 7 | 5 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

- PFS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX

Data cutoff: October 7, 2022; Median follow-up = 12.62 months (zolbetuximab + CAPOX) vs 12.09 months (placebo + CAPOX).
Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: OS




| | Zolbetuximab + CAPOX | Placebo + CAPOX |
|---|---|---|
| **No. events/no. patients** | 144/254 | 174/253 |
| **Median OS, months** (95% CI) | **14.39** (12.29–16.49) | **12.16** (10.28–13.67) |
| **HR** (95% CI) | **0.771** (0.615–0.965) | |
| ***P*-value** | **0.0118** | |

**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 243 | 233 | 226 | 211 | 203 | 193 | 187 | 171 | 150 | 138 | 125 | 108 | 100 | 87 | 80 | 68 | 61 | 47 | 38 | 31 | 27 | 22 | 21 | 18 | 13 | 12 | 9 | 8 | 6 | 4 | 2 | 2 | 2 | 2 | 1 | 0 |
| Placebo + CAPOX | 253 | 243 | 235 | 220 | 210 | 197 | 181 | 168 | 152 | 136 | 125 | 115 | 104 | 92 | 82 | 70 | 59 | 49 | 40 | 27 | 22 | 20 | 16 | 12 | 10 | 10 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 2 | 0 | 0 | 0 |

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

Data cutoff: October 7, 2022; Median follow-up = 17.71 months (zolbetuximab + CAPOX) vs 18.43 months (placebo + CAPOX).

Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.

# GLOW: Response

| | Zolbetuximab + CAPOX (N = 195) | Placebo + CAPOX (N = 205) |
|---|---|---|
| **Patients[a], n** | 105 | 100 |
| **ORR[b], % (95% CI)** | 53.8 (46.58–60.99) | 48.8 (41.76–55.84) |
| **BOR[c,d], n (%)** | 163 (83.6) | 188 (91.7) |
| CR | 6 (3.1) | 3 (1.5) |
| PR | 99 (50.8) | 97 (47.3) |
| SD | 46 (23.6) | 57 (27.8) |
| PD | 10 (5.1) | 25 (12.2) |
| **Median DOR[b], months, (range)** | 6.28 (5.39-8.28) | 6.18 (4.53-6.41) |

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a] Patients with measurable disease. [b] Per RECIST version 1.1 by independent review committee. [c] Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown. [d] Patients with missing data had no post-baseline imaging assessment.
Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141.