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The Role of Biomarkers in Upper Gastrointestinal Cancers

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Upper gastrointestinal (GI) cancers include esophageal, esophagogastric junction, and stomach cancers, which together represent the second leading cause of cancer-related mortality worldwide in both sexes, with approximately 1,100,000 deaths in 2022. The disease is usually diagnosed at an advanced non-curable stage, and conventional chemotherapy treatment is associated with poor prognosis. Advances have been made in the development of new therapies, including immunotherapy and targeted therapies. Biomarker identification has expanded treatment options and guides treatment selection. This article reviews the molecular characterization of GI cancers, which has been the subject of increasing research, and biomarker-targeted agents, representing a continually evolving landscape in upper GI cancers.

Introduction

Upper gastrointestinal (GI) cancers generally refer to malignancies of the esophagus, gastroesophageal junction (GEJ), and stomach. From a histological standpoint, GEJ and stomach cancers are usually adenocarcinomas, while squamous cell carcinomas (SCC) are most frequently located in the upper and middle parts of the esophagus. In Canada in 2023, stomach and esophageal cancer represented the 12th most common cancers in terms of incidence, with 6,800 new cases, and the 6th in terms of mortality, with 4,400 deaths.[1] Between 2010 and 2019, a study cohort from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER), showed an increase in the incidence of esophageal cancers in young people.[2] Most commonly, upper GI cancers are detected at an advanced stage for which treatment with curative intent is not possible. Over the years, advances have been made in the chemotherapy regimens for these types of cancers. Nevertheless, the prognosis remains poor, and a minority of patients will survive more than five years. More recently, promising new therapies have been developed, including immunotherapy and targeted therapies. The addition of these therapies to chemotherapy has improved outcomes for selected patients with upper GI cancers. The identification of biomarkers has expanded treatment options and is important to guide treatment selection.

A molecular classification has also emerged from molecular and genomic analysis of gastric cancer, as reported by The Cancer Genome Atlas (TCGA). Gastric adenocarcinomas can be categorized into four subtypes: tumors positive for Epstein-Barr virus (EBV), microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. Identifying these molecular subtypes and other biomarkers has allowed for a better understanding of the disease and the development of new targeted therapies.[3] In this article, we will discuss the role of the main biomarkers in upper GI cancers.

Biomarker Assessment

The multidisciplinary pan-Canadian expert working group recommends reflex testing for human epidermal growth factor 2 (HER2), mismatch repair (MMR) and/or microsatellite instability (MSI), claudin 18 isoform 2 (CLDN 18.2), and programmed cell death ligand 1 (PD-L1) in all patients at the time of diagnosis of gastric or GEJ adenocarcinoma.[4]

Immunohistochemistry (IHC) is a cost-effective method that uses antibodies to detect and localize specific antigens or proteins in cells or on the cell membrane. IHC is useful for the assessment of predictive and/or prognostic biomarkers, such as overexpression of transmembrane receptors involved in the activation of signaling pathways, such as human

epidermal growth factor 2 (HER2) and fibroblast growth factor receptor (FGFR). IHC is also used to determine the expression level of Claudin 18 isoform 2 (CLDN 18.2), a tight-junction molecule member of the claudin family. A cell surface protein that plays an essential role in immune checkpoint function, programmed cell death ligand 1 (PD-L1) can also be evaluated with IHC, as well as loss of mismatch repair (MMR) protein expression, which is also called MMR deficiency (dMMR).

IHC is the also the main method used for biomarker assessment in gastric or GEJ adenocarcinoma, preferentially on primary tumour specimens as done in clinical trials. In some cases, molecular testing must be performed to clarify IHC results. For example, when protein overexpression is equivocal, such as IHC 2+ for HER2, gene amplification of *HER2/neu* must be assessed by fluorescence in situ hybridization (FISH). Regarding MMR testing, some cases of heterogeneity in nuclear staining within the tumor may require further evaluation with polymerase chain reaction (PCR) to detect microsatellite instability (MSI).[5] Next-generation sequencing (NGS) in gastric and esophageal cancer is not recommended in standard clinical practice, as no actionable mutations have been identified yet.

Biomarker expression in esophageal and gastric cancers is heterogeneous, and variation within the primary tumor or between primary and metastatic sites can be observed, as well as temporal heterogeneity, due to the natural progression of the tumor or tumor evolution under treatment.[6]

The implementation of reflex predictive biomarker testing remains challenging as it requires sufficient laboratory personnel and pathologist resources; multidisciplinary collaboration involving pathologists is essential.

Biomarkers in Upper GI Cancers (*Table 1)*

HER2

HER2, encoded by the *ERBB2* (also known as *HER2/neu*) gene, was the first biomarker introduced into routine clinical practice for gastric and GEJ adenocarcinoma. It is a membrane receptor belonging to the epidermal growth factor receptor (EGFR) family of receptors and has intracellular tyrosine kinase activity, which is associated with growth and development. Two major mechanisms can lead to oncogenesis: mutation or amplification of *ERBB2*, of which the latter is generally correlated with overexpression of HER2. In gastric and GEJ adenocarcinomas, only HER2 amplification and/or overexpression is a predictive biomarker for HER2-targeted therapies, and is found in 10–20% of gastric and 30% of GEJ cancers, with intratumoral heterogeneity.[7] The randomized Phase 3 trial, TOGA, established the combination of trastuzumab, an anti-HER2 humanized monoclonal antibody, and chemotherapy as a new standard-of-care for first-line treatment in HER2-positive advanced gastric or GEJ cancers, by showing a statistically significant gain in overall survival (OS) over chemotherapy alone (13.8 vs. 11.1 months).[8] More recently, the randomized Phase 3 trial KEYNOTE-811 demonstrated a significant improvement in progression-free survival (PFS) (10 vs. 8.1 months) and OS (20 vs. 16.8 months), with the addition of pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, to trastuzumab plus chemotherapy, in the first-line treatment of HER2-positive advanced gastric or GEJ adenocarcinomas, with expression of PD-L1 (combined positive score [CPS] ≥1).[9] In subsequent-line therapy, including patients pre-treated with trastuzumab, trastuzumab deruxtecan, an antibody-drug conjugate, there was a significant improvement in overall response rate (ORR) (51% vs. 14%) and in OS (12.5 vs. 8.4 months) compared to physician choice of chemotherapy, in the DESTINY-Gastric01 randomized Phase 2 trial.[10] Because loss of HER2 expression after failure of trastuzumab-containing chemotherapy is now well described, it is recommended to consider biopsy at progression to evaluate changes in HER2 expression.

Unlike breast cancer, dual HER2 blockade with trastuzumab and pertuzumab (a humanized monoclonal antibody that inhibits the dimerization of HER2 with other HER2 family receptors) is not effective in HER2-positive gastric or GEJ cancers, nor at an advanced stage, as shown in the negative JACOB trial,[11] nor in the perioperative setting combined with FLOT chemotherapy (fluorouracil, leucovorin, oxaliplatin, and docetaxel), according to the results of the INNOVATION trial.[12]

PD-L1

PD-L1 expression is reported to be elevated in up to 40–65% of GEJ cancers. Two scoring methods of IHC data are used to assess PD-L1 expression in different types of cancer. The CPS evaluates the

	Prevalence	Testing	Treatment	Gain (primary endpoint in bold)	Trials / [references]
HER-2	Gastric: 10–20% GEJ: 30%	IHC If 2+: FISH	Trastuzumab + chemotherapy vs. placebo + chemotherapy	**mOS:** 13.8 vs. 11.1 months, *p=0.0046*	TOGA[8]
			PD-L1 CPS ≥1: Trastuzumab + chemotherapy + pembrolizumab vs. trastuzumab + chemotherapy + placebo	**mPFS S:** 10.0 vs. 8.1 months, *p=0.0002* **mOS:** 20.0 vs. 16.8 months, *p=0.004*	KEYNOTE-811[9]
PD-L1	40–65%, SCC >AC	IHC	AC Nivolumab + chemotherapy* vs. chemotherapy*	CPS ≥5: **mOS:** 14.4 vs. 11.1 months, *[HR: 0.7; 95% CI: 0.61-0.81]* **mPFS:** 13 vs 8 months, *[HR: 0.7; 95% CI: 0.6-0.81]*	CheckMate-649[16]
			Pembrolizumab + chemotherapy vs. chemotherapy*	PD-L1 CPS ≥10: **mOS:** 15.7 vs. 11.8 months, *[HR: 0.65; 95% CI: 0.53-0.79]* **mPFS:** 8.1 vs. 5.6 months, *[HR: 0.62; 95% CI: 0.51-0.76]*	KEYNOTE-859[17]
			SCC Pembrolizumab + cisplatin-5FU vs. cisplatin-5FU	PD-L1 CPS ≥10: **mOS:** 13.9 vs. 8.8 months, *p<0.0001* **mPFS:** 7.5 vs 5.5 months, *p<0.0001*	KEYNOTE-590[21] (SCC : 73.5%, AC 26.5% ; GEJ + oesophageal)
			nivolumab + FOLFOX vs. FOLFOX	PD-L1 TPS ≥1: **mOS:** 15.4 vs. 9.1 months, *p<0.001* **mPFS:** 6.9 vs. 4.4 months, *p=0.002*	CheckMate-648**[20]
			Ipilimumab-nivolumab vs. FOLFOX	**mOS:** 13.7 vs. 9.1 months, *p=0.001* **mPFS:** 4.0 vs. 4.4 months, *p=0.9*	

	Prevalence	Testing	Treatment	Gain (primary endpoint in bold)	Trials / [references]
dMMR	10%	IHC -If heterogeneity in nuclear staining: PCR for MSI assessment	<u>Advanced/metastatic:</u> Ipilimumab-nivolumab vs. chemotherapy*	**mOS:** NR vs. 10 months **ORR:** 70 vs. 57%	CheckMate-649 *(subgroup :44 patients)*[16]
			Nivolumab + chemotherapy* vs. chemotherapy*	**mOS:** 38.7 vs. 12.3 months **ORR:** 55 vs. 39 %	
			Pembrolizumab vs. chemotherapy (cisplatin + 5FU or capecitabine)	<u>PD-L1 CPS ≥1</u> **mOS:** NR vs. 8.5 months PD-L1 CPS ≥10 mOS NR vs. 13.6 months	KEYNOTE-062[26]
			<u>Early stage:</u> Ipilimumab + nivolumab/ surgery/nivolumab	59%: pCR 3 patients: cCR, no surgery	NEONIPINIGA *(Phase 2, 32 patients)*[25]
CLDN -18.2	30–40%	IHC	Zolbetuximab + FOLFOX vs. placebo + FOLFOX	**mPFS:** 11 vs. 8.9 months, *p=0.0024* **mOS:** 18.2 vs. 15.6 months, *p= 0.0075*	SPOTLIGHT[29]
			Zolbetuximab + CAPOX vs. placebo + CAPOX	**mPFS:** 8.2 vs. 6.8 months, *p=0.0007* **mOS:** 14.4 vs. 12.2 months, *p=0.118*	GLOW[30]
FGFR2b ***NOT APPROVED IN CANADA***	5–10%	IHC	Bemarituzumab + FOLFOX vs. placebo + FOLFOX	**mPFS:** 9.5 vs. 7.4 months, *p=0.073* **mOS:** 19.2 vs. 13.5 months *[HR: 0.77; 95% CI: 0.52-1.14]*	FIGHT[31]

Table 1. Prevalence, testing, and biomarker-based therapies in advanced upper GI cancers (*dMMR tumors: advanced and early stages*); *courtesy of Nathalie Baudoux, MD and Francine Aubin, MD, FRCPC.*

*FOLFOX or CAPOX
**open-label trial

Abbreviations: 5FU: fluorouracil, **AC:** adenocarcinoma, **CAPOX:** capecitabine and oxaliplatin, **cCR:** clinical complete response, **CI:** confidence interval, **CLDN 18.2:** claudin 18.2, **CPS:** combined positive score, **dMMR:** deficient mismatch repair, **FGFR2b:** fibroblast growth factor receptor 2b, **FISH:** fluorescence in situ hybridization, **FOLFOX:** folinic acid, fluorouracil, and oxaliplatin, **GEJ:** gastroesophageal junction, **GI:** gastrointestinal, **HER2:** human epidermal growth factor receptor 2, **HR:** hazard ratio, **IHC:** immunohistochemistry, **mOS:** median overall survival, **mPFS:** median progression-free survival, **MSI:** microsatellite instability, **NR:** not reached, **ORR:** overall response rate, **pCR:** pathological complete response, **PCR:** polymerase chain reaction, **PD-L1:** programmed cell death ligand 1, **SCC:** squamous cell carcinoma, **TPS:** tumor proportion score

number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) relative to all viable tumor cells, and the tumoral proportion score (TPS) evaluates the percentage of viable PD-L1-positive tumor cells. PD-L1 is well-known for its heterogeneity in the tumor and the tumor microenvironment, and expression may vary between the primary site and metastases, as well as before and after treatment.[13] CPS is used in gastric and GEJ adenocarcinomas, and a positive score predicts response to immunotherapy.[14,15] In the CheckMate 649 Phase 3 trial, patients with unresectable or metastatic gastric or GEJ adenocarcinomas were randomized to nivolumab plus chemotherapy (FOLFOX [folinic acid, fluorouracil, and oxaliplatin] or CAPOX [capecitabine and oxaliplatin) or chemotherapy alone. Improved OS was demonstrated for the entire population, but this effect was driven by the PD-L1 CPS ≥5 subgroup (14.4 vs. 11.1 months).[16] The efficacy subgroup analysis based on PD-L1 expression in this study showed limited OS benefit for the subgroup with PD-L1 CPS <5. In the KEYNOTE-859 trial, which included a similar population, pembrolizumab plus chemotherapy demonstrated a significant OS benefit over chemotherapy alone, particularly in the CPS ≥10 population (15.7 vs. 11.8 months).[17] The combination of immunotherapy and chemotherapy is now a standard treatment for eligible patients with gastric or GEJ adenocarcinomas with positive PD-L1 CPS, for which a benefit is mainly demonstrated for those with PD-L1 CPS 5.[18,19]

Therapies in advanced or metastatic esophageal SCC are also guided by PD-L1 expression, which is generally higher than in gastric and GEJ adenocarcinomas. The CheckMate 648 Phase 3 trial randomized patients with untreated, unresectable, or metastatic SCC to ipilimumab plus nivolumab, nivolumab plus chemotherapy, or chemotherapy alone. The two combination therapies had better OS than chemotherapy alone in all randomized populations; however, the patients with PD-L1 TPS ≥1 seemed to benefit more.[20] In the same setting, the Phase 3 trial KEYNOTE-590 demonstrated a gain in OS and PFS for pembrolizumab plus chemotherapy for patients with esophageal cancer, particularly in the CPS ≥10 subgroup.[21]

It has been demonstrated that EBV-positive tumors usually exhibit high levels of PD-L1 expression, which may partly explain the good response to immunotherapy in this tumor subtype.[22] While interesting, stronger data are needed before recommending EBV testing by EBV-encoded RNA in situ hybridization (EBER ISH) routinely in clinical practice.

dMMR/MSI-high

The role of the DNA MMR system is mainly to recognize and correct DNA mismatches generated during DNA replication. dMMR alters the length of repetitive DNA sequences, leading to high microsatellite instability (MSI-H). Loss of MMR proteins, such as MLH1, MSH2, MSH6, and PMS2, is associated with a germline mutation of one of several MMR genes found in Lynch syndrome or, most frequently, with hypermethylation of the *MLH1* promoter in sporadic tumors. Approximately 10% of gastric and GEJ adenocarcinomas are dMMR/MSI-H, and the incidence increases in patients older than 85 years.[23] MMR status has a prognostic and therapeutic impact on upper GI cancer, both in localized and in advanced stages. Indeed, a meta-analysis showed that patients diagnosed with operable GEJ cancer with MSI-H status do not benefit from perioperative chemotherapy with detrimental outcomes in OS and PFS.[24] Nevertheless, it is important to note that the chemotherapy regimen used in these trials did not include FLOT, which is now the standard of care for this indication. In patients with dMMR/MSI-H locally advanced resectable gastric/GEJ adenocarcinoma, NEONIPINIGA, a Phase 2 trial, evaluated the pathological complete response (pCR) rate after surgery and 12 weeks of neoadjuvant ipilimumab 1 mg/kg (2 doses) and nivolumab 240 mg (6 doses).[25] After surgery, upon the investigator's decision, patients received nine doses of adjuvant nivolumab. Of the 32 patients included, 29 had surgery and 17 had a pCR. Three patients did not have surgery due to complete radiological and endoscopic responses. Additional follow-up and data from other studies are needed to confirm the role of adjuvant perioperative immunotherapy. The INFINITY study (NCT04817826) investigates the

combination of durvalumab and tremelimumab as neoadjuvant definitive treatment in resectable gastric or GEJ MSI-H cancers. In advanced stages, data about the efficacy of immunotherapy for dMMR/MSI-H cancers are available from large Phase 3 trials previously discussed. In the first line setting, among 22 patients with dMMR/MSI-H tumors included in the CheckMate 649 trial, the combination of ipilimumab and nivolumab improved OS compared to chemotherapy (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.08–0.92).[16] Finally, an exploratory analysis of one Phase 2 (KEYNOTE-059) and two Phase 3 (KEYNOTE-061, KEYNOTE-062) studies indicated better outcomes in terms of ORR, PFS, and OS for those treated with pembrolizumab alone or pembrolizumab plus chemotherapy, compared to chemotherapy alone, regardless of the line of therapy in which it was received.[26]

CLDN 18.2

The CLDNs are a family of tight junction transmembrane proteins that play an important role in regulating tissue permeability, paracellular transport, and signal transduction. CLDN 18.2 is an isoform of CLDN and is mainly expressed in normal gastric tissues.[27] During malignant transformation, alteration in cell polarity and particularly the disruption of tight junctions leads to exposure of the CLDN 18.2 epitope, making it accessible for targeting treatments such as monoclonal antibodies. CLDN 18.2 positivity among metastatic gastric cancers is about 30–40%.[28] Zolbetuximab, a chimeric monoclonal antibody that targets CLDN 18.2 with antitumor activity induced through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), has been evaluated in two Phase 3 trials in combination with standard chemotherapy. The first study, SPOTLIGHT, included previously untreated patients with CLDN 18.2+ unresectable or metastatic gastric or GEJ adenocarcinomas. Patients were randomized between mFOLFOX6 plus zolbetuximab versus mFOLFOX plus placebo. The addition of zolbetuximab to mFOLFOX was associated with a statistically significant improvement in PFS (11 vs. 8.9 months) and OS (18.2 vs. 15.6 months).[29] In the second trial, GLOW, patients were randomized to CAPOX plus zolbetuximab versus CAPOX plus placebo.[30] A statistically significant gain in PFS (8.2 vs. 6.8 months) and OS (14.4 vs. 12.2 months) was shown with the addition of zolbetuximab. A combined analysis of these two trials confirmed a statistically significant gain in OS (16.4 vs. 13.7 months) and PFS (9.2 vs. 8.2 months).[31] Zolbetuximab represents a new first-line therapy for patients with CLDN 18.2+ tumors. Nevertheless, the best standard treatment is not well established for patients with overlapping expression of PD-L1 and CLDN 18.2. Future studies will be required to determine the best therapy for this subpopulation.

FGFR2b

FGFR are a family of transmembrane tyrosine kinase receptors involved in activating signaling pathways responsible for cell proliferation, survival, angiogenesis, and migration (metastasis). The most common alteration is FGFR2b amplification, which results in FGFR2 protein overexpression, and occurs in MMR-proficient tumors, which are generally without PD-L1 expression or HER2 amplifications.[32] This subtype represents approximately 5–10% of gastric cancers and is associated with poor outcomes.[33] FGFR2 overexpression, which can occur without gene amplification in cases of epigenetic changes, occurs in ranges between 30% and 60% of all gastric cancers. The randomized Phase 2 FIGHT trial explored the efficacy and safety of bemarituzumab, a humanized monoclonal antibody specific to FGFR2b.[34] Patients with untreated advanced gastric or GEJ adenocarcinomas with FGFR2b overexpression and/or FGFR2 gene amplification were randomized to the combination of mFOLFOX6 plus bemarituzumab or mFOLFOX6 plus placebo. The combination therapy showed a numerically but not statistically significant longer median PFS (9.5 vs. 7.4 months) and OS (19.2 vs. 13.5 months) than chemotherapy alone, and efficacy was more pronounced in those with FGFR2b overexpression in ≥10% of tumor cells. The Phase 3 FORTITUDE-102 study is ongoing to determine if bemarituzumab could be a new treatment option in combination with chemotherapy and immunotherapy.

Conclusion

Upper GI cancers represent a heterogenous disease that is mostly diagnosed at an advanced stage and is associated with a poor prognosis with conventional treatments. The identification of biomarkers has led to the development of new therapies. Biomarkers are also useful to predict which patients will benefit from immunotherapy. These predictive biomarkers are important to select the best treatment approach for each patient, allowing personalized treatment strategies. Patients with advanced esophagogastric adenocarcinoma should have their tumor tested for MMR status, and HER2, PD-L1, and CLDN 18.2 expression at first diagnosis. The utility of other emerging biomarkers, such as FGFR2b overexpression or MET gene alterations, is currently investigated in clinical trials.[35] Further progress in biomarker research is essential to shape the landscape of personalized therapies in oncology.

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