به نام آنکه تن را نور جان داد
خرد را سوی دانایی عنان داد

The Sequencing of treatment in metastatic gastric cancr

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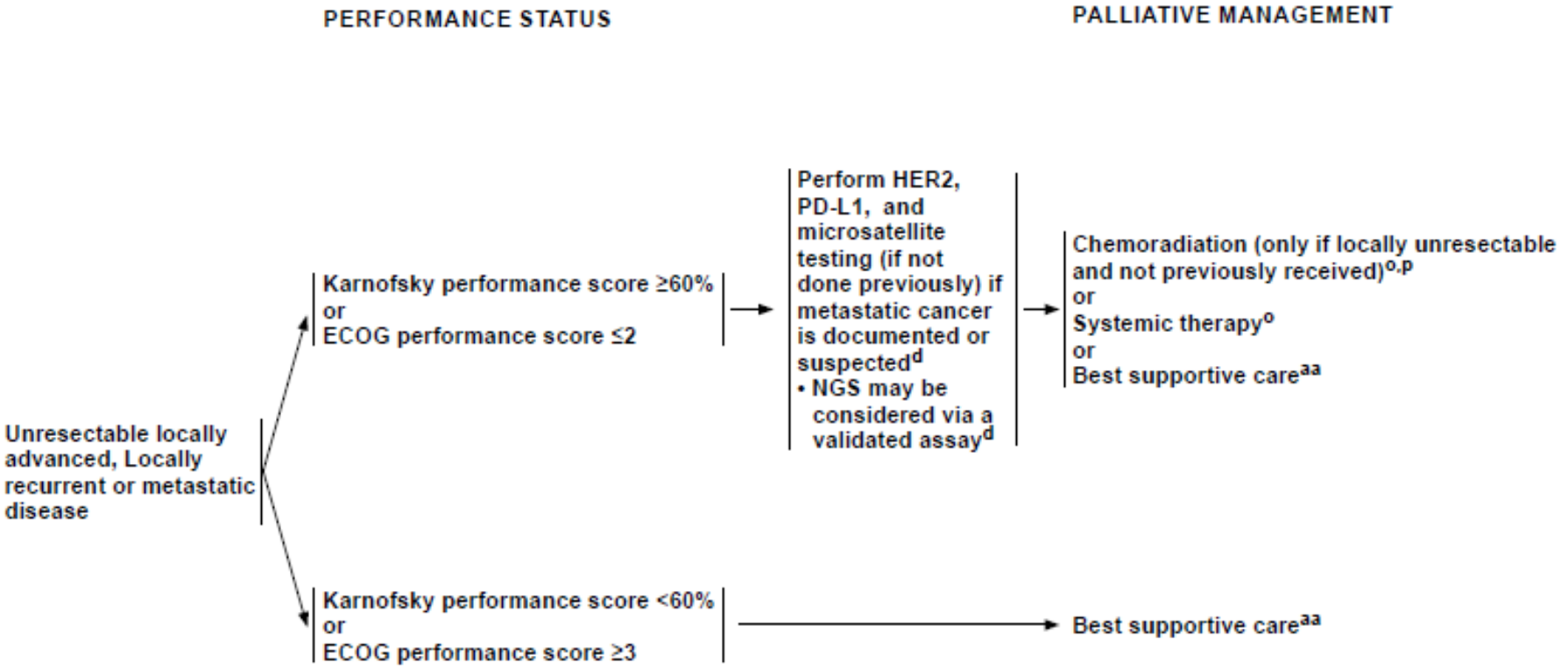
Introduction

- Gastric cancer is not a **top-10 malignancy** in the United States but represents **one of the most** common causes of cancer **death** worldwide.

- **Biological differences** between tumors from Eastern and Western countries add to the **complexity of identifying standard-of-care** therapy based on international trials.

- Gastric cancers from Eastern countries, such as Japan and Korea, have lower proportions with signet ring histology and proximal stomach involvement.

- Because of the lower proportion of cases with these adverse factors, most large, randomized trials from the East demonstrate **survival rates that are 30% to 40%** higher than trials from the West.



Treatment of Metastatic and Unresectable Gastric Cancer

- **Several cytotoxic agents** are active in advanced gastric cancer, including fluoropyrimidines, platinums, taxanes, and irinotecan
- The choice of treatment depends on patient
  - **performance status**
  - medical **comorbidities**
  - **toxicity profile** of the regimen.

- **Combination regimens** offer higher response rates and improved survival compared with single-agent therapy.
- There is **no universal standard first-line** therapy,
- A **fluoropyrimidine and platinum** doublet is typically the preferred **backbone** regimen for most patients.

- Oxaliplatin is the choice platinum in most modern regimens

- A meta-analysis REAL-2 trial and other randomized trial phase II compared **Oxaliplatin-based** and cicplatin-based regimens and showed that Oxaliplatin was associated with significant improvement in PFS and OS and less cytopenia and alopecia, but more neurotoxicity and diarrhea

- In **very fit patients** a triplet regimen combining a **fluoropyrimidine**, **oxaliplatin**, and **docetaxel** can be considered.

- There is no role for epirubicin in contemporary regimens for advanced disease

- Single-agent therapy with a fluoropyrimidine, irinotecan, or taxane can be considered in patients who are **not candidates for intensive therapy**

- In patients with overexpression or amplification of **HER2** trastuzumab should be added to cytotoxic first-line chemotherapy

- In patients with a **PD-L1** combined positive score **(CPS) ≥5**, nivolumab should be added to first-line chemotherapy

- **In the second-line** treatment for metastatic gastric cancer, cytotoxic chemotherapy agents not already used in the first line can be attempted
- **In fit patients**, paclitaxel plus ramucirumab is a preferred second-line regimen after progression on a fluoropyrimidine and platinum doublet
- Otherwise, **single-agent** cytotoxic chemotherapy or ramucirumab monotherapy can be considered

RAINBOW trial

randomized patients who had progressed on first-line chemotherapy

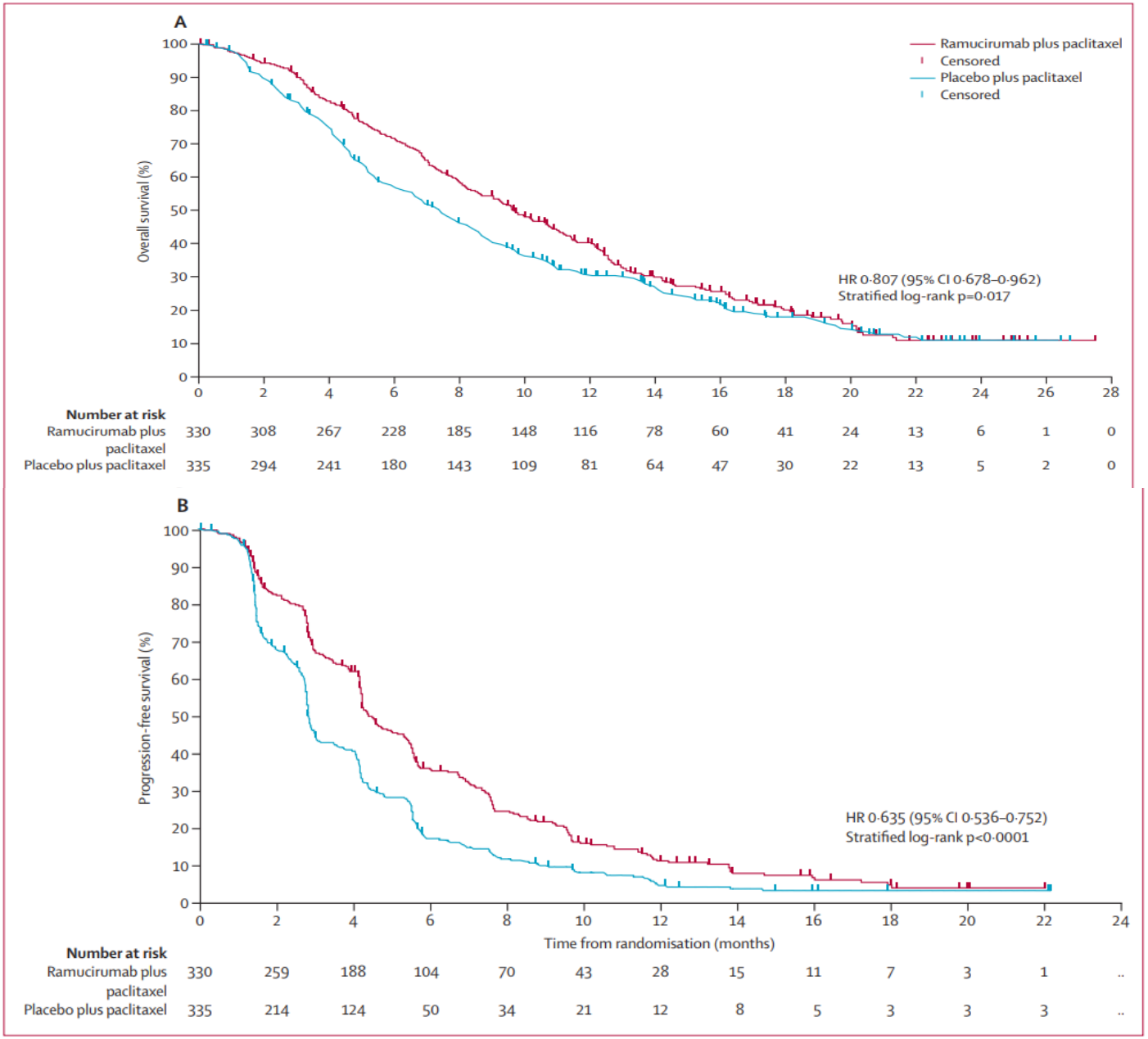


Figure 2: **Kaplan-Meier curves of overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

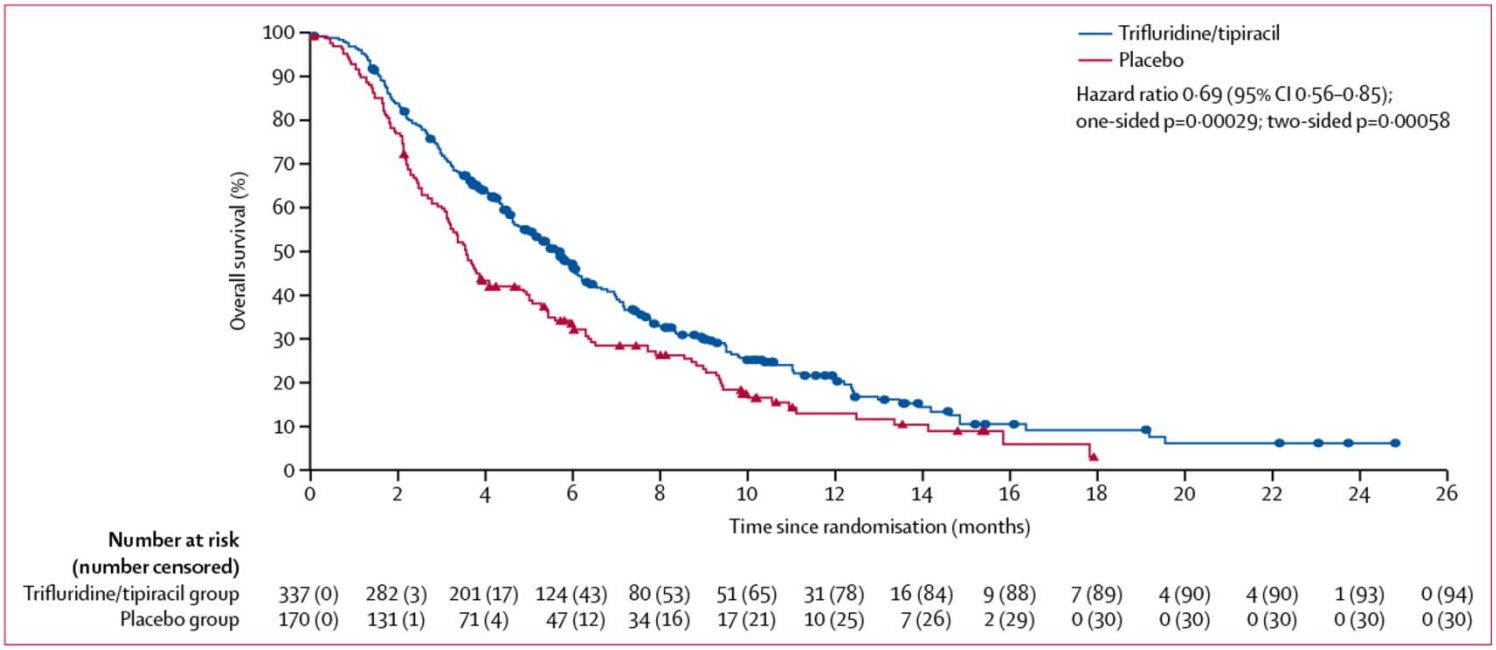


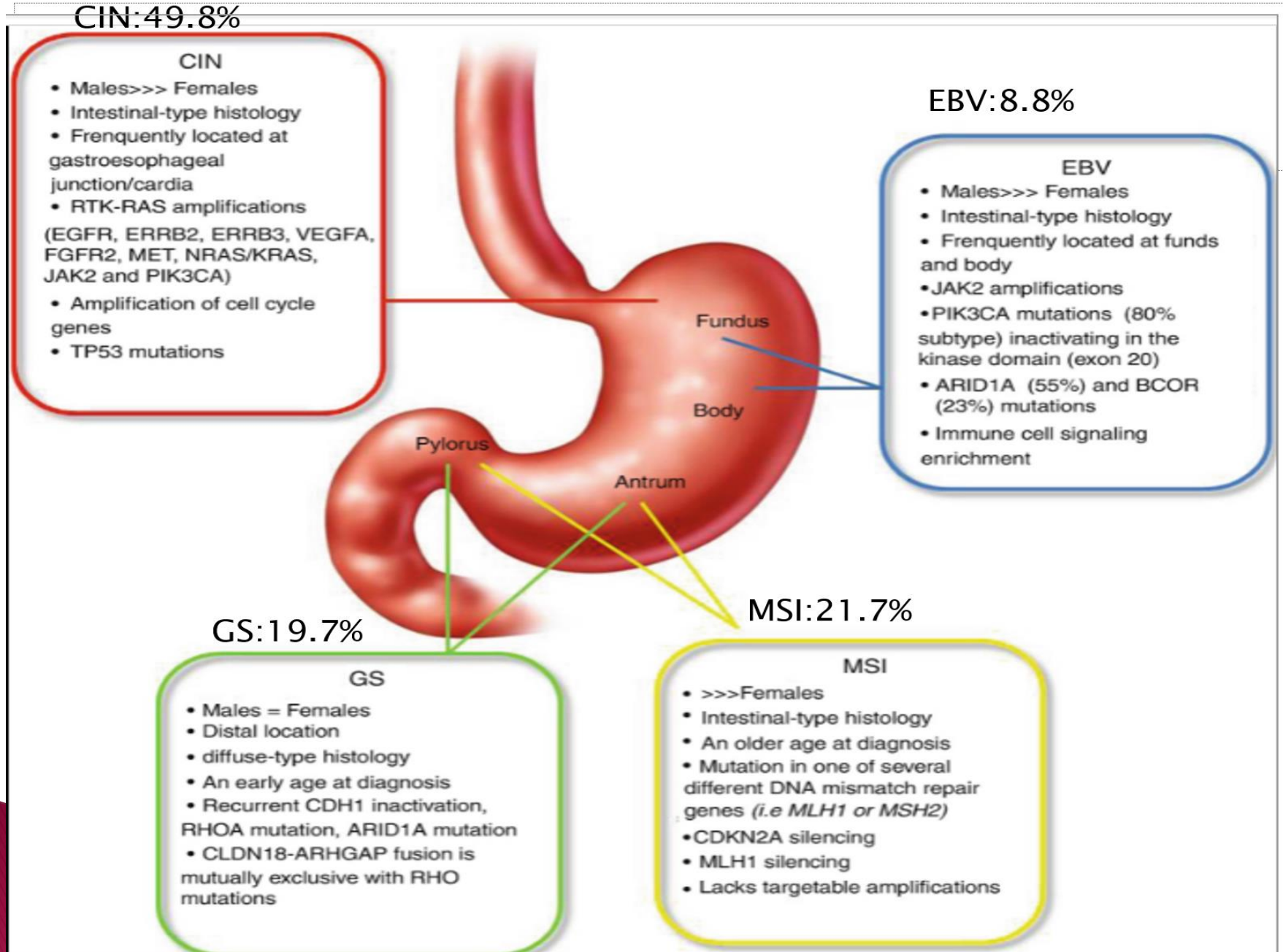
Figure 2: Overall survival in the intention-to-treat population

- The **oral cytotoxic agent trifluridine–tipiracil**, combining an antimetabolite trifluridine with a thymidine phosphorylase inhibitor (tipiracil), has been shown in the phase 3 setting to have a **survival benefit** over placebo (5.7 vs 3.6 months)
- In heavily treated and refractory gastric cancer and is now an approved **third-line** regimen.

Immunotherapy in Gastric Cancer

- In the last decade, immune checkpoint blockade has emerged as an exciting treatment strategy across a spectrum of malignancies.
- This includes monoclonal antibodies that inhibit programmed cell death protein 1 (PD-1), PD-L1, and cytotoxic T-lymphocyte antigen 4 (CTLA-4).

Gastric adenocarcinomas and categorized gastric cancer into 4 subtypes



Mismatch repair (MMR)

- **Mismatch repair** (MMR) genes are responsible for **fixing errors** that occur during DNA replication.
- Tumors with defects in the **MMR** (dMMR)harbor significantly **more mutations** than tumors with intact MMR machinery (MMR-proficient).

- Across tumor types, patients with **dMMR/high levels of MSI** cancers are **more likely to respond to PD-1 blockade** than those with MMR-proficient cancers.
- this is because of high levels of **neoantigens** and **PD-L1-positive T-cell infiltration** in dMMR tumors.

Table 1. Pivotal clinical trials of anti-PD-1/PD-L1 therapies for gastric cancer

Target	Phase	Trial	Line	Agents (experimental)	Control
PD-1	III	ATTRACTION-2 (NCT02267343)	3rd or later	Nivolumab	PBO
PD-1	II	KEYNOTE-059 (NCT02335411)	3rd or later	Pembrolizumab	–
PD-L1	III	JAVELIN300 (NCT02625623)	3rd	Avelumab	Irinotecan/taxanes/BSC
PD-1	III	KEYNOTE-061 (NCT02370498)	2nd	Pembrolizumab	Paclitaxel
PD-1	III	KEYNOTE-063 (NCT03019588)	2nd	Pembrolizumab	Paclitaxel
PD-1	III	KEYNOTE-062 (NCT02494583)	1st	Pembrolizumab or Pembrolizumab+CTx	XP/FP
PD-L1	III	JAVELIN100 (NCT02625610)	1st maintenance	Avelumab	CapeOX/FOLFOX
PD-1/CTLA-4	III	CheckMate-649 (NCT02872116)	1st	+Nivolumab Ipilimumab+Nivo	CapeOX/FOLFOX
PD-1	III	ATTRACTION-4 (NCT02746796)	1st	+Nivolumab	SOX/CapeOX
PD-1	III	KEYNOTE-811 (NCT03615326)	1st	+Pembrolizumab	FP/CapeOX/SOX +Tmab
PD-1	III	KEYNOTE-859 (NCT03675737)	1st	+Pembrolizumab	FP/CapeOX
PD-1/Lag-3	II/III	MAHOGANY (NCT4082364)	1st	margetuximab INCMGA00012	CapeOX/FOLFOX +Tmab
PD-1	III	KEYNOTE-585 (NCT03221426)	Neoadjuvant	+Pembrolizumab	XP/FP/FLOT
PD-1	III	ATTRACTION-5 (NCT03006705)	Adjuvant	+Nivolumab	S-1/CapeOX
PD-1	III	CheckMate-577 (NCT02743494)	Adjuvant	Nivolumab	PBO

Agents (experimental)	Control	Primary Endpoint	Result	Difference mOS (m)
Nivolumab	PBO	OS	Positive	+1.2 (HR 0.63)
Pembrolizumab	–	ORR	Positive	–
Avelumab	Irinotecan/taxanes/BSC	OS	Negative	−0.4 (HR 1.1)
Pembrolizumab	Paclitaxel	OS/PFS	Negative	+0.8 (HR 0.82)
Pembrolizumab	Paclitaxel	OS	Terminated	–
Pembrolizumab or Pembrolizumab+CTx	XP/FP	OS/PFS	Negative	−0.5 (HR 0.91) +1.4 (HR 0.85)
Avelumab	CapeOX/FOLFOX	OS	Negative	−0.5 (HR 0.91)
+Nivolumab Ipilimumab+Nivo	CapeOX/FOLFOX	OS/PFS	positive	+3.3 (HR 0.71) for CPS≥5 patients
+Nivolumab	SOX/CapeOX	OS/PFS	positive for PFS/negative for OS	+0.3 (HR 0.9)
+Pembrolizumab	FP/CapeOX/SOX +Tmab	OS/PFS	Ongoing	–
+Pembrolizumab	FP/CapeOX	OS/PFS	Ongoing	–
margetuximab INCMGA00012	CapeOX/FOLFOX +Tmab	OS	Ongoing	-
+Pembrolizumab	XP/FP/FLOT	OS/EFS/pCR	Ongoing	–
+Nivolumab	S-1/CapeOX	RFS	Ongoing	–
Nivolumab	PBO	DFS	Ongoing	–

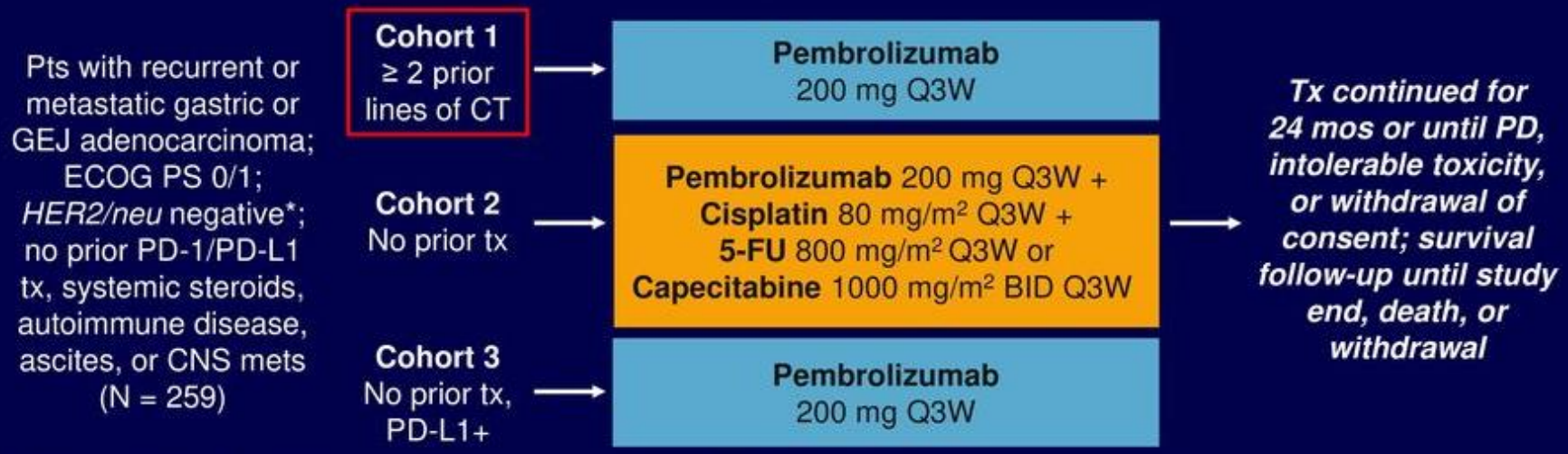
- KEYNOTE-158 was a phase 2 trial that enrolled patients with **treatment-refractory**, noncolorectal MSI-H/dMMR cancers to receive pembrolizumab

- Of the **24 patients with gastric cancer**, there were **11 responses** (including 4 complete responses), and the median **PFS was 11** months.

- This trial ultimately led to the tissue-agnostic US **FDA approval of pembrolizumab for patients with unresectable or metastatic MSI-H or dMMR tumors** of any solid tumor type, including gastric cancer, who progressed after prior treatment and have **no satisfactory alternative** treatmen

KEYNOTE-059: Study Design

- Open-label, multicohort phase II study



**HER2/neu* positive allowed in cohort 1 if prior trastuzumab administered.

- **Primary endpoints:** ORR, safety; **secondary endpoints:** DoR, PFS, OS
- Exploratory biomarker endpoints: efficacy by MSI, GEP

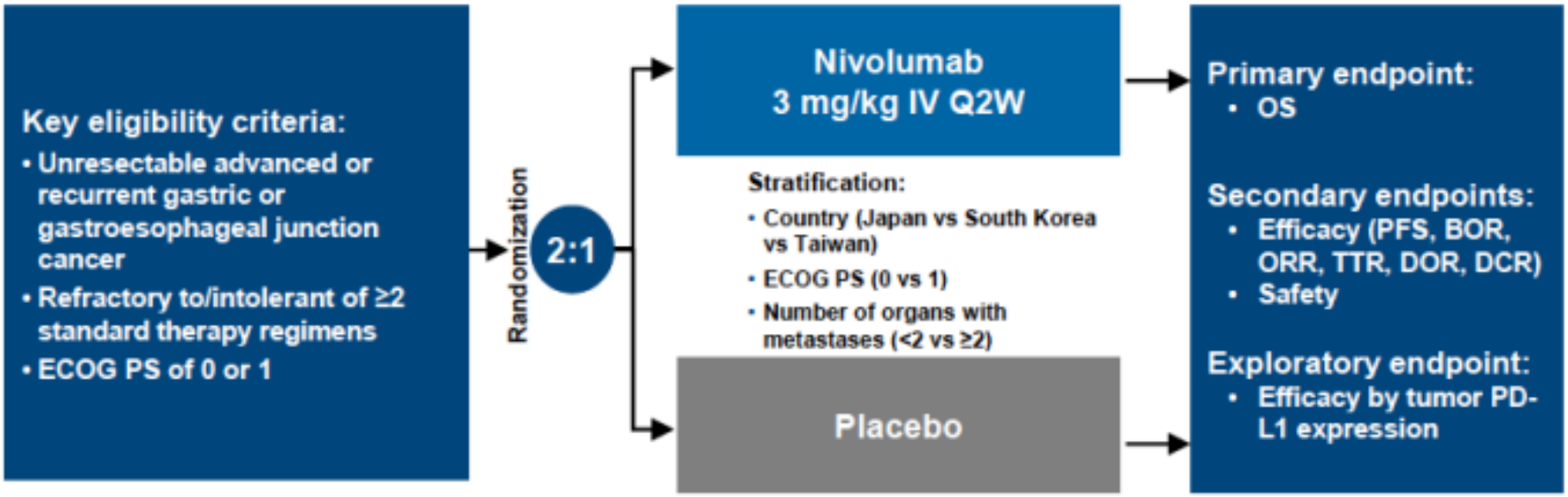
Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

- **KEYNOTE-059**

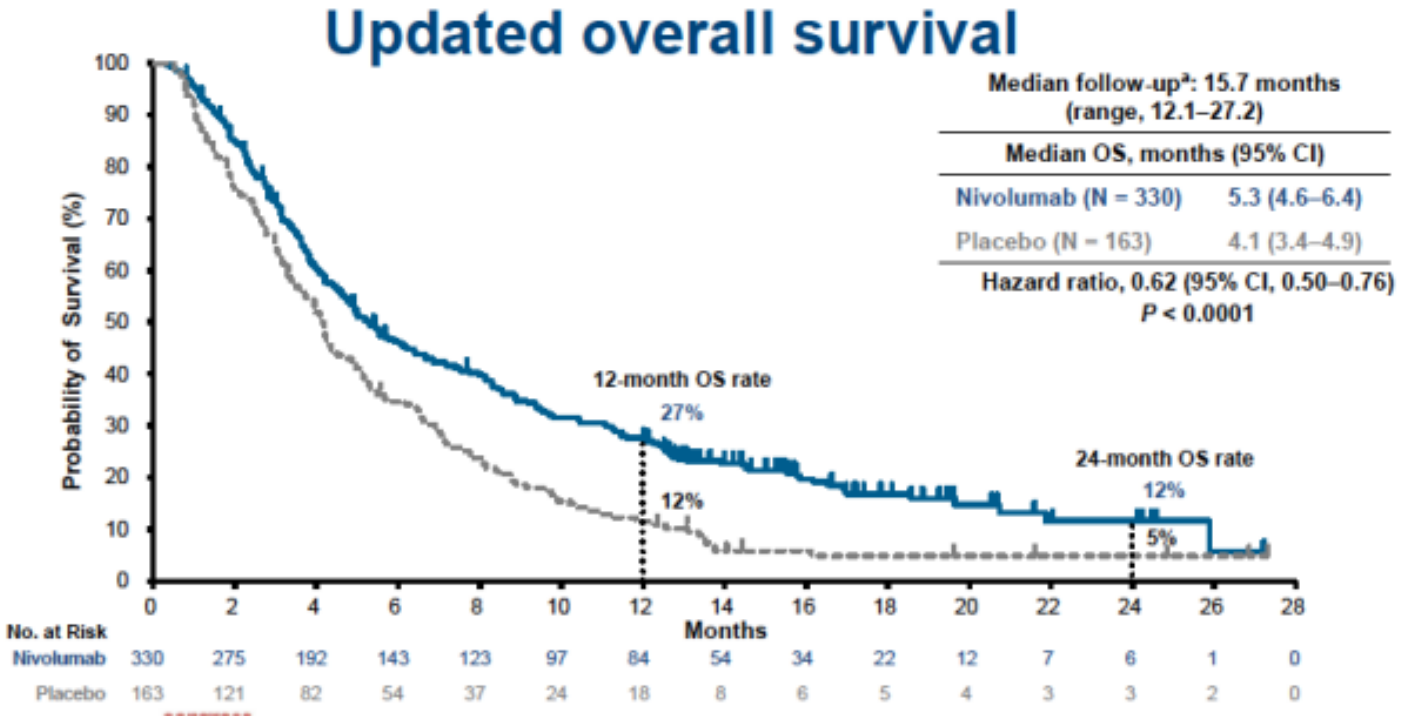
- **Overall**, the ORR was 11.6%, and the median duration of response (DoR) was 8.4 months.
- However, **in PD-L1-positive (CPS ≥1)** patients, the ORR was 15.5%, and the median DoR was 16.3 months
- These results were the basis of the **FDA approval** of pembrolizumab **for third-line treatment** of PD-L1- positive (**CPS ≥1**) gastric adenocarcinoma.

Study design of ATTRACTION-02



- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug
- Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

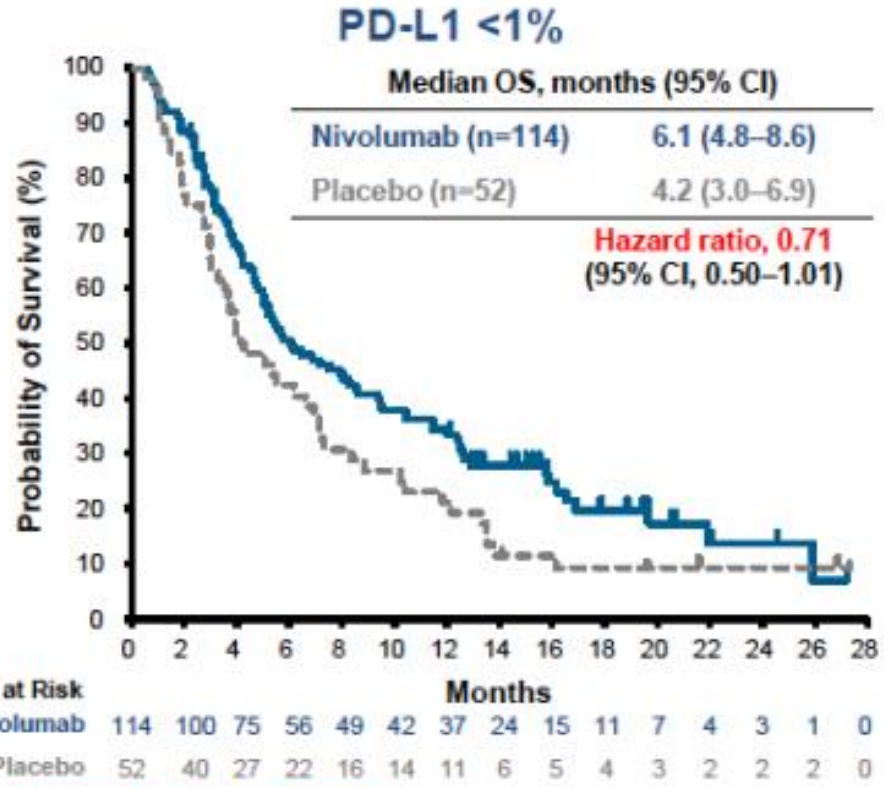
ATTRACTION-02

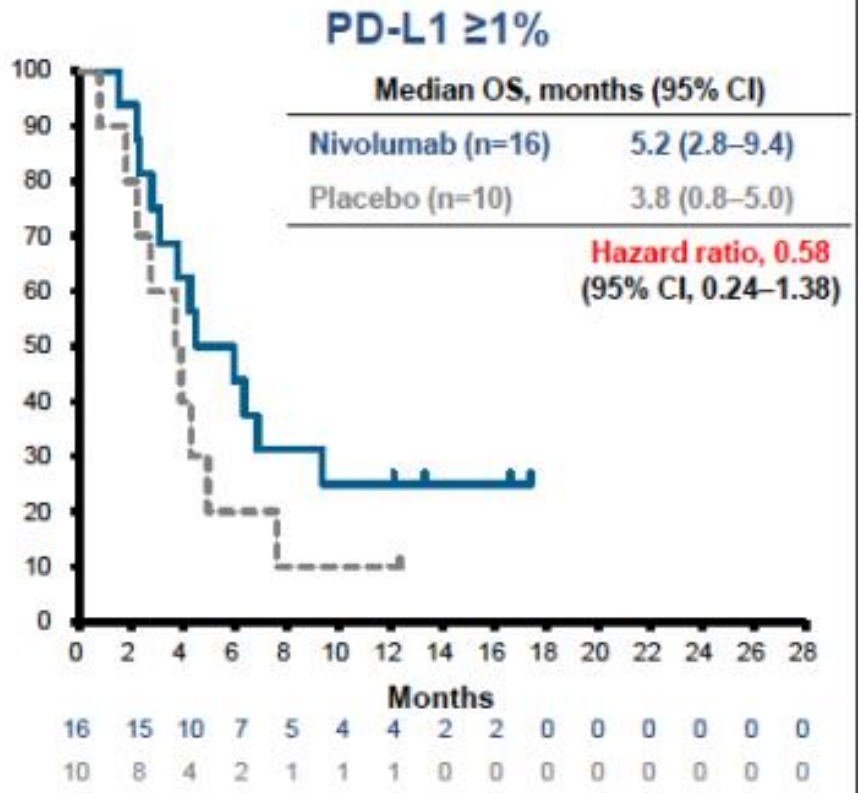


Nivolumab is now approved in Japan for advanced gastric cancer refractory to conventional chemotherapy, **regardless of PD-L1 expression**

ATTRACTION-02

Overall survival by PD-L1 expression <1% vs ≥1%





MADRID 2017 ESMO Congress

PD-L1 evaluable patients (N=192)

Boku N et al. 6160

CheckMate 649 study design

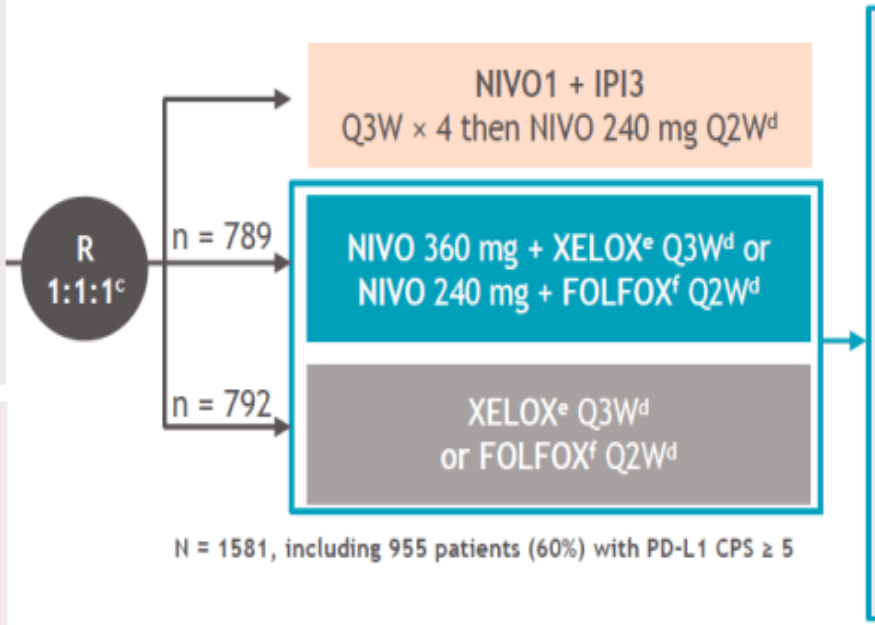
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria

- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:

- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:

- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

- **CheckMate-649**
- In initial results, patients with PD-L1 CPS ≥5 receiving **nivolumab plus chemotherapy** compared with chemotherapy alone had **improved OS** (14.4 vs 11.1 months) at a prespecified **interim analysis** and **improved PFS** (7.7 vs 6.1 months) at final analysis

- This is a practice-changing study that establishes **chemotherapy plus nivolumab** as a new standard of care for **first-line treatment of HER2-negative** gastric cancer in patients with **PD-L1 CPS ≥5.**

- On April 16, 2021, the **FDA approved** nivolumab in **combination** with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma

Tumor Mutation Burden

- **TMB** is another biomarker currently under investigation.
- TMB quantifies the **number of somatic mutations per coding area of a genome.**

- It has been hypothesized that a **heavily mutated tumor** can **produce a large number of neoantigens**, resulting in **T-cell infiltration** and **potentially increased responsiveness to checkpoint blockade.**

- In June 2020, the **FDA granted accelerated approval** for the treatment of patients with unresectable or metastatic **TMB-high**

- TMB-H (≥10 mutations per megabase) solid tumors that progressed after prior treatment and **had no satisfactory alternative treatment** options.

- this was based upon a prospectively planned retrospective analysis of previously treated patients with advanced solid tumors and TMB-H enrolled on **KEYNOTE-158**

- **tissue TMB (tTMB)** could be a novel and useful predictive biomarker for **response to pembrolizumab monotherapy** in patients with previously treated recurrent or metastatic advanced solid tumours.

Epstein-Barr Virus

- **EBV** is a human herpes virus implicated in several malignancies, including **gastric adenocarcinoma.**
- EBV-positive gastric cancer is a distinct subset of gastric cancer identified by TCGA and is associated with a **rich CD8-positive**
- T-cell infiltrate and increased PD-L1 and PD-L2 expression, which may potentially make it **more susceptible to PD-1 blockade.**

- Several reports have described robust responses of EBV-positive tumors to immune checkpoint blockade; however, this needs to be prospectively studied

HER2-Positive Gastric Cancer

- Approximately **15% to 20%** of advanced gastric and gastroesophageal junction adenocarcinomas have overexpression or amplification of HER2.
- **HER2 positivity** is more commonly seen in:
- **intestinal-type** cancers compared with diffuse-type or mixed-type cancers,
- in the TCGA **CIN** subtype,
- and in cancers arising from the **gastroesophageal junction**

- The pivotal **phase 3 ToGA trial** established the addition of **trastuzumab to chemotherapy as the standard of care in the first-line treatment** of advanced **HER2-positive** gastric adenocarcinoma

- **Lapatinib**, a tyrosine kinase inhibitor affecting both HER2 and EGFR, **does not improve survival** when combined with chemotherapy in both **first-line and second-line** settings in metastatic HER2-positive gastric adenocarcinoma

- **Trastuzumab emtansine**, an antibody-drug conjugate of trastuzumab bound to the tubulin inhibitor emtansine, **does not prolong OS in the second-line** treatment of HER2-positive patients.

- **Pertuzumab**, a humanized monoclonal antibody that binds to a different epitope on the HER2 receptor, in addition to trastuzumab and chemotherapy, **also failed to show a survival benefit in the first-line** JACOB trial

- Finally, **trastuzumab beyond progression has not been shown to improve survival.** In patients who progressed on first-line trastuzumab plus chemotherapy, trastuzumab plus paclitaxel did **not improve PFS** compared with paclitaxel alone

- Exploratory analysis revealed that **HER2 positivity was lost after first-line chemotherapy** in 11 of 16 evaluable patients.
- Given the potential for loss of HER2 expression over time, **second-line trials** targeting HER2 should require **re-demonstration of HER2 positivity**

- **Novel HER2-targeted agents**

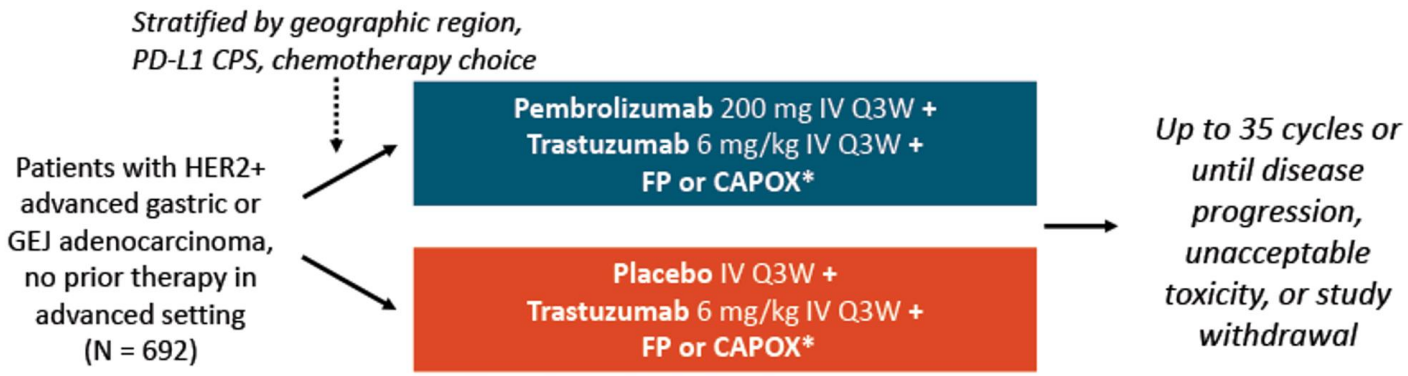
- **ZW25** has been shown to be well tolerated with single-agent activity in a heavily pretreated group of HER2-positive malignancies.
- **Margetuximab** has also demonstrated tolerability and antitumor activity in HER2-positive cancers.
- **Most promising** at this point in time is **trastuzumab deruxtecan,** a humanized monoclonal anti-HER2 antibody attached to a cytotoxic topoisomerase I inhibitor through a cleavable linker.
- **DESTINY-Gastric01** was a randomized phase 2 trial that evaluated **trastuzumab deruxtecan versus chemotherapy** in a refractory population of patients with HER2-positive gastric and gastroesophageal adenocarcinoma who had progressed on ≥2 prior therapies, including trastuzumab.

- **Trastuzumab deruxtecan** showed improvements in
- OS (12.5 vs 8.4 months) and
  RR (51% vs 14%) compared with chemotherapy

HER2-directed therapy plus immunotherapy

KEYNOTE-811: Pembrolizumab + Trastuzumab + CT for HER2+ Advanced Gastroesophageal Cancer

- Randomized, double-blind, placebo-controlled phase III study



*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m² IV Days 1-5 Q3W + cisplatin 80 mg/m² IV Q3W
CAPOX: capecitabine 1000 mg/m² BID Days 1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W

- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication
- **Primary endpoints:** OS, PFS per RECIST v1.1 by BICR
- **Secondary endpoints:** ORR and DoR per RECIST v1.1 by BICR, safety

Janjigian ASCO 2021. Abstr 4013.

Slide credit: clinicaloptions.com

adding pembrolizumab to trastuzumab and chemotherapy markedly **reduces tumour size**, induces **complete responses** in some participants, and significantly **improves objective response rate**

- **HER2-directed therapy plus immunotherapy,**

- A phase 2 trial demonstrated that **pembrolizumab could be safely combined with trastuzumab plus chemotherapy in HER2-positive, metastatic** gastroesophageal adenocarcinoma.
- **91% RR and a median OS of 27.3 months**, which were much higher than what was seen with chemotherapy plus trastuzumab **(RR, 47%),**
- suggesting that there **may be a synergistic benefit of combining checkpoint blockade** with standard trastuzumab plus chemotherapy.

- The results of triplet treatment of chemotherapy, trastuzumab and pembrolizumab in first-line advanced gastric cancer in the PANTERA study were also presented at ASCO-GI 2021

Antiangiogenic Therapy

- **Ramucirumab,** a monoclonal antibody against **VEGFR**-2, has a **proven survival benefit in the second-line treatment** of gastric cancer, **both as monotherapy and in combination** with paclitaxel.

- **Lenvatinib has been safely combined with pembrolizumab**, with a **69% RR in the first-line and second-line** treatment of advanced gastric cancer.
- The addition of **regorafenib to nivolumab has also been shown to be safe,** with encouraging antitumor activity in the phase 1 setting.

- We look forward to exploring the efficacy of combined VEGF inhibition and PD-1 blockade in larger cohorts of patients.

Investigational Biomarkers and Future Therapies

- **Targeting EGFR** is a therapeutic strategy in development in gastric cancer
- Although EGFR inhibitors are active in several cancers, these drugs **have not shown efficacy** in the phase 3 setting in unselected patients.

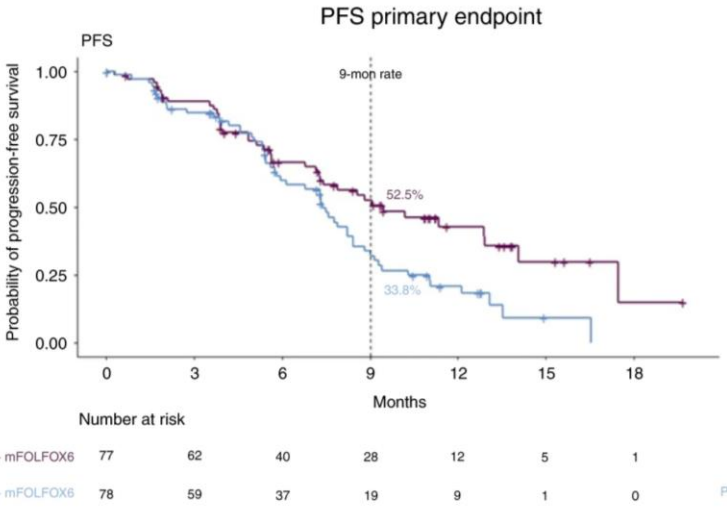
- **Claudin 18.2**, a protein expressed by a subset of gastric cancers, is a **novel target for drug development.**
- **Zolbetuximab**,a chimeric monoclonal antibody that binds to Claudin 18.2, is tolerable, with antitumor activity both as monotherapy and in combination with chemotherapy in patients with Claudin 18.2–positive gastroesophageal adenocarcinoma, and is **being further investigated in the phase 3 setting**

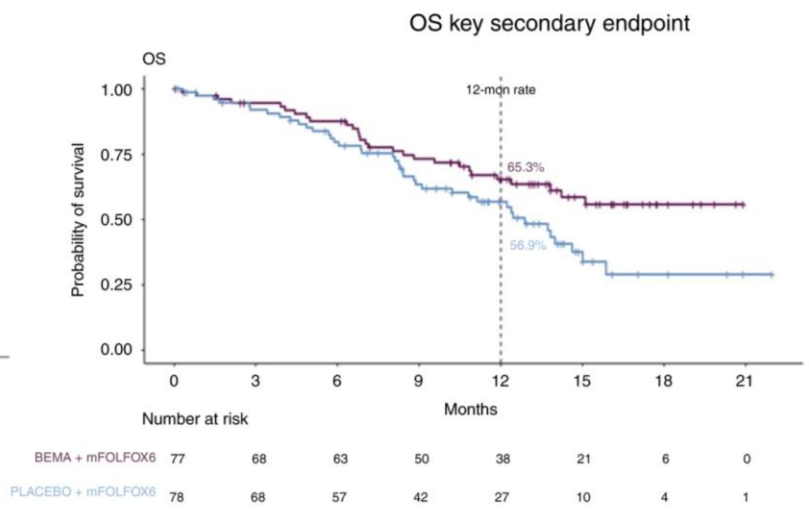
- **PET using novel tracers, such as radiolabeled trastuzumab,** may help assess and monitor tumor heterogeneity over time and is an area of active investigation.

FIGHT trial

bemarituzumab plus mFOLFOX6 versus placebo plus mFOLFOX6.

From: Highlights from ASCO-GI 2021 from EORTC Gastrointestinal tract cancer group





bemarituzumab +chemotherapy: Improve OS in patients with FGFR2b-positive, HER2-negative **frontline advanced gastric** or GEJ.

The results of the phase 2 FIGHT trial were presented during a presentation at the 2021 ASCO Annual Meeting.

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]
- Fluorouracil[b,i] and irinotecan[j,20]
- Paclitaxel with or without cisplatin or carboplatin[j,21-25]
- Docetaxel with or without cisplatin[j,26-29]
- Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]

Useful in Certain Circumstances
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[g,h,12]

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Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[35]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]
- Docetaxel (category 1)[28,29]
- Paclitaxel (category 1)[24,25,37]
- Irinotecan (category 1)[37-40]
- Fluorouracil[b,i] and irinotecan[38,41,42]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]

Other Recommended Regimens
- Ramucirumab (category 1)[44]
- Irinotecan and cisplatin[14,45]
- Fluorouracil and irinotecan + ramucirumab[b,i,46]
- Irinotecan and ramucirumab[47]
- Docetaxel and irinotecan (category 2B)[48]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
- Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[54]
- Dostarlimab-gxly[g,h,k] for MSI-H or dMMR tumors[55]


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