ASCO Gastrointestinal Cancers Symposium

Patient centric management of gastric cancer

Metastatic Gastric Cancer: Advancements in systemic therapies

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Medical Oncology
Climate Medicine

Learning Objectives

- Cancer control continuum and cross cutting areas
- Biomarker testing and systemic therapy
- Personalization of systemic therapies
- Role of multidisciplinary approach
- Future direction

PRESENTED BY: Lakshmi Balasubramanian MD, MS, DCM

Cancer control continuum and cross cutting areas

Etiology
- Environmental factors
- Genetic factors
- Gene-environment interactions
- Medication (or pharmaceutical) exposure
- Infectious agents
- Health behaviors

Prevention
- Tobacco control
- Diet
- Physical activity
- Sun protection
- HPV vaccine
- Limited alcohol use
- Chemoprevention

Detection
- Pap/HPV testing
- Mammography
- Fecal occult blood test
- Colonoscopy
- Lung cancer screening

Diagnosis
- Shared and informed decision making

Treatment
- Curative treatment
- Non-curative treatment
- Adherence
- Symptom management

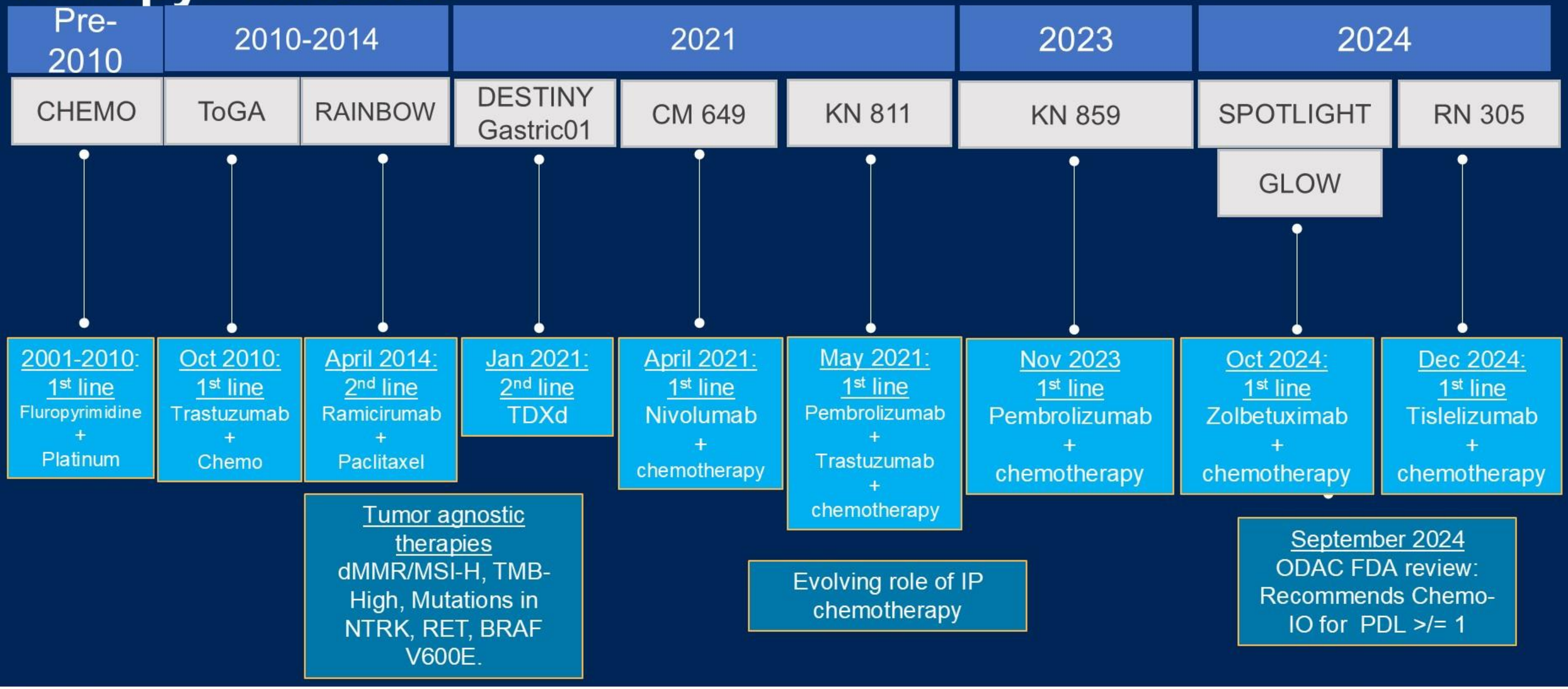
Survivorship
- Coping
- Health promotion for survivors

Communications
Decision Making
Implementation Science

Health Disparities
Health Care Delivery
Epidemiology

Image Source: NCI; Adapted from David B. Abrams, Brown University School of Medicine

Recent advances in metastatic gastric cancer systemic therapy: Timeline



Biomarkers in metastatic gastric cancer

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Anti-Her-2 therapy

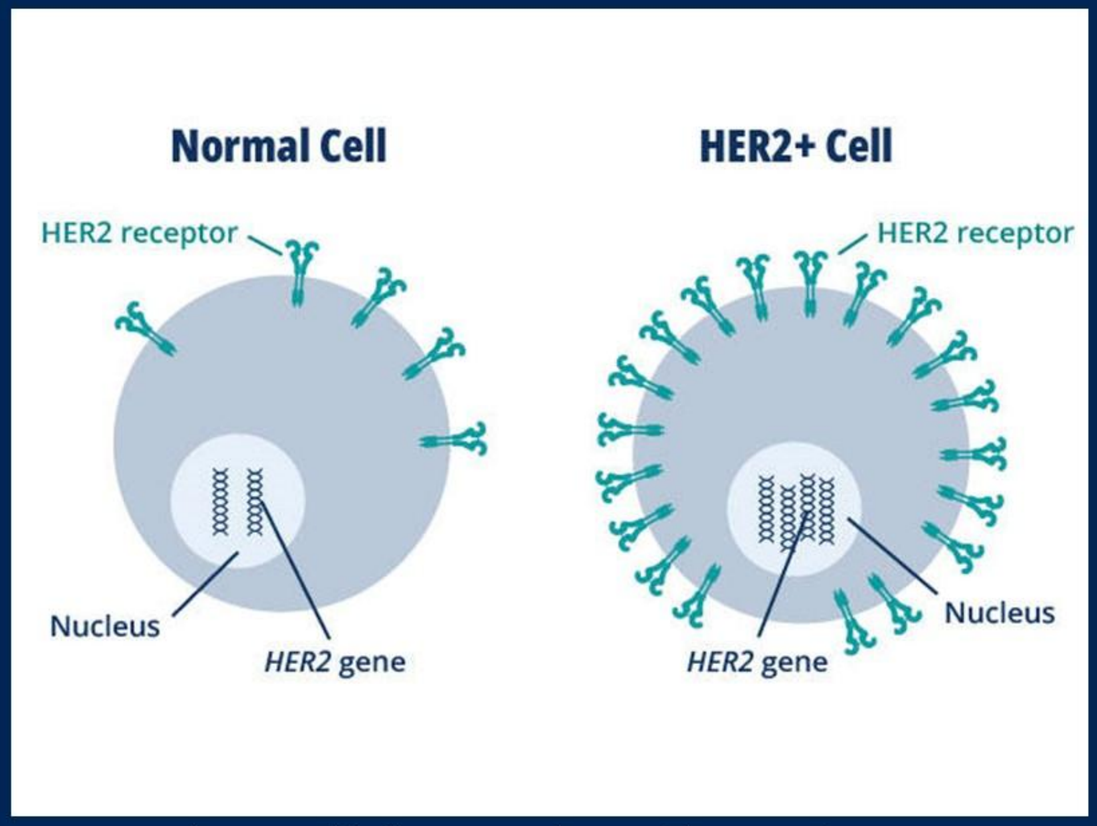


Image source: https://www.cancer.gov/news-events/cancer-currents-blog/2023/fda-tucatinib-her2-colorectal-cancer

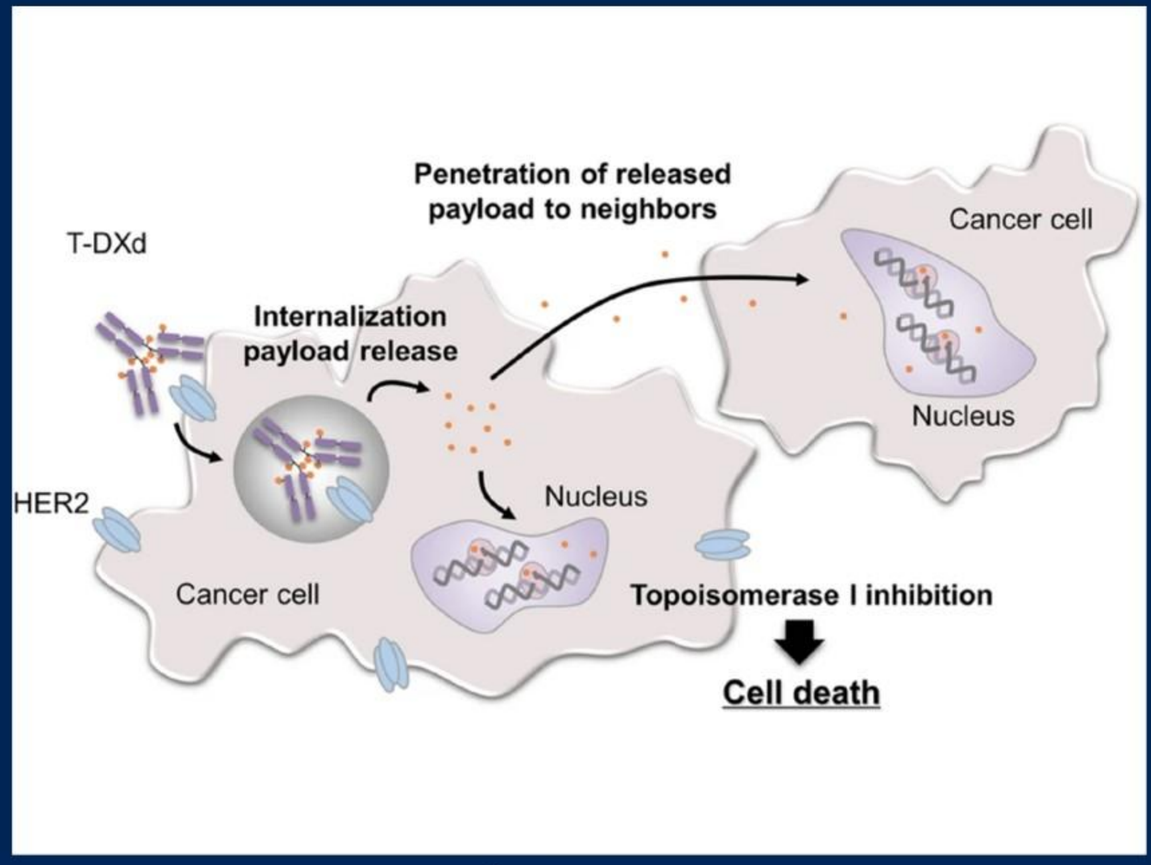


Image source: https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_enlarged/public/cgov_image/media_image/2021-10/PenetrationofReleasedPayloadtoNeighbors.png?itok=4JjqdNHM

Immunotherapy

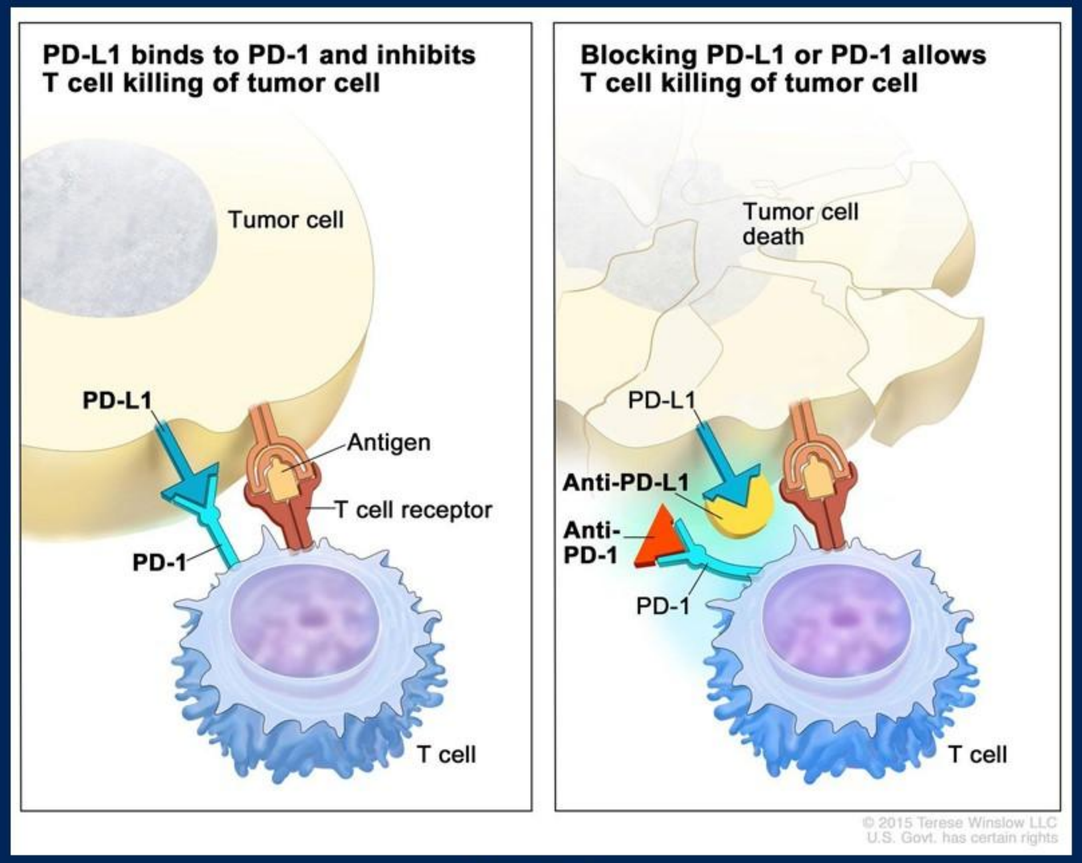


Image source:
https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_enlarged/public/cgov_image/media_image/2019-09/nci-vol-10396-150.jpg?h=30063a04&itok=DGHB7TA1

Claudin 18.2 directed therapy

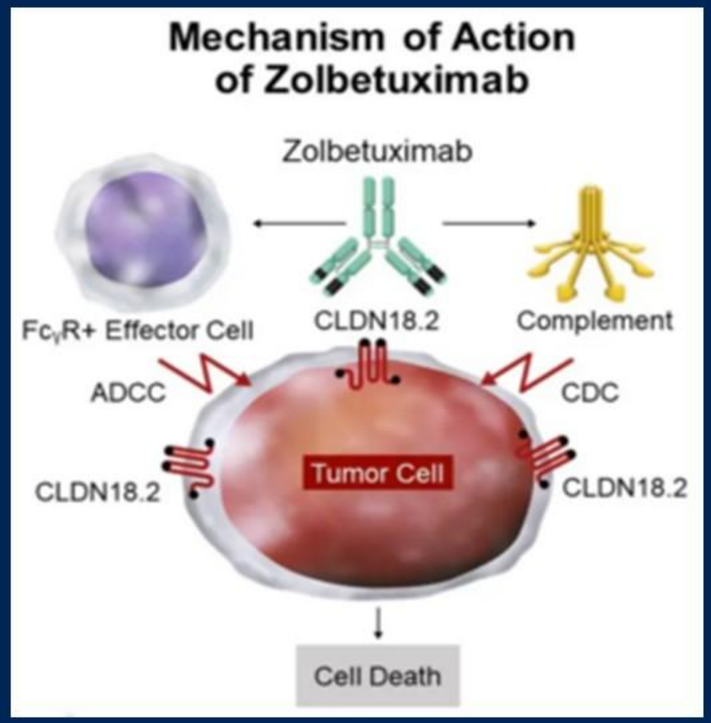


Image source: ecan.org/2024

Summary: Biomarker testing in metastatic gastric cancer

First line setting

- **Her 2-neu**: IHC 3+ or IHC 2+ & FISH positive.
- **PDL1**: CPS or TAP. (Varying guidelines)
- **Claudin 18.2:** Moderate to strong positive >/= 75% cells
- **MMR/MSI:** Deficient MMR or MSI-high

Subsequent therapies

- **Repeat Her 2-neu** at progression prior to second line therapy.
- **Next-generation sequencing** if not done in first line setting
- **Tumor agnostic actionable alterations**: MMR/MSI, TMB, NTRK, RET, BRAF V600E.

Case Example 1: Patient selection for first line systemic therapy

37 y/o Female

- **Local ER** : Abdominal distention and discomfort, early satiety, and 12 lb weight loss x 3 months. Her weight at presentation was 110 lbs.
- **CT scan in ER:** Gastric wall thickening + moderate ascites.
- **Admitted local hospital**
- **US guided paracentesis:** Positive cytology in peritoneal fluid
  - 1 peritoneal nodule atypical-nondiagnostic.
- **GI evaluation** with biopsy: Diffuse erythema in cardia 2 cm gastric ulcer.
- **Pathology :** H. pylori negative, diffuse type, grade 3 adenocarcinoma of the stomach, **Her 2 neu IHC 1+ (negative). FISH pending**.

Case Example 1: Patient selection for first line systemic therapy

- She is referred to a tertiary center.
- **PET:** Avidity in multiple sites (gastric cardia, one regional lymph node, 2 liver lesions 1 and 2 cm, scattered omental nodule).
- **Additional biomarker testing**

Patient summary: Young female, high symptom burden, high volume disease.

Biomarker summary:

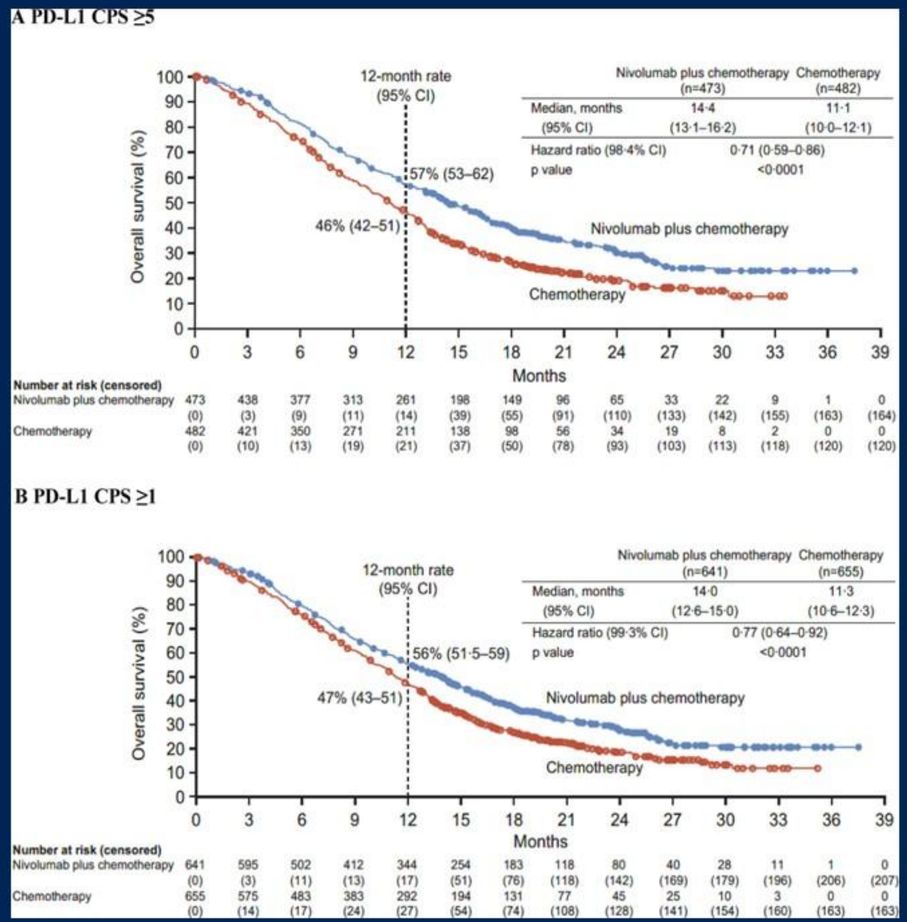
PDL1 CPS 5 **Claudin 18.2: Positive**

MMR proficient **Her 2 neu IHC 1+. FISH amplified 2.0.**

CHECKMATE 649: Nivolumab+chemo vs Chemo

END POINTS

- The median overall survival (OS): Improved
  - ❖PDL1 ≥5%: 14.4 mo vs 11.1 mo
  - ❖All patients: 13.8 mo vs 11.6 mo
- Statistically significant improvement in OS in PDL1 ≥5 and in all patients.
- PFS and ORR: Improved
- CM 649 used CPS score

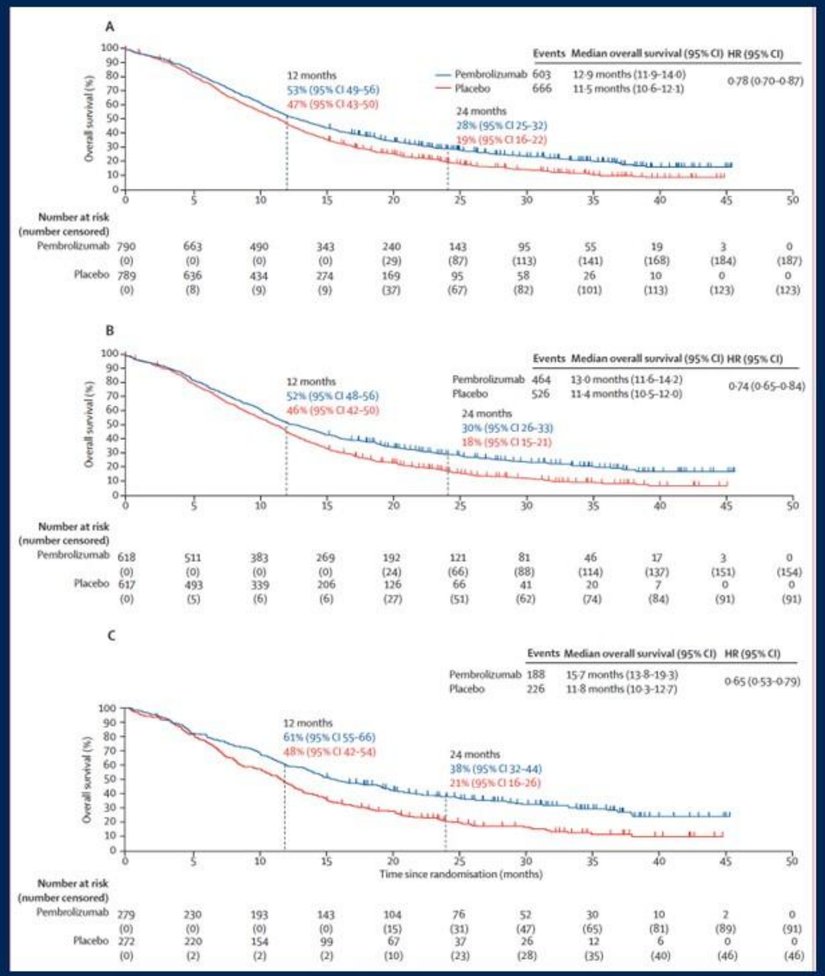


Source: Janjigian YY et al. The Lancet. 2021 Jul 3;398(10294):27-40.

KEYNOTE 859: Pembrolizumab+chemo vs Placebo+chemo

END POINTS

- The median overall survival (OS): Improved
  - ❖PDL1 ≥10%: 15.7 mo vs 11.8 mo
  - ❖All patients: 12.9 mo vs 11.5 mo
- Statistically significant improvement in OS in PDL1 ≥10 and in all patients.
- PFS and ORR: Improved
- KN 859 used CPS score

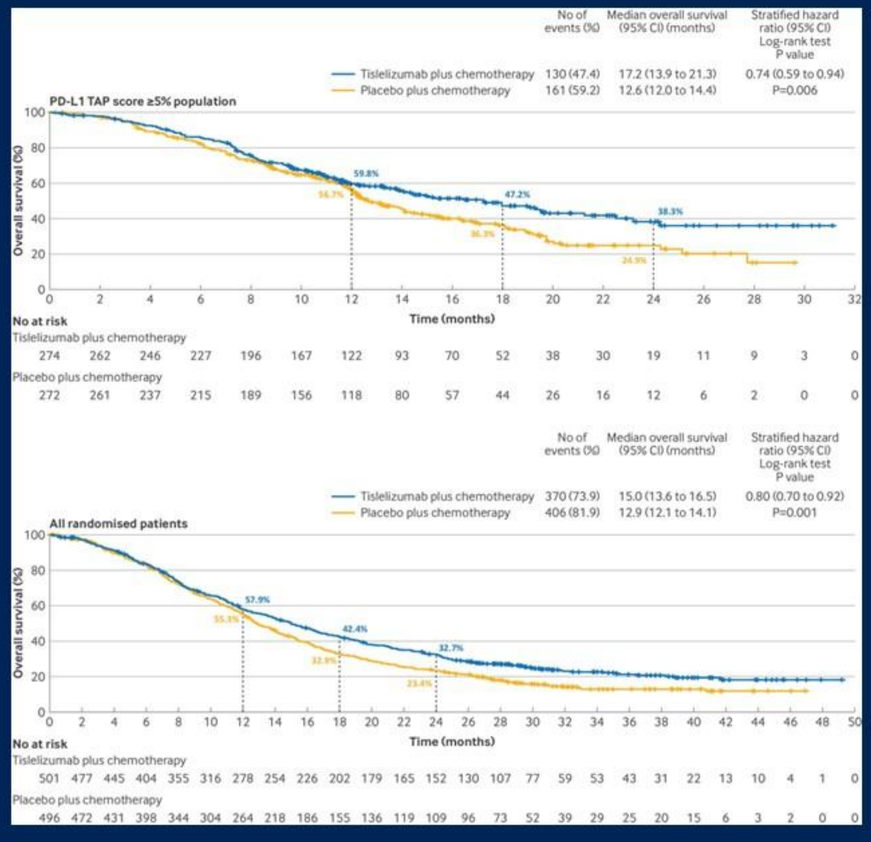


Source: Rha SY et al. The Lancet Oncology. 2023 Nov 1;24(11):1181-95.

RATIONALE-305: Tislelizumab+chemo vs Placebo+chemo

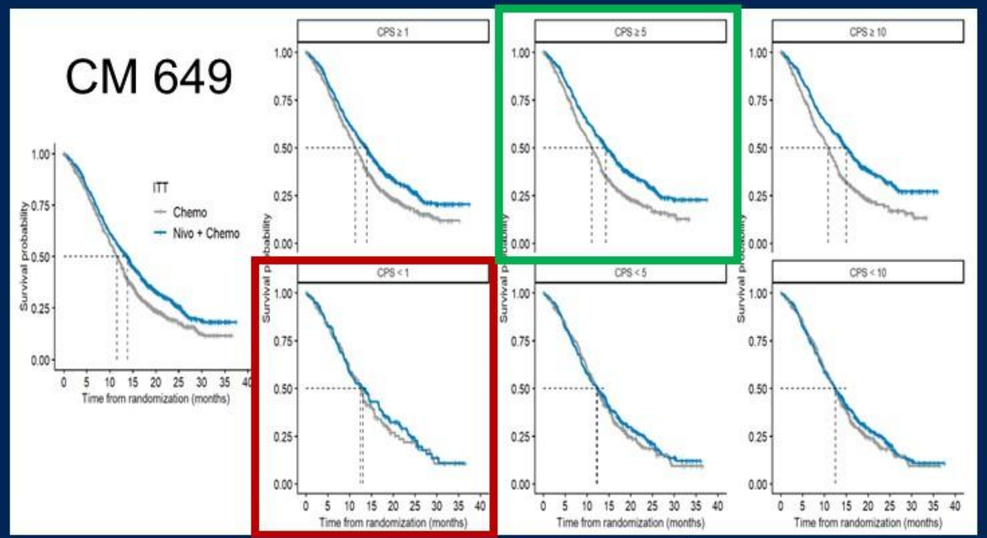
END POINTS

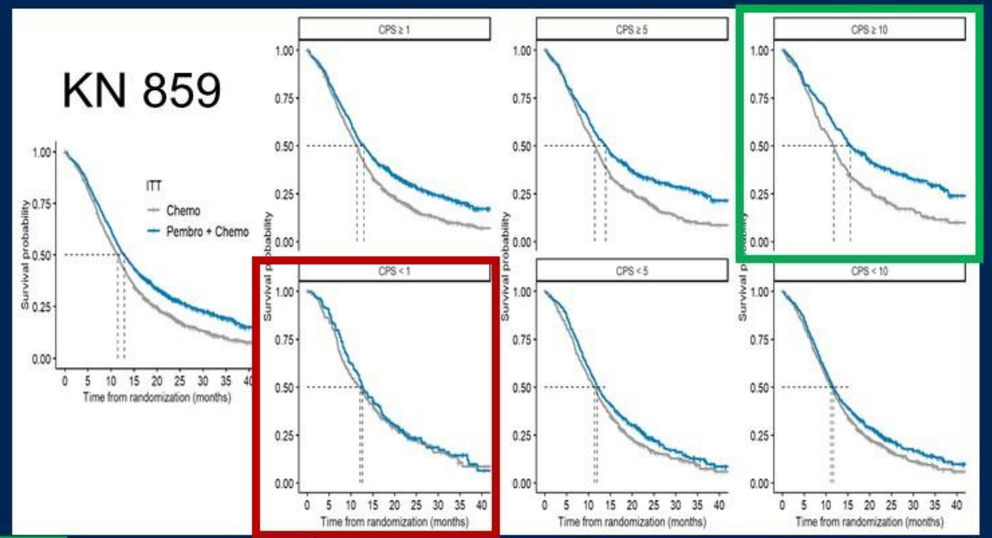
- The median overall survival (OS) : Improved
  - ❖PDL1 ≥ 5%: 16.4 mo vs 12.8 mo
  - ❖All patients: 15 mo vs 12.9 mo
- Statistically significant improvement in OS in PDL1 ≥5 and in all patients.
- PFS and ORR: Improved
- RN 305 used TAP score

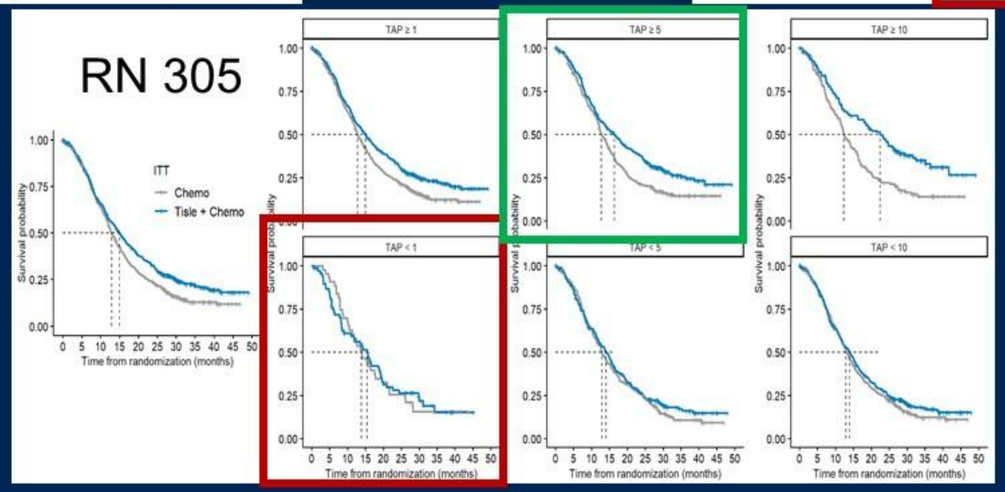


Source: Qiu MZ et al. bmj. 2024 May 28;385.

FDA Analyses of OS of Chemo-IO combinations

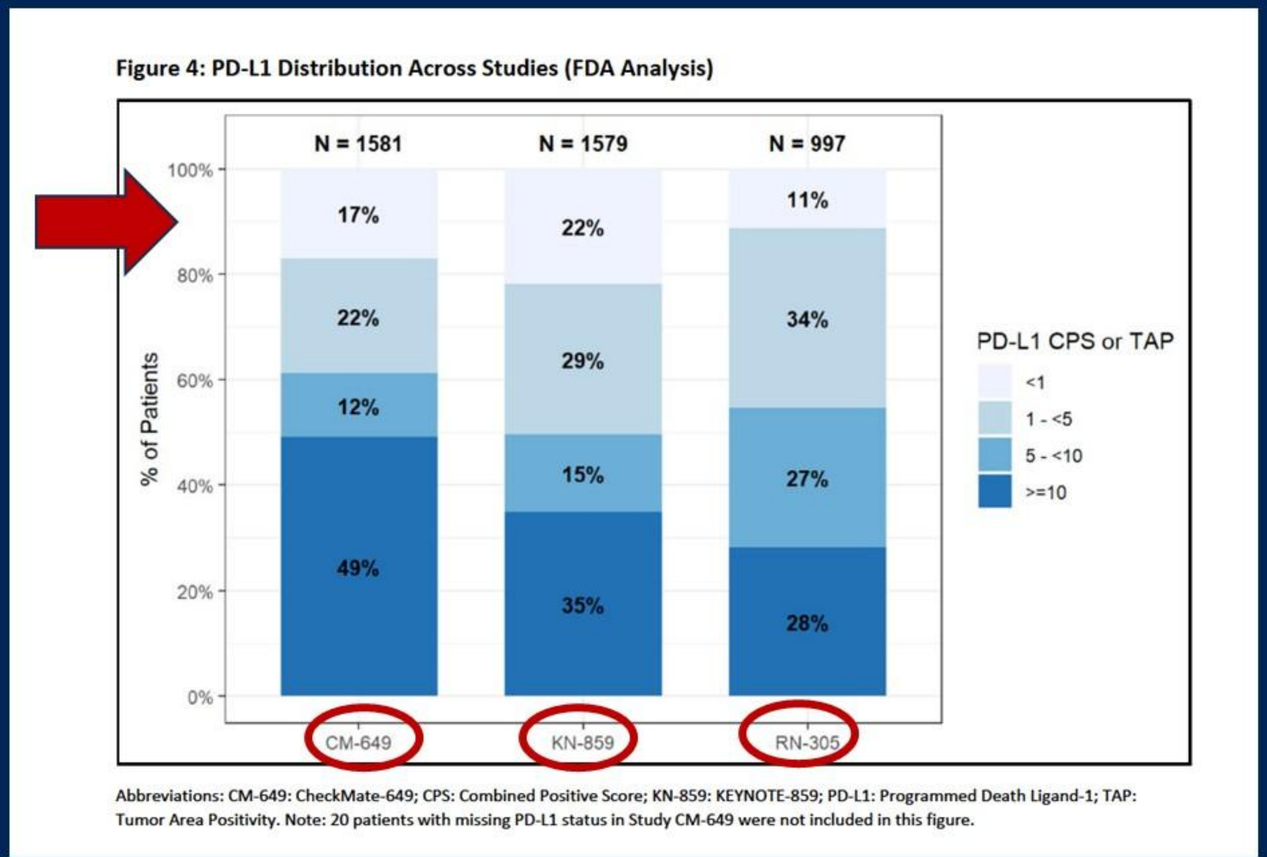






Source: https://www.fda.gov/media/182138/download

Evolution of ongoing debate PDL1 in metastatic gastric cancer



- Initial FDA Approval: PDL1 agnostic
  - ❑ Chemo + Nivolumab
  - ❑ Chemo + Pembrolizumab
  - ❑ FDA ODAC September 2024 review:
    - Limited benefit of ICI in Low PDL1 status (10-2-1 vote).
    - Recommended PDL1 CPS or TAP at least ≥ 1
  - ❑ RN 305-Chemo + Tislelizumab: FDA PDL1 ≥ 1

Source: https://www.fda.gov/media/182138/download

Current NCCN guidelines for chemoimmunotherapy regimens (Her 2 negative, non MSI-H)

NCCN guidelines v5.2024- Dec 20, 2024:

- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, **and nivolumab** for **PD-L1 CPS ≥ 5 (category 1).**
- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin or cisplatin, and **pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥10; category 2B for PD-L1 CPS 1 < 10)**
- **Useful in Certain Circumstances** : Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and **nivolumab (PD-L1 CPS <5) (category 2B)**

Source: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

ASCO guidelines (2022) for Nivolumab for metastatic gastric adenocarcinoma (Her 2 negative, non MSI-H)

- **PD-L1 CPS ≥5**, first-line therapy with **nivolumab in combination** with fluoropyrimidine- and platinum based chemotherapy is recommended. (EB/M/S)
- Qualifying statements:
  - For 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.**
  - **For PD-L1 CPS 0,** first-line therapy with fluoropyrimidine- and platinum based **chemotherapy**, **without the addition of nivolumab**, is recommended.

Source: https://society.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2022-Immunotherapy-Targeted-Tx-Adv-Gastroesophageal-Cancer-Summary-Table.pdf

EMA guidelines for IO for metastatic gastric adenocarcinoma (Her 2 negative, non MSI-H)

<u>EMA (European Medicines Agency) /European Commission (EC) approval:</u>

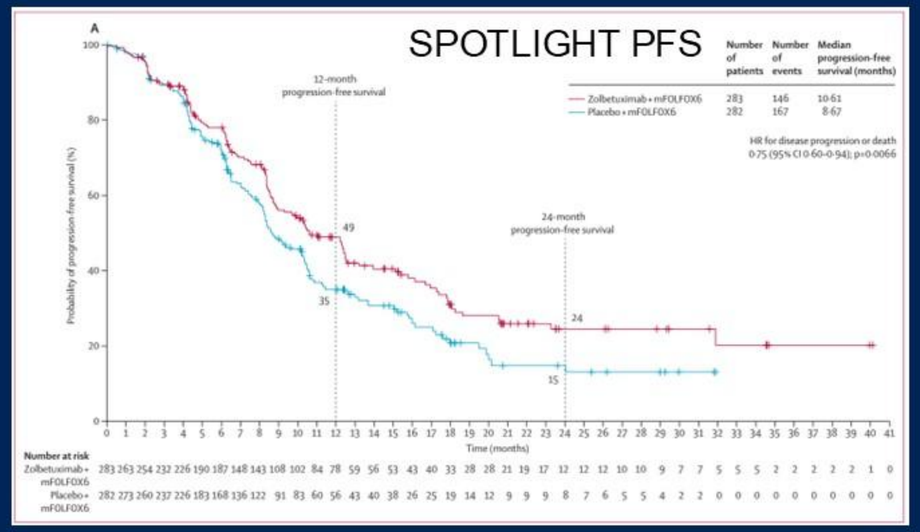
- All patients: platinum-fluoropyrimidine containing chemotherapy
- PD-L1 positive
- CPS ≥ 5: Nivolumab+chemotherapy
- CPS ≥ 1: Pembrolizumab+chemotherapy
- TAP ≥ 5: Tislelizumab+chemotherapy

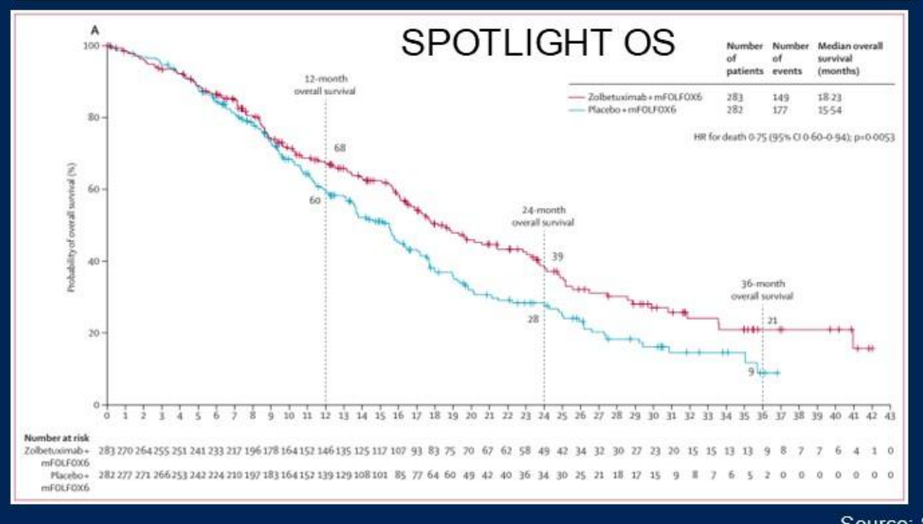
Source:https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-290-1#:~:text=Information,0
https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-400-1
https://ir.beigene.com/news/european-commission-approves-beigene-s-tevimbra-for-first-line-treatment-of-advanced-metastatic-esophageal-squamous-cell-carcinoma-and/22ce8afc-1ba7-4525-82dd-058f6cfea63c/

Summary: Chemo + IO for MGC: Response pattern

- **ORR: Improved favoring IO (50-60% vs 40-45%)**
- PFS, OS: Improved
- Gradient Increase in response to PDL1 level
- High level consensus
  - Nivo or Tesli PDL1 ≥5 and
  - Pembro ≥10

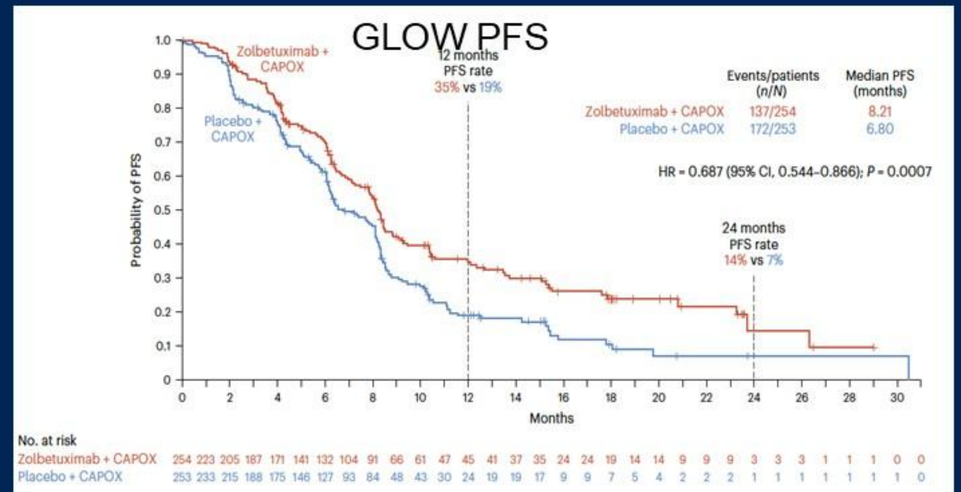
Claudin 18.2 directed therapy: Zolebetuximab

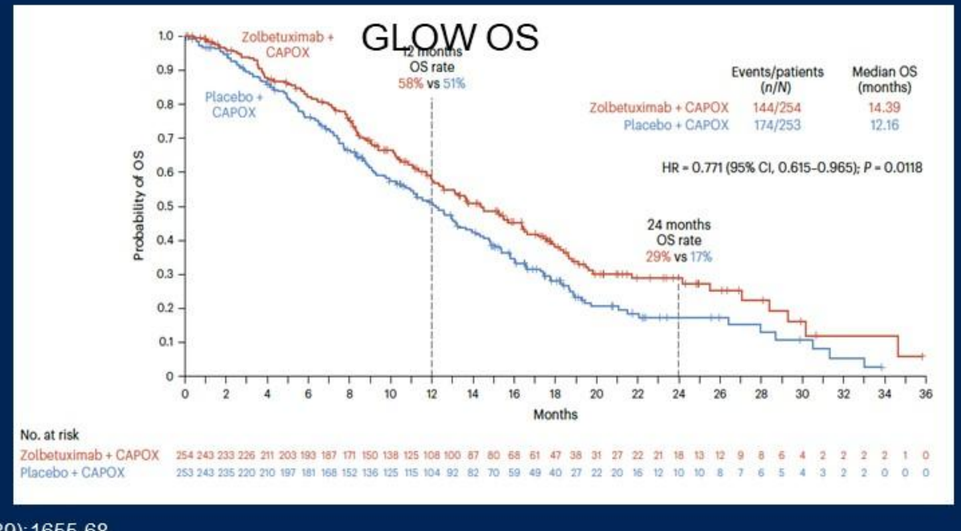




END POINTS

1. PFS and OS: Improved
2. ORR: Not improved (42%)
3. Notable Toxicities: N/V at first infusion





Source: Shitara K, et al. The Lancet. 2023 May 20;401(10389):1655-68.
Shah E et al. Nature medicine. 2023 Aug;29(8):2133-41):1655-68.

Modified Case Example 1: Patient selection for first line systemic therapy

37 y/o female

PET: Avidity in multiple sites (peritoneum, gastric cardia, one regional lymph node, scattered omental nodules).

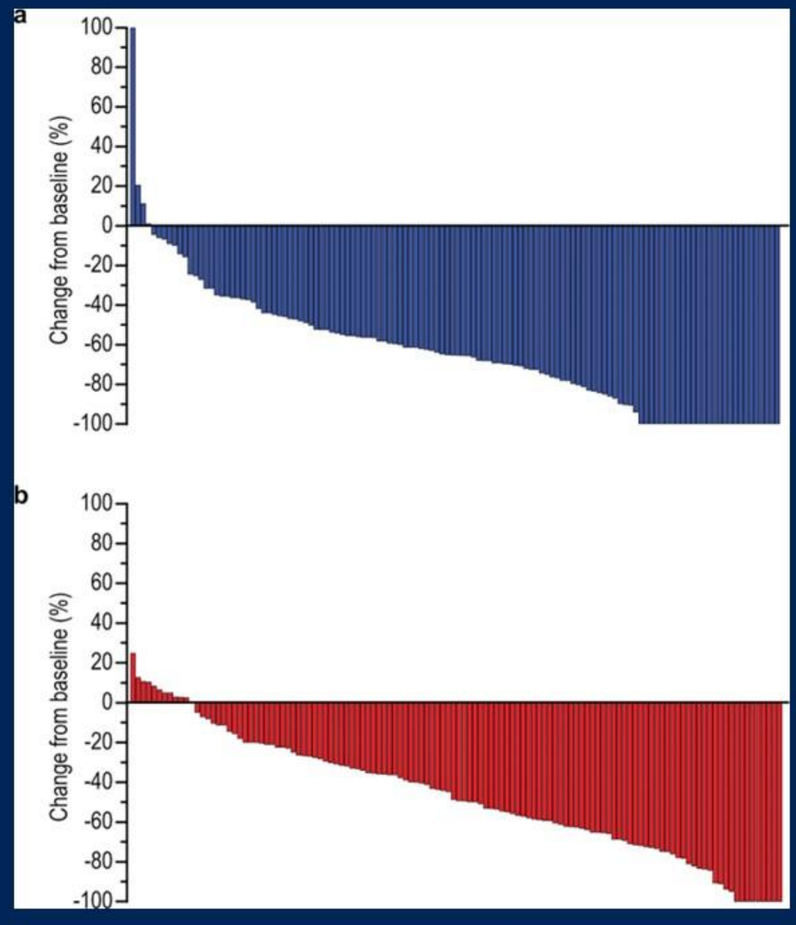
Patient summary: Young female, high symptom burden, high volume disease.

Biomarker summary:

1. **PDL1 CPS 5**
2. **Claudin 18.2: Positive**
3. **Her 2 neu IHC 2+ (positive). FISH amplified 2.0**
4. **MMR proficient**

KN 811: First line Anti-Her2 +/- Anti-PD1 systemic therapy with Chemotherapy

- Chemo (CAPOX or FP) + Trastuzumab +/- Pembrolizumab
- **High ORR**: 74.4% (Pembro) Vs 51.9% (placebo).
- **Deeper responses** (Pembro): median change from baseline, –65% vs –49%)
- **More Complete responses**: (11.3% vs 3.1%)
- **Improved Overall Survival** (Median OS 20 mo vs 16.8 mo)



Source: Janjigian et al. Nature. 2021 Dec 23;600(7890):727-30.

MMR/MSI in First line systemic therapy

Fluoropyrimidine + Platinum backbone (FOLFOX or CAPEOX)

- **Her 2 +ve: Add Trastuzumab & +/- PDL1 CPS >/=1 Add Pembrolizumab**: KN 811
- **PDL 1 +ve: Add IO:**
  - ➢**Add Pembrolizumab**: KN 859 or
  - ➢**Add Nivolumab:** CM 649 or
  - ➢**Add Tislelizumab:** RN 305
- **CLDN 18.2 +ve: Add Zolbetuzimab** : SPOTLIGHT and GLOW
- **dMMR/MSI-H: independent of PDL1 status**
  - **Add Pembrolizumab** : KN 062
  - **Add Nivolumab:** CM 649

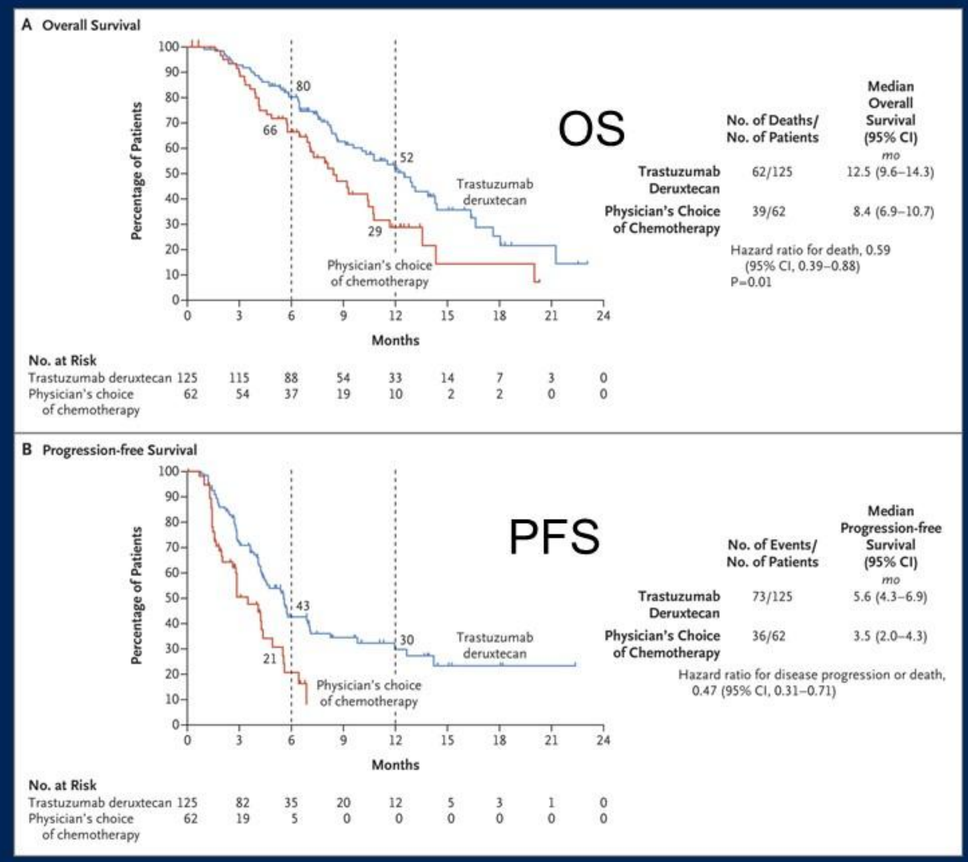
Immunotherapy alone

- **dMMR/MSI-H** independent of PDL1 status
  - ➢Pembrolizumab: KN 059
  - ➢Dostarlimab: GARNET
  - ➢Nivolumab/Ipilimumab: CM 649
  - ❖Otherwise not a candidate for more aggressive systemic therapy or lower symptom burden.

Source: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

Second line: Anti-her2 therapy with TDXd: DESTINY-Gastric01

- **TDXd superior to Physician's choice**
  - Objective response high: 51% vs 14%
  - Deeper responses
  - Median duration of response: 11.3 vs 3.9 mo
  - Overall survival: Improved
  - 12 month OS: 52% vs 29%
- Myelosuppression and interstitial lung disease were the notable toxic effects



Source: Shitara K, et al. New England Journal of Medicine. 2020 Jun 18;382(25):2419-30.

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Case example #2: Peritoneal carcinoma as only disease

49 y/o otherwise healthy female

- **At PCP** : C/o abdominal discomfort, early satiety, and 20 lb weight loss for at least 3 months. Her weight at presentation was 145 lbs. There was mild epigastric tenderness but no abdominal distention.
- **CT scan**: Mild gastric wall thickening.
- **GI evaluation**: EGD with biopsy revealed a 5 cm ulcer. Pathology revealed a H. pylori negative diffuse type, moderately to poorly differentiated adenocarcinoma of the stomach.

Case example#2: Peritoneal carcinoma as only disease

- **Biomarkers:**
  - Her 2 neu IHC 0 (negative)
  - MMR proficient
  - **PDL1 CPS 20**
  - Claudin 18.2 negative.
- **PET** revealed uptake in the cardia.
- **Diagnostic staging laparoscopy**:
  - Positive cytology
  - Biopsy: Two 1-2 cm peritoneal nodules with malignancy.
- **Treatment:** Patient receives 6 cycles of FOLFOX +Pembro.
- **Restaging:** PET negativity.

Special considerations: Peritoneal Limited GC (PLGC) and Low Peritoneal Cancer Index (PCI)

- Criteria of Unresectability for Cure
- IC/HIPEC may be effective in selected patients with Low PCI (NCCN)
- Modalities:
  - Intraperitoneal Chemotherapy (IC/NIPEC)
  - Bidirectional therapy (BD)
  - Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
  - Cytoreductive surgery (CRS)
- Investigational: Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC) and IC/HIPEC in high PCI >10.

Source: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

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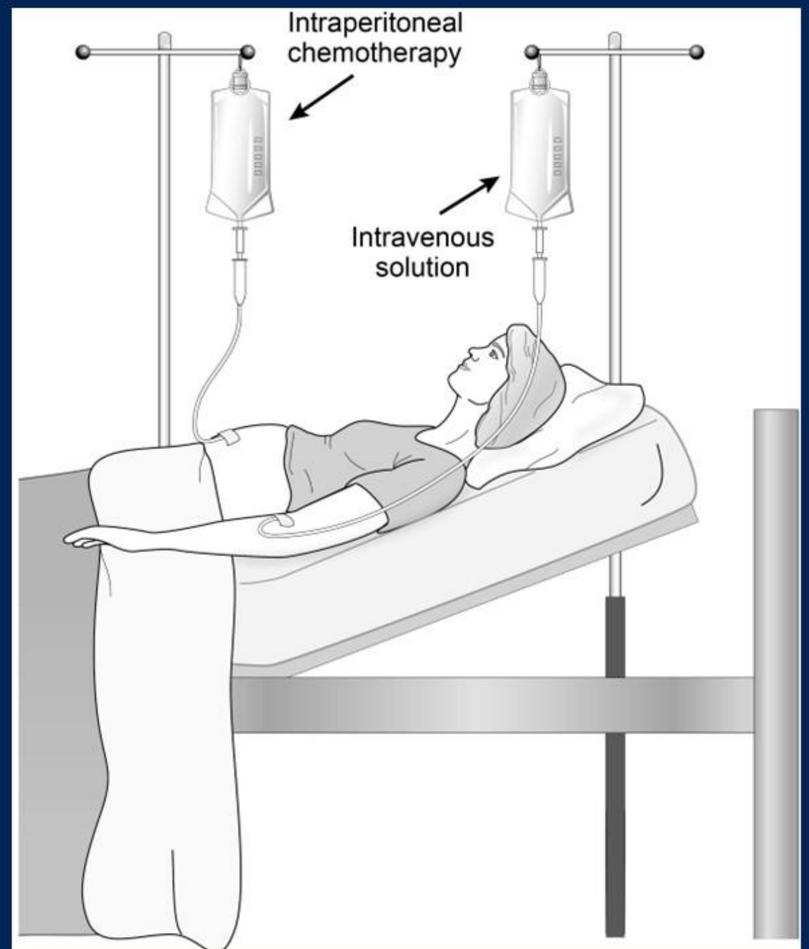
NIPEC (Normothermic Intraperitoneal Chemotherapy)

- NIPEC may be effective in selected patients (NCCN)
  - ✓Low burden of tumor
  - ✓Multidisciplinary planning is essential
  - ✓Must be candidate for CRS
  - ✓Minimum 3 months of systemic therapy.
  - ✓In conjunction with cytoreductive surgery (CRS)
  - ✓Low peritoneal cancer index (PCI ≤10)



Source: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
Image source: https://patient.uwhealth.org/healthfacts/4208

Bidirectional Chemotherapy, CRS/HIPEC

DRAGON-01 (GI ASCO Abstract #327)

- Phase 3 (China)
- IP Paclitaxel + Chemo Vs Chemo alone
- Chemo: Oral S1 and IV Paclitaxel.

Outcomes of PLGC undergoing Bidirectional (BD) Chemotherapy, CRS with HIPEC. (GI ASCO Abstract #328)

- Retrospective single center (Singapore)
- BD Chemo: IP Paclitaxel + Chemo (Oral S1 & IV Paclitaxel or CAPOX)
- PCI stratification
- 7 Patients went on to CRS D2 Gastrectomy and HIPEC (Cisplatin)

Emerging targets and therapies

FGFR 1-4 and Monoclonal Antibodies	Her 3 antibodies and ADC	KRAS amplifications and mutations
Bispecific antibody	New immune checkpoints (LAG 3)	BiTE and chemokines

Ancillary care coordination

Genetic testing

Testing criteria for diffuse gastric cancer

CDH1 variants

Supportive care

Nausea/vomiting

Zolbetuximab

Nutrition

Palliative care

Bleeding

Obstruction

Pain

Key takeaways in MGC cancers

- There is a need to address gap in patient access to care and practice-changing drugs
- Biomarker testing is essential for patients' therapy selection
- Multidisciplinary care is being integrated in select situations
- Emerging technologies and strategies are diverse