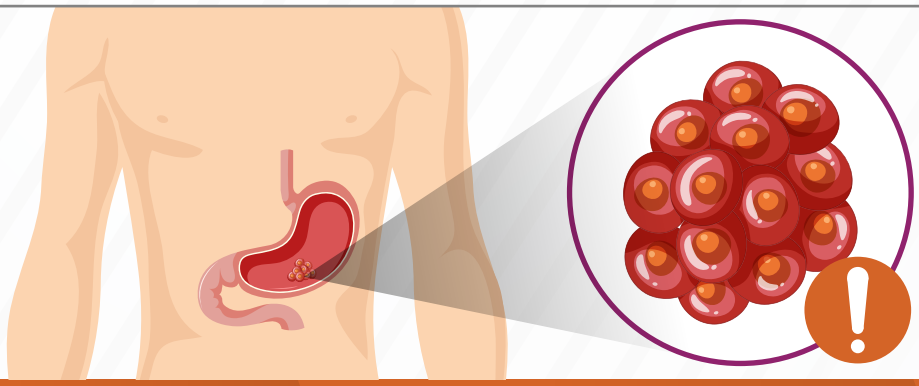
WILEY

The Evolving Therapeutic Landscape of Gastric Cancer

Clinically Useful Pathology Biomarkers

Biomarkers in gastric cancer (GC)[1]



GC is the fifth most common cancer and a leading cause of cancer-related mortality

OS rates are low

Surgical resection and chemotherapy are the most preferred management strategies

New strategies are being developed for the accurate detection and optimised treatment of GC

Biomarkers are an important consideration in GC

Play a key role in personalised GC treatment

Help determine treatment strategies

Predict clinical outcomes

Advantages

Reduced toxicity

Economical

Better patient selection for trials

High success rates of clinical trials

Visit https://gastric-cancer.knowledgehub.wiley.com/ for more information

Established biomarkers in GC

HER2

Overexpressed in most GC cells[1]

ToGA trial[2]
Trastuzumab + chemotherapy → PFS↑ OS↑

KEYNOTE 811[3]
Pembrolizumab + chemotherapy and trastuzumab → Overall response rate↑

HER2 intra-tumoural heterogeneity and trastuzumab efficacy

Homogenous HER2 → Survival[4]↑

Loss of HER2 positivity → Rastuzumab resistance → Need for rebiopsy[5]

PD-L1

PD-L1 CPS is an effective biomarker in cancer

PD-L1 and TMB show significant spatial and temporal heterogeneities in GEA > Multiple biopsies needed to decide if ICI therapy is appropriate[6]

Assay platforms need to be standardised and validated before use

MMRd/MSI

Prognostic and predictive biomarkers in GCs[7]

MSI is a marker for MMRd that indicates a hypermutable state[7]

MSI and PD-L1 are robust markers for predicting chemotherapy benefit in resectable GCs[7,8]

Abbreviations

CPS – combined positive score | GEA – gastroesophageal adenocarcinoma | HER2 – human epidermal growth factor receptor 2
ICI – immune checkpoint inhibitor | MMRd – mismatch repair deficiency | MSI – microsatellite instability
OS – overall survival | PD-L1 – programmed cell death ligand 1 | PFS – progression free survival
TMB – tumour mutation burden

Visit https://gastric-cancer.knowledgehub.wiley.com/ for more information

Emerging biomarkers for GC

EBV[9]

EBV-positive GCs

- ↑Response to ICIs after tumour resection
- Could play a key role in predicting sensitivity to platinum drugs

FGFR2[12]

FGFR2 alterations present widely in GCs

FGFR heterogeneity 1/α

- Treatment efficiency
- Sensitivity to therapy

CLDN 18.2

Co-expressed with HER2 and PD-L1 in 25% of GCs[10]

CLDN 18.2-positive status[10]

Treatment outcomes

OS

Zolbetuximab + mFOLFOX6 in CLDN 18.2 +/ HER2- GCs targeted therapy[11]

- ↑PFS
- ↑OS

Improved biomarker testing

Challenges[13]

Genomic alterations differ within the primary tumour and between the primary and metastatic tumours

Current tissue sampling techniques for biomarker testing do not effectively guide precision medicine

Solution[14]

Liquid biopsy in GC displays higher sensitivity and specificity in cancer diagnosis and prognosis

Components of liquid biopsy

CTCs

ctDNA

Exosomes and non-coding RNAs (miRNAs, circRNAs)

*** Abbreviations**

CLDN – claudin | CTC – circulating tumour cell | ctDNA – circulating tumour DNA
EBV – Epstein-Barr virus | FGFR2 – fibroblast growth factor receptor 2 | miRNA – microRNA | circRNA – circular RNA

Visit https://gastric-cancer.knowledgehub.wiley.com/ for more information

ctDNA in advanced GC to counteract heterogeneity[15]

- Identifies FGFR2 amplification which may be missed during tissue testing
- Minimally invasive
- May assess concurrent genomic alterations to guide treatments
- Future trials that will provide more validation and evidence are underway

Understanding the pathogenesis of GCs and their correlations with available biomarkers will enable the development of new treatment strategies with improved patient outcomes

References

1. Sato, Y., Okamoto, K., Kawano, Y., Kasai, A., Kawaguchi, T., Sagawa, T., … & Takayama, T. (2023). Novel biomarkers of gastric cancer: Current research and future perspectives. *Journal of Clinical Medicine, 12*(14), 4646.
2. Bang, Y. J., Van Cutsem, É., Feyereislova, A., Chung, H. C., Shen, L., Sawaki, … & Kang, Y. K. (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *The Lancet, 376*(9742), 687–697.
3. Janjigian, Y. Y., Kawazoe, A., Yañez, P., Li, N., Lonardi, S., Kolesnik, O., … & Chung, H. C. (2021). The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature, 600*(7890), 727–730.
4. Yagi, S., Wakatsuki, T., Yamamoto, N., Chìn, K., Takahari, D., Ogura, M., … & Horiuchi, Y. (2018). Clinical significance of intratumoral HER2 heterogeneity on trastuzumab efficacy using endoscopic biopsy specimens in patients with advanced HER2 positive gastric cancer. *Gastric Cancer, 22*(3), 518–525.
5. Pietrantonio, F., Caporale, M., Morano, F., Scartozzi, M., Gloghini, A., De Vita, F., … & Di Bartolomeo, M. (2016). HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. *International Journal of Cancer, 139*(12), 2859–2864.
6. Zhou, K. I., Peterson, B. E., Serritella, A., Thomas, J., Reizine, N., Moya, S., … & Catenacci, D. V. (2020). Spatial and temporal heterogeneity of PD-L1 expression and tumor mutational burden in gastroesophageal adenocarcinoma at baseline diagnosis and after chemotherapy. *Clinical Cancer Research, 26*(24), 6453–6463.
7. Choi, Y. Y., Kim, H., Shin, S., Kim, H. Y., Lee, J., Yang, H. K., … & Cheong, J. (2019). Microsatellite instability and programmed cell death-ligand 1 expression in stage II/III gastric cancer. *Annals of Surgery, 270*(2), 309–316.
8. Pietrantonio, F., Miceli, R., Raimondi, A., Kim, Y. W., Kang, W. K., Langley, R. E., … & Smyth, E. (2019). Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. *Journal of Clinical Oncology, 37*(35), 3392–3400.
9. Corallo, S., Fucà, G., Morano, F., Salati, M., Spallanzani, A., Gloghini, A., … & Di Bartolomeo, M. (2020). Clinical behavior and treatment response of Epstein-Barr Virus-Positive metastatic gastric cancer: Implications for the development of future trials. *Oncologist, 25*(9), 780–786.
10. Kubota, Y., Kawazoe, A., Mishima, S., Nakamura, Y., Kotani, D., Kuboki, Y., … & Shitara, K. (2023). Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer. *ESMO Open, 8*(1), 100762.
11. Shitara, K., Lordick, F., Bang, Y., Enzinger, P. C., Ilson, D. H., Shah, M. A., … & Ajani, J. A. (2023). Zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients (pts) with claudin-18.2+ (CLDN18.2+) / HER2− locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary results from phase 3 SPOTLIGHT study. *Journal of Clinical Oncology, 41*(4_suppl), LBA292.
12. Klempner, S. J., Madison, R., Pujara, V., Ross, J. S., Miller, V. A., Ali, S. M., … & Chao, J. (2019). FGFR2-altered gastroesophageal adenocarcinomas are an uncommon clinicopathologic entity with a distinct genomic landscape. *Oncologist, 24*(11), 1462–1468.
13. Pectasides, E., Stachler, M. D., Derks, S., Liu, Y., Maron, S. B., Islam, M., … & Catenacci, D. V. (2018). Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. *Cancer Discovery, 8*(1), 37–48.
14. Zhang, Z., Wu, H., Chong, W., Shang, L., Jing, C., & Li, L. (2022). Liquid biopsy in gastric cancer: Predictive and prognostic biomarkers. *Cell Death and Disease, 13*(10), 903.
15. Jogo, T., Nakamura, Y., Shitara, K., Bando, H., Yasui, H., Esaki, T., … & Yoshino, T. (2021). Circulating tumor DNA analysis detects FGFR2 amplification and concurrent genomic alterations associated with FGFR inhibitor efficacy in advanced gastric cancer. *Clinical Cancer Research, 27*(20), 5619–5627.

Published by WILEY

Visit https://gastric-cancer.knowledgehub.wiley.com/ for more information