Personalized treatment of advanced HER2-negative gastric or gastroesophageal junction cancer: Current status and future perspectives

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Challenges and unmet needs for patients with advanced HER2-negative GC/GEJC

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What is the current burden of disease of advanced GC/GEJC?

Current burden of disease of advanced GC/GEJC

Incidence and background

- With >1 million new cases in 2020 and an estimated 769,000 deaths, GC represents one of the most common causes of cancer death worldwide[1]
- Incidence rates are approximately twofold higher in men than in women[1]
- The majority of GC/GEJC tumours are adenocarcinomas[2,3]
- The incidence of GEJC is increasing in the West, likely due to its links with obesity and gastroesophageal reflux disease[4]
- Localized GC can be cured with surgery, but most patients with early-stage GC are asymptomatic and up to 50% have unresectable disease[5]

Factors leading to high mortality of GC[6]

- Silent evolution
- Late clinical presentation
- Underlying genetic heterogeneity
- Effective mechanisms of chemoresistance to treatments

GC, gastric cancer; GEJC, gastroesophageal junction cancer.

1. Sung H, et al. *CA Cancer J Clin.* 2021;71:209–49; 2. Greally M, et al. *Cancer*. 2019;125:1990–2001; 3. National Organization for Rare Disorders. 2019. Available at: https://rarediseases.org/rare-diseases/stomach-cancer/ (accessed March 2023); 4. Oo AM, Ahmed S. *Mini-invasive Surg*. 2019;3:13; 5. Olnes MJ, Martinson HA. *Cancer Gene Ther*. 2021;28:924–34; 6. Marin JJG, et al. *Cancers*. 2020;12:2116.

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What do current US guidelines advise for the treatment of HER2-negative advanced GC/GEJC?

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Current US guidelines for immunotherapy treatment of HER2-negative advanced GC/EC/GEJC

- For patients with HER2-negative GEJC, the NCCN 2023 guidelines recommend nivolumab combined with a fluoropyrimidine and oxaliplatin, or pembrolizumab combined with a fluoropyrimidine and oxaliplatin or cisplatin as first-line immunotherapy[1]
- For patients with HER2-negative GC, first-line immunotherapy is limited to nivolumab combined with a fluoropyrimidine and oxaliplatin according to NCCN 2023 guidelines[2]
- In March 2021, the FDA approved pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for metastatic or locally advanced EC/GEJC based on results from the KEYNOTE-590 trial[3]
- In April 2021, the FDA approved nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic GC/EC/GEJC based on results from the CheckMate-649 trial[4]

EC, esophageal cancer; FDA, US Food and Drug Adminstration; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network.

1. NCCN. Esophageal and esophagogastric junction cancers. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf (accessed 7 March 2023);
2. NCCN. Gastric cancer. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/gastric.pdf (accessed 22 March 2023); 3. FDA. 2021. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma (accessed 20 March 2023); 4. FDA. 2021. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal (accessed 14 March 2023).

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Categories of evidence in the NCCN guidelines for the treatment of HER2-negative advanced EC/GEJC

Recommended immunotherapy treatment options are split into the following categories of evidence:

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin and **nivolumab**
Category 1: PD-L1 CPS ≥5
Category 2B: PD-L1 CPS <5

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin and **pembrolizumab**
Category 2A: PD-L1 CPS ≥10
Category 2B: PD-L1 CPS <10

Fluoropyrimidine (fluorouracil or capecitabine), cisplatin and **pembrolizumab**
Category 1: PD-L1 CPS ≥10
Category 2B: PD-L1 CPS <10

Categories of evidence are defined as:
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

CPS, combined positive score; EC, esophageal cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1.

1. NCCN. Esophageal and esophagogastric junction cancers. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf (accessed 7 March 2023).

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What are the data supporting the use of nivolumab in HER2-negative advanced GC/GEJC?

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CheckMate-649

Nivolumab + chemotherapy vs chemotherapy as first-line treatment for advanced GC/GEJC/EAC: A multi-centre, randomized, open-label, phase III trial

Chemotherapy group
(PD-L1 CPS ≥5 patients)
n=482

- Median age: 62 years
- Primary tumour site:
  - GC 69%
  - GEJC 18%
  - EAC 13%

11.1 months mOS

6.0 months mPFS

Nivolumab + chemotherapy group
(PD-L1 CPS ≥5 patients)
n=473

- Median age: 63 years
- Primary tumour site:
  - GC 70%
  - GEJC 18%
  - EAC 12%

14.4 months mOS

7.7 months mPFS

Nivolumab + chemotherapy resulted in significant improvements in OS and PFS vs chemotherapy alone in PD-L1 CPS ≥5 patients

CPS, combined positive score; EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; m, median; OS, overall survival; mPFS, progression-free survival; PD-L1, programmed death-ligand 1.

Janjigian YY, et al. *Lancet*. 2021;398:27–40.

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CheckMate-649

Nivolumab + chemotherapy vs chemotherapy as first-line treatment for advanced GC/GEJC/EAC: A multi-centre, randomized, open-label, phase III trial

Chemotherapy group
(all randomized patients)
n=792

- Median age: 61 years
- Primary tumour site:
  - GC 70%
  - GEJC 16%
  - EAC 14%

11.6 months mOS

6.9 months mPFS

Nivolumab + chemotherapy group
(all randomized patients)
n=789

- Median age: 63 years
- Primary tumour site:
  - GC 70%
  - GEJC 17%
  - EAC 13%

13.8 months mOS

7.7 months mPFS

EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; mOS, median overall survival; mPFS, median progression-free survival.

Janjigian YY, et al. *Lancet*. 2021;398:27–40.

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What are the data supporting the use of pembrolizumab in HER2-negative advanced EC/GEJC?

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KEYNOTE-590

Pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment of patients with advanced EC/GEJC: A randomized, placebo-controlled, phase III trial

Placebo + chemotherapy group
(all randomized patients)
n=376

- Median age: 62 years

9.8 months OS

5.8 months PFS

Pembrolizumab + chemotherapy group
(all randomized patients)
n=373

- Median age: 64 years

12.4 months OS

6.3 months PFS

Pembrolizumab + chemotherapy resulted in significant improvements in OS and PFS vs placebo + chemotherapy in all randomized patients (EC/GEJC squamous cell carcinoma and adenocarcinoma)

EC, esophageal cancer; GEJC, gastroesophageal junction cancer; OS, overall survival; PFS, progression-free survival.
Sun JM, et al. *Lancet*. 2021;398:759–71.

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KEYNOTE-590

Pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment of patients with advanced EC/GEJC: a randomized, placebo-controlled, phase III trial

Placebo + chemotherapy group
(PD-L1 CPS ≥10 patients)
n=197

9.4 months — OS

5.5 months — PFS

Pembrolizumab + chemotherapy group
(PD-L1 CPS ≥10 patients)
n=186

13.5 months — OS

7.5 months — PFS

Pembrolizumab + chemotherapy resulted in significant improvements in OS and PFS vs placebo + chemotherapy in PD-L1 CPS ≥10 patients with EC/GEJC squamous cell carcinoma and adenocarcinoma

CPS, combined positive score; EC, esophageal cancer; GEJC, gastroesophageal junction cancer; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death-ligand 1.

Sun JM, et al. *Lancet*. 2021;398:759–71.

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What clinical challenges remain in the treatment of HER2-negative advanced GC/GEJC?

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Ongoing clinical challenges for the treatment of advanced GC/GEJC

- Identifying better, more reliable biomarkers to predict efficacy for immunotherapy[1]
- Identifying better treatment options for patients with low PD-L1[1]

- Studying the optimal sequencing and combinations of targeted therapies[1]

- Identifying extra targetable therapies/combinations that lead to more durable responses[2]
- Identifying more active regimens in the refractory setting[2]

GC, gastric cancer; GEJC, gastroesophageal junction cancer; PD-L1, programmed death-ligand 1.

1. Leiting JL, Grotz TE. *World J Gastrointest Oncol*. 2019;11:652–64; 2. Greally M, et al. *Cancer*. 2019;125:1990–2001.

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Novel and emerging first-line targeted therapies for advanced HER2-negative GC/GEJC

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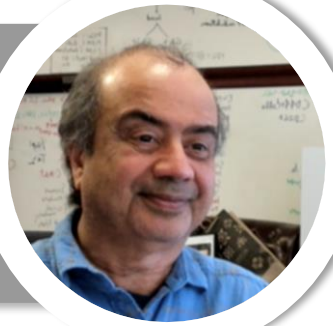

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What new targeted therapy approaches are being explored in advanced GC/GEJC?

Targeted therapy approaches

Gastroesophageal adenocarcinomas are heterogeneous at multiple levels (clinically and molecularly)

Established subsets that are currently targeted therapeutically

HER2[1]
PD-L1 high[1]
MSI high[1]
EBV positive[2]

Subsets that are likely to emerge in the near future

KRAS mutation[6]
DDRd[7]

Emerging subsets for which therapies are in development

Claudin 18.2[3]
FGFR2b[4]
DKK1[5]

Agnostic approvals[8]

TMB high
RET fusion
NTRK fusion
BRAF mutation

BRAF, v-raf murine sarcoma viral oncogene homologue B1; DDRd, DNA-damage response deficiency; DKK1, dickkopf WNT signalling pathway inhibitor 1; EBV, Epstein–Barr virus; FGFR2b, fibroblast growth factor receptor 2b; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MSI, microsatellite instability; PD-L1, programmed death-ligand 1; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; TMB, tumour mutational burden.

1. NCCN. Gastric cancer. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/gastric.pdf (accessed 23 March 2023); 2. Sun K, et al. *Front Oncol.* 2020;10:583463; 3. Singh P, et al. *J Hematol Oncol.* 2017;10:105; 4. Catenacci DV, et al. *Future Oncol.* 2019;15:2073–82; 5. Klempner SJ, et al. *Mol Cancer Ther*. 2021;20:2240–9; 6. Wang JY, et al. *Ann Oncol.* 2021;32:906–16; 7. Turkington RC, et al. *J Clin Oncol.* 2017;35:4026; 8. Bhamidipati D, Subbiah V. *Trends Cancer.* 2023;9:237–49.

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What is the evidence base for the use of bemarituzumab in HER2-negative advanced GC/GEJC?

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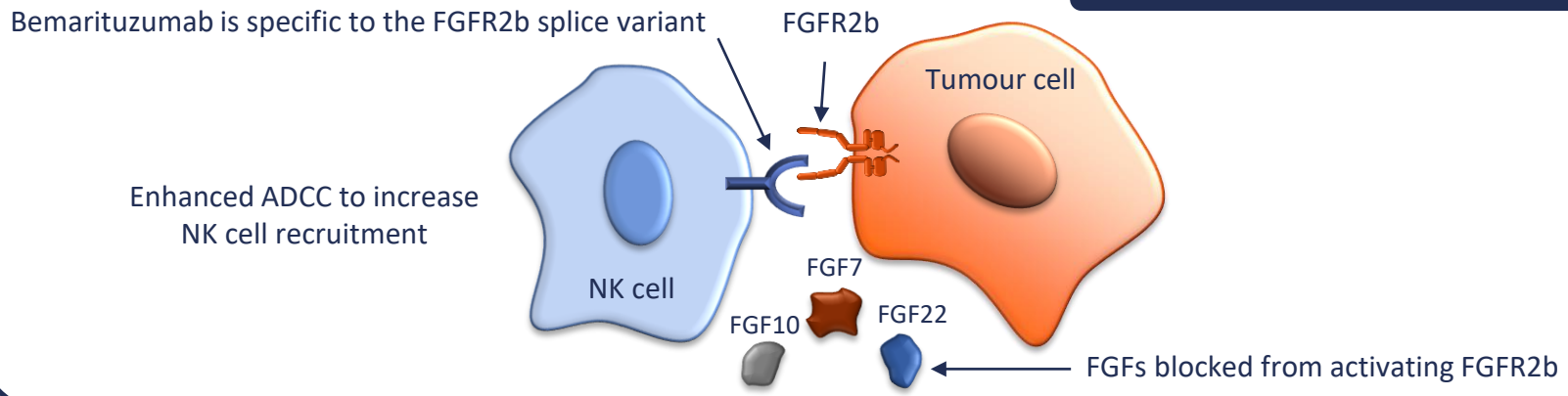
Bemarituzumab for HER2-negative advanced GC/GEJC

A first-in-class anti-FGFR2b antibody

Bemarituzumab was granted breakthrough therapy designation by the FDA in April 2021 as a first-line treatment in combination with modified FOLFOX6 for patients with FGFR2b-overexpressing and HER2-negative metastatic and locally advanced GC/GEJC[1]

Bemarituzumab: Mechanism of action[2]



ADCC, antibody-dependent cell-mediated cytotoxicity; FDA, US Food and Drug Agency; FGF, fibroblast growth factor; FGFR2b, FGF receptor 2b; FOLFOX6, fluoropyrimidine, leucovorin and oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; NK, natural killer.

1. Cancer Network. 2021. Available at: www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-bemarituzumab-for-frontline-fgfr2b-gastric-gej-cancers (accessed 22 March 2023); 2. Catenacci DV, et al. *Future Oncol.* 2019;15:2073–82.

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FIGHT: A randomized placebo-controlled phase II study

Bemarituzumab in patients with FGFR2b-selected GC/GEJC

Placebo group
n=78

- Median age: 59.5 years
- Site of primary cancer:
  - Gastric 91%
  - GEJ 9%

mPFS:

7.4 months (95% CI 5.8–8.4)

Bemarituzumab group
n=77

- Median age: 60.0 years
- Site of primary cancer:
  - Gastric 86%
  - GEJ 14%

mPFS:

9.5 months (95% CI 7.3–1.9)

Despite no statistically significant improvement in PFS (HR 0.68 [95% CI 0.44–1.04]; p=0.073), treatment with bemarituzumab showed promising clinical efficacy

CI, confidence interval; FGFR2b, fibroblast growth factor receptor 2b; GC, gastric cancer; GEJ, gastroesophageal junction; GEJC, GEJ cancer; HR, hazard ratio; m, median; PFS, progression-free survival.

Wainberg ZA, et al. *Lancet Oncol.* 2022;23:1430–40.

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Ongoing phase III clinical trials with FGFR2 inhibitors

Bemarituzumab

- A randomized, multi-centre, double-blind, placebo-controlled phase III study of bemarituzumab plus chemotherapy vs placebo plus chemotherapy in subjects with previously untreated advanced gastric or gastroesophageal junction cancer with FGFR2b overexpression (FORTITUDE-101)[1]
- A phase Ib/III study of bemarituzumab plus chemotherapy and nivolumab vs chemotherapy and nivolumab alone in subjects with previously untreated advanced gastric and gastroesophageal junction cancer with FGFR2b overexpression (FORTITUDE-102)[2]

Anlotinib

- A randomized, double-blind, placebo-controlled, multi-centre clinical trial to compare the efficacy and safety of anlotinib vs placebo in patients with gastric cancer (ALTER0503)[3]

FGFR2, fibroblast growth factor receptor 2.

1. ClinicalTrials.gov. NCT05052801. Available at: https://clinicaltrials.gov/ct2/show/NCT05052801 (accessed 15 March 2023); 2. ClinicalTrials.gov. NCT05111626. Available at: https://clinicaltrials.gov/ct2/show/NCT05111626 (accessed 15 March 2023); 3. ClinicalTrials.gov. NCT02461407. Available at: https://clinicaltrials.gov/ct2/show/NCT02461407 (accessed 15 March 2023).

What is the evidence base for the use of zolbetuximab in HER2-negative advanced GC/GEJC?

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Zolbetuximab

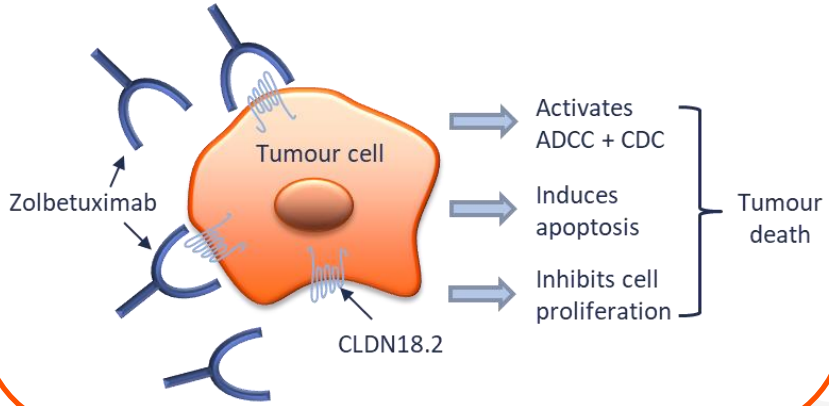
A monoclonal antibody that specifically binds to CLDN18.2

Claudins

- Form important components of tight cell junctions
- Establish paracellular barriers that control the flow of molecules between the cells
- Represent a useful target for various therapeutic strategies as they are surface proteins
- CLDN18.2 expression has been shown to have prognostic value in gastric cancer
- CLDN18.2 has highly restricted expression pattern in normal tissues, with frequent ectopic activation in a diversity of cancers

Zolbetuximab: Mechanism of action

- Structurally chimeric IgG1 monoclonal antibody that specifically binds to CLDN18.2 on tumour cell surface



ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; CLDN18.2, claudin 18.2; IgG1, immunoglobulin G1.

Singh P, et al. *J Hematol Oncol*. 2017;10:105.

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FAST: A randomized phase II study

Zolbetuximab + EOX vs EOX alone as a first-line treatment in patients with advanced CLDN18.2-positive advanced GC/GEJC

EOX group
n=84

- Median age: 57 years
- Tumour site:
  - Stomach 81.0%
  - GEJ 14.3%
  - Esophagus 4.8%

26.2%	ORR
81.0%	DCR
23.0 weeks	mDOR

EOX + zolbetuximab group
n=77

- Median age: 59 years
- Tumour site:
  - Stomach 80.5%
  - GEJ 16.9%
  - Esophagus 2.6%

37.7%	ORR
83.1%	DCR
32.6 weeks	mDOR

Zolbetuximab + EOX led to significant improvements in PFS ($p<0.0005$) and OS ($p<0.0005$) compared with EOX alone

CLDN18.2, claudin 18.2; DCR, disease control rate; EOX, epirubicin + oxaliplatin + capecitabinem; GC, gastric cancer; GEJ, gastroesophageal junction; GEJC, GEJ cancer; mDOR, median duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Sahin U, et al. *Ann Oncol.* 2021;32:609–19.

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Ongoing clinical trials with zolbetuximab

Following the success of the FAST trial, two other clinical trials with zolbetuximab have been reported as meeting their primary endpoints of progression-free survival

The phase III **SPOTLIGHT** trial (NCT03504397) compared the efficacy and safety of zolbetuximab plus modified FOLFOX6 vs placebo plus modified FOLFOX6 in unresectable or metastatic HER2-negative/CLDN18.2-positive GC/GEJ[1]

The phase III **GLOW** trial (NCT03653507) had a similar design to SPOTLIGHT, but with CAPOX as the chemotherapy partner and comparator[2]

CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX6, fluoropyrimidine, leucovorin and oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2.

1. Shitara K, et al. *J Clin Onc.* 2023;41:LBA292; 2. Xu R, et al. *J Clin Onc.* 2023;41:405736.

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What are the future directions for treatment of advanced GC/GEJC in light of emerging biologic therapies?

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Future directions for GC/GEJC therapy

Targeted therapies in development include:

- DKN-01: a DKK1-inhibiting IgG4 antibody[1]

New technologies include:

- Bispecific T-cell engagers (BiTE)[2]
- Bispecific and trispecific antibodies[3]
- CAR T-cell therapy[2]
- Antibody–drug conjugates (ADC)[4]

CAR, chimeric antigen receptor; DKK1, dickkopf WNT signalling pathway inhibitor 1; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IgG4, immunoglobulin G4.

1. Klempner SJ, et al. *Mol Cancer Ther*. 2021;20:2240–9; 2. Zhang J, et al. *Chin J Cancer Res*. 2020;32:263–70; 3. Runcie K, et al. *Mol Med.* 2018;24:50;
4. Wang N, et al. *Front Oncol.* 2022;12:889017.

Importance of biomarker testing for personalized therapy in advanced GC/GEJC

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What are the recommended testing methods for biomarkers in advanced GC/GEJC?

NCCN recommended biomarker testing methods in advanced GC

IHC	PD-L1 (CPS), HER2, dMMR
NGS	NGS may be considered via a validated assay
ctDNA	A negative result should be interpreted with caution, as this does not exclude the presence of tumour mutations or amplifications

CPS, combined positive score; ctDNA, circulating tumour DNA; dMMR, mismatch repair deficient; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1.

NCCN. Gastric cancer. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/gastric.pdf (accessed 23 March 2023).

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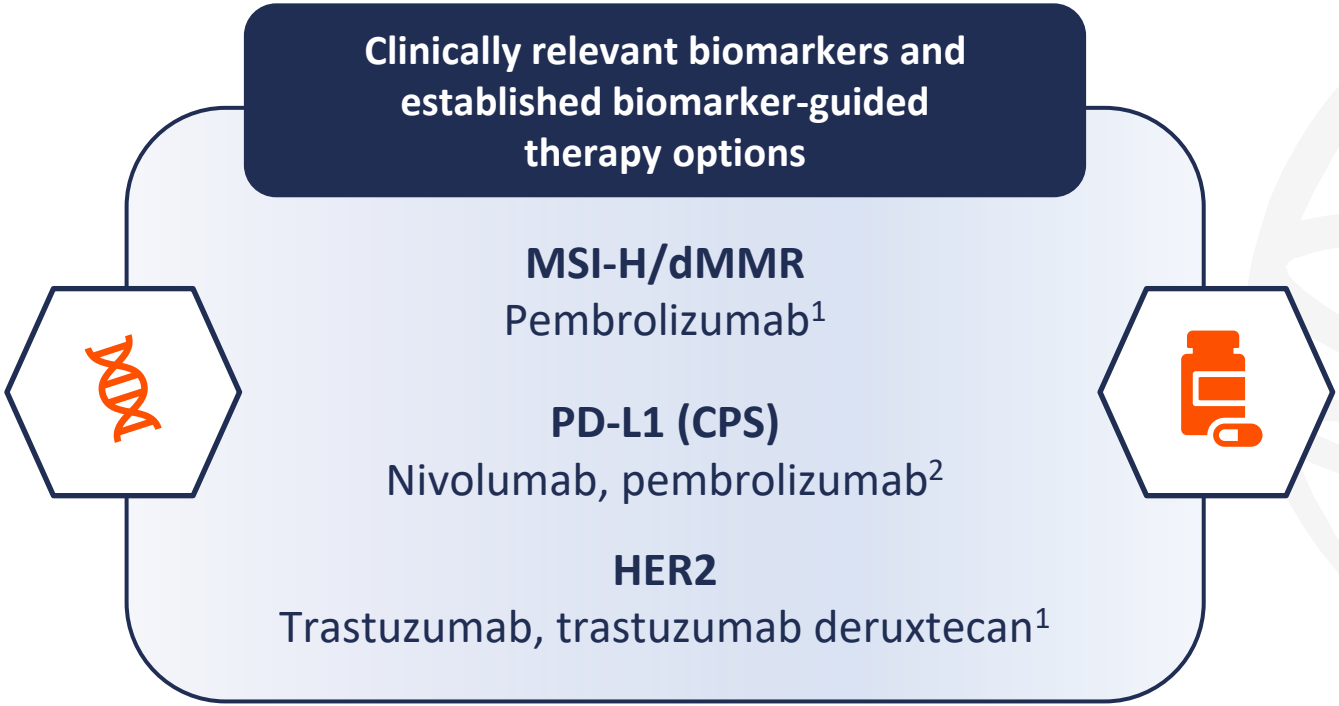
What are the available biomarkers that predict response to targeted therapies for advanced GC/GEJC?

Established biomarkers in advanced GC/GEJC



CPS, combined positive score; dMMR, mismatch repair deficient; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability high; PD-L1, programmed death-ligand 1.

1. Nakamura Y, et al. *Nat Rev Clin Oncol.* 2021;18:473–87; 2. Choi S, et al. *Biomedicines*. 2022;10:543.

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What are the emerging biomarkers for advanced GC/GEJC?

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Emerging molecular targets for advanced GC/GEJC

New insights into tumour biology continue to increase the understanding of molecular subtypes[1]

CLDN18.2

In the **SPOTLIGHT** phase III clinical trial, 2,244 patients were assessed for CLDN18.2 status, and **38.5%** of patients had moderate-to-strong CLDN18.2 expression in ≥75% of tumour cells assessed via IHC[2]

FGFR2

In the **FIGHT** phase II clinical trial, 910 patients were assessed for FGFR2b status, and **30%** of patients had a positive result for overexpression of tumour FGFR2b or amplification of tumour FGFR2 assessed via IHC and plasma NGS of cell-free ctDNA, respectively[3]

CLDN18.2, Claudin 18.2; ctDNA, circulating tumour DNA; FGFR2, fibroblast growth factor receptor 2; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IHC, immunohistochemistry; NGS, next-generation sequencing.

1. Nakamura Y, et al. *Nat Rev Clin Oncol.* 2021;18:473–87; 2. Shitara K et al. Presented at: ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–21 January 2023. Abstr LBA292; 3. Wainberg ZA, et al. *Lancet Oncol.* 2022;23:1430–40.

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What are the challenges surrounding biomarker testing in advanced GC/GEJC?

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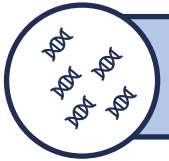
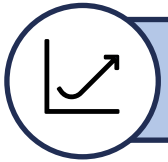
Challenges surrounding biomarker testing in advanced GC/GEJC

Tissue availability[1]



Tumour spatial and temporal heterogeneity[1]



Learning curves and adaptation: How to incorporate into rapidly changing standards of care[2]

Application in clinical practice and treatment decisions[2]

GC, gastric cancer; GEJC, gastroesophageal junction cancer.

1. Hong X, Liu F. *Front Oncol*. 2022;12:850373; 2. Selleck MY, et al. *Biomark Insights*. 2017;12:1177271917715236.

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