Precision Medicine and Targeted Therapies for Gastric Cancer and Other GI Malignancies

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This activity is designed to inform physicians about the current availability and use of targeted therapies and precision medicine in gastric cancer (GC) and other gastrointestinal (GI) cancers.

Target Audience:
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with GC or other GI cancers. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives:
After completing this CME/CE activity, participants should be better prepared to:

- *Describe the biomarker-based rationale behind GI cancer classifications*
- *Explain the development history leading to the approval of targeted therapies in GC and other GI cancers*
- *Discuss emerging targeted strategies and new indications for precision medicine in GI cancers*

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Introduction

Gastric cancer (GC) is among the most common malignancies in the United States. In 2017, it is estimated that 28,000 new cases of GC will be diagnosed, accounting for 1.7% of all new cancers.[1] It is further estimated that nearly 11,000 people will die of GC in the United States alone in 2017, accounting for nearly 2% of cancer-related deaths.[1] The incidence of and death from GC has steadily decreased over the past half-century, decreasing from the most common cancer in the United States to the 15th most common.[1,2] GC occurs most often in the elderly population, with a median age of diagnosis of 68 years.[1] Although survival has increased, the percentage of patients surviving more than 5 years remains low, at just 30.6%.[1] On a global scale, approximately 990,000 people are diagnosed with GC each year, of whom about 738,000 die from this disease, making GC the fourth most common cancer by incidence and the second most common cause by death.[2]

Gastric cancers are solid tumors with complex genetic and environmental interactions that contribute to their initiation and progression. Most GCs (90%) are adenocarcinomas. Traditionally, GCs are divided into 2 main subtypes on the historical basis of the Laurén classification: intestinal and diffuse.[3,4] The World Health Organization (WHO) also has a classification system that divides GC into papillary, tubular, mucinous, and poorly cohesive carcinomas.[5]

In the era of precision medicine and next-generation sequencing (NGS), a solely histological classification of GC is insufficient to detail the complexity of disease. A comprehensive and biomarker-based classification system lends itself to better patient care. Both the Laurén and WHO classification systems allow for a better understanding of the biology of GC, but have limited clinical utility in guiding patient therapy due to the complex molecular heterogeneity of the disease.[6]

A Genetic-Based Classification

Recently, several comprehensive studies have attempted to provide new approaches to subdividing GCs. Two systems, based on molecular markers, have been developed to complement currently used histological classifications.

One comprehensive analysis from The Cancer Genome Atlas (TCGA) evaluated 295 GC tumors, primarily from the United States and Western Europe.[7] The TCGA analysis included somatic copy-number alterations (SCNAs), whole-exome sequences, RNA sequencing (including both messenger and microRNA), and DNA methylation analysis. A total of 4 molecular subgroups were identified. The first group, which accounted for 8.8% of GCs, was positive for Epstein-Barr virus (EBV) and had several other molecular commonalities. The second group, which accounted for 21.7% of GCs, was microsatellite instability–high (MSI-H). The third group of patients, accounting for 19.7% of disease, had a low level of SCNAs and was considered genomically stable (GS). The final group, accounting for 49.8% of disease, was characterized by a high levels of SCNAs and chromosomal instability (CIN).[7]

The EBV subtype, as identified by TCGA, regularly displayed recurrent *PIK3CA* mutations, DNA hypermethylation, high levels of PD-L1 and PD-L2 expression, and amplification of *JAK2* proteins, as well as rare *TP53* mutations. The MSI subgroup, besides displaying high levels of MSI, is often hypermutated, including oncogenic driver genes such as *KRAS* or *NRAS*. The GS subtype, more common in younger patients, is characterized by mutations in the *RHOA* gene. Finally, the CIN subtype displays high levels of aneuploidy as well as receptor tyrosine kinase (RTK) activation, including *EGFR*, VEGFR, and *MET*.[7]

A second GC classification was performed by the Asian Cancer Research Group (ACRG), which studied GCs in a Korean population.[6] While ultimately similar to TGCA, ACRG did not identify a distinct EBV-positive subtype, but rather noted a group of GCs defined by an expression signature of epithelial-to-mesenchymal transition (EMT).[8] The ACRG identified 4 groups of GCs: First, the microsatellite-stable (MSS)/EMT subgroup accounted for 15.3 of GCs; second, a MSS/*TP53*-mutation–positive group accounted for 35.7% of GCs; third, an MSS/*TP53*-mutation–negative group accounted for 26.35% of GCs; and fourth, an MSI group accounted for 22.7% of GCs.[6] A summary of alternative molecular marker divisions and their incidence in patients is presented in the **Table**.

TABLE. Summary of TCGA and ACRG Classifications of Gastric Cancer

TCGA		ACRG	
Subtype	**% of GCs**	**Subtype**	**% of GCs**
EBV	8.8	MSS/*TP53*$^+$	35.7
GS	19.7	MSS/EMT	15.3
MSI	21.7	MSI	22.7
CIN	49.8	MSS/*TP53*$^-$	26.3

ACRG indicates Asian Cancer Research Group; CIN, chromosomal instability; EBV, Epstein-Barr virus; EMT, epithelial-to-mesenchymal transition; GC, gastric cancer; GS, genomically stable; MSI, microsatellite instability; MSS, microsatellite-stable; TCGA, The Cancer Genome Atlas.

Targeted Therapies in Gastric Cancer

Trastuzumab

Trastuzumab is a humanized monoclonal antibody (mAb) that interferes with human epidermal growth factor receptor type 2 (HER2). Trastuzumab has become a staple of HER2-positive breast cancer care, and its use has expanded to GCs.[9]

The Trastuzumab for Gastric Cancer (ToGA) trial (NCT01041404) was an open-label, placebo-controlled, phase III trial that randomized patients with HER2-positive GC or gastroesophageal junction (GEJ) cancer to receive a chemotherapy regimen of capecitabine/cisplatin or fluorouracil (5-FU)/cisplatin with or without trastuzumab. A total of 594 patients were randomly assigned between the 2 groups.[10]

The median overall survival (OS) was 13.8 months (95% CI, 12-16) in patients who received trastuzumab in combination with chemotherapy compared with 11.1 months (95% CI, 10-13) in patients who received chemotherapy alone (HR, 0.74; 95% CI, 0.60-0.91; *P* = .0046). Median progression-free survival (PFS) for patients receiving trastuzumab was 6.7 months (95% CI, 6-8) compared with 5.5 months (95% CI, 5-6) for patients receiving chemotherapy alone (HR, 0.71; 95% CI, 0.59-0.85; *P* = .0002). The objective response rate (ORR) for patients receiving the trastuzumab combination was 47% compared with 35% for those receiving chemotherapy alone.[10]

The most common adverse events (AEs) of any grade for patients receiving trastuzumab were nausea (67%), vomiting (50%), and neutropenia (53%), and did not differ significantly from patients receiving chemotherapy alone. Across either treatment group, 68% of patients experienced grade 3/4 AEs. The most common grade 3/4 AEs for patients receiving the trastuzumab combination were neutropenia (27%), anemia (12%), diarrhea (9%), and nausea (7%).[10]

The results of this trial led to the 2010 approval of trastuzumab in combination with cisplatin and either capecitabine or 5-FU for patients with HER2-positive, metastatic GC or GEJ cancer who have not received prior treatment for metastatic disease.[11]

Trastuzumab is being investigated in other disease types, including colorectal cancer (CRC). Early in 2017, a biosimilar, trastuzumab-dkst, was approved under the same indication as the reference product.[12]

Ramucirumab

Another target in GC is VEGFR2, which plays a critical role in the pathogenesis and progression of disease. VEGFR2 is a transmembrane RTK that binds to other VEGF proteins, causing increased cell proliferation, migration, and inflammation. Approximately 50% of GCs express VEGF, with *VEGFA* and *VEGFD* overexpression being associated with a poor prognosis. Ramucirumab is a mAb VEGFR-2 antagonist shown to be efficacious in GC cancers.[13]

The first phase III trial establishing ramucirumab in GC was the REGARD trial (NCT00917384), in which 355 patients with advanced GC or GEJ cancer that had progressed on first-line platinum-based or fluoropyrimidine-containing chemotherapy were randomized 2:1 to receive best supportive care plus ramucirumab monotherapy or placebo.[14]

Although the best ORR was low for patients receiving ramucirumab (4%), the rate of stable disease was 45% compared with 21% for patients receiving placebo; the disease control rate (DCR) was 49% and 23%, respectively.[14] Patients receiving ramucirumab had a median OS of 5.2 months compared with 3.8 months in the placebo arm (HR, 0.776; 95% CI, 0.603-0.998; *P* = .047). The survival benefit of ramucirumab was reported to have remained unchanged after multivariable adjustment for other prognostic factors. Six-month PFS also was improved for patients receiving ramucirumab, to 42% versus 32%.[14] Rates of hypertension were higher for patients in the ramucirumab group (16%) compared with the placebo group (8%), whereas rates of other AEs were primarily similar between groups, 95% and 88%, respectively.[14]

Next, the phase III RAINBOW study (NCT01170663) of 665 patients with advanced GC or GEJ cancer who had progressed on or within 4 months of first-line chemotherapy randomized them 1:1 to receive paclitaxel in combination with ramucirumab or paclitaxel with placebo.[15] Median OS was reported to be 9.6 months (95% CI, 8.5-10.8) in the paclitaxel-plus-ramucirumab arm versus 7.4 months (95% CI, 6.3-8.4 months) in patients receiving the placebo (HR, 0.807; 95% CI, 0.678-0.962; *P* = .017). Median PFS also was improved for patients receiving the ramucirumab combination, 4.4 months compared with 2.9 months for patients receiving placebo (HR, 0.635; 95% CI, 0.536-0.752; *P* <.0001). The ORR for patients receiving ramucirumab was 28% versus 16% for those receiving placebo. In addition, the DCR was 80% and 64% for ramucirumab and placebo, respectively.[15]

Common grade ≥3 AEs for patients receiving the ramucirumab/paclitaxel combination included neutropenia (41%), leukopenia (17%), hypertension (14%), fatigue (12%), anemia (9%), and abdominal pain (6%). All listed AEs, except anemia, were significantly higher in patients receiving ramucirumab than those receiving placebo.[15]

Based on the results from the REGARD trial, the US FDA approved ramucirumab as a single agent for patients with GC or GEJ cancer in April 2014.[16] Then, in November 2014, following the results of the RAINBOW study, ramucirumab was approved in combination with paclitaxel for the treatment of GC and GEJ cancer following failure of first-line treatment.[16,17] The European Medicines

Agency (EMA) also approved ramucirumab as monotherapy or in combination with paclitaxel for this patient population in September 2014.[13]

Emerging Targets

Inhibition of checkpoint proteins, specifically PD-1 and its ligand PD-L1, have been an increasing focus of immunotherapy strategies across tumor types. The PD-1/PD-L1 axis works primarily to suppress an overresponse of effector T cells as a part of the immune system's defense against self-cannibalism.[18]

In May 2017, the FDA approved pembrolizumab for all patients with metastatic or unresectable MSI-H or mismatch repair–deficient solid tumors, the FDA's first tissue- or site-agnostic approval.[19] Checkpoint inhibitors increasingly have become an option in GC.

Results of the phase II SWOG 1406 (NCT02164916) trial were presented at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium in January 2017. For patients with metastatic CRC who have mutations in *BRAF* V600, the addition of the BRAF inhibitor vemurafenib to cetuximab and irinotecan significantly improved PFS. The trial met its primary endpoint, improving median PFS from 2.0 months with cetuximab/irinotecan to 4.4 months with the addition of vemurafenib. Grade 3/4 AEs were significantly higher in the experimental arm and included neutropenia (28%), anemia (13%), and nausea (15%).[20]

Other targeted therapies under investigation include binimetinib, a MEK inhibitor, in combination with BRAF and EGFR antibodies; cobimetinib, another MEK inhibitor, in combination with PD-L1 inhibitor atezolizumab; and claudiximab, which targets claudin 18.2.[13]

For more information on precision medicine in GC and GI cancers, as well as insights into the future of targeted therapies, please see our interview with Dr Loaiza-Bonilla below.

***AJHO*®: What is "precision medicine," and what role can it have in treating patients with gastrointestinal [GI] cancer?**

Dr Loaiza-Bonilla: Precision medicine and precision oncology are basically the implementation of a high level of evidence—disease-specific and biomarker-driven evidence—to inform either diagnostic or treatment recommendations for improved and optimized cancer care. The purpose of precision medicine in the field of oncology is to find the right options at the right time for the right patient. I think throughout the general field of oncology, the use of personalized approaches can improve outcomes, lead physicians to the best diagnosis, and result in the identification of the right biomarkers, which, when targeted, lead to better responses. Certainly, GI cancers are not an exception to this approach.

What is the role of next-generation sequencing [NGS] in precision medicine? What do physicians need to know about NGS?

When we're looking at diagnostics in oncology and talking about precision medicine, it's important to recognize that, in the past, pharmaceutical companies and clinical trials did not limit patient populations based on molecular alterations. Their approach focused mainly on histology and a "one size fits all" approach. Over time, we found that there was a change in the treatment paradigm from the phenotype to the genotype, where we're looking at the specific biomarkers on tumors to determine treatment. The best way to find these biomarkers is by the use of NGS techniques.

With the advent of targeted therapies and clinical trials run by cooperative groups and pharmaceutical companies, we have now begun to focus on niche subgroups of patients who carry a specific molecular alteration. They use these basket trials in which specific biomarkers determine participation, regardless of histology. Next-generation sequencing plays a key role in that. The type of vendors available for NGS depends on the institution. For example, large cancer centers often have their own panels for the identification and validation of markers for their own targeted therapies being researched. For community-based clinics, there are also commercially available companies that perform NGS, either through liquid biopsies or traditional tissue testing.

Commercially available tumor-profiling services can complement this local tumor testing, and help to find the right treatment options for patients for whom no clinical trial options could be found. Hopefully, these technologies continue to become more available, affordable, and reimbursable, once we show their value in large subsets of patients. Something of utmost importance is to develop a system that assists clinicians in ordering these tests when the time is right, and then guide them in using and operationalizing these results to the benefit of the cancer research field, patients, and public health.

In 2014, The Cancer Genome Atlas identified 4 subtypes of GI cancer. Can you discuss the importance of this study and the main takeaways?

The Cancer Genome Atlas [TCGA] is a widespread effort that is done across multiple types of malignancies, aiming to elucidate any specific biomarkers that characterize different tumors. In GI cancers, particularly in gastric cancer [GC], there was a finding that not all GCs are equal. In the past, we had a classification system called the Laurén classification, which grouped GCs by diffuse type and intestinal type. Now, with the work of TCGA, we have a new and useful classification that can help explore thera-

pies in specific patient subpopulations whose tumors have determined biomarker abnormalities.

TCGA identified 4 distinct groups of GI cancer: Group 1, about 9% of patients, are positive for Epstein-Barr virus; Group 2, about 22% of patients, are microsatellite instability–high [MSI-H], with a tendency to accumulate mutations in multiple sequences of DNA; Group 3, about 20% of patients, have a low level of copy number alterations and are considered genomically stable [GS]; and Group 4, about 50% of patients, are chromosomally unstable, which may correlate with tumor mutation burden [TMB].

In 2015, the Asian Cancer Research Group [ACRG] proposed a separate classification system. Can you discuss this system and the differences between the 2 systems? Is there 1 that we should use over the other?

Certainly I'll discuss it. I believe that both efforts, the TCGA and the ACRG classifications, are useful—equally useful—and there is a significant level of clinical correlation between them. The 2 systems were just used in different populations during different periods of time, but, in the end, many of those groups overlapped. For example, the ACRG had a subtype called the "microsatellite stable with markers of epithelial-to-mesenchymal transition group," which is similar to the third group of TCGA, the GS group. More than 80% of cases of this subtype were stage III/IV with diffuse type histology by Laurén classification. So, putting it into perspective, it's important to differentiate the molecular subtypes in GC, which may tailor treatment based on specific alterations to improve outcomes in this difficult-to-treat cancer. Either classification is useful, and gives us insights into the different subgroups of GC that we should try to tackle.

Trastuzumab, a monoclonal antibody [mAb], is approved to treat patients with HER2-positive metastatic GC or gastroesophageal junction cancer. How do you use trastuzumab in your patients, and what does this indication tell us about the future of precision medicine in GI cancer?

Based on the results of the ToGA trial, trastuzumab is now routinely added to first-line chemotherapy in patients with advanced or metastatic GC with HER2 overexpression by immunohistochemistry, or in some cases, by *ERBB2* gene amplification detected by NGS. The chemotherapy backbone in the pivotal trial was cisplatin and capecitabine or fluorouracil (5-FU). However, the addition of trastuzumab to other combination chemotherapy regimens such as EOX [epirubicin, oxaliplatin, capecitabine], DCF [docetaxel, cisplatin, and 5-fluorouracil], and FOLFOX [folinic acid, fluorouracil, and oxaliplatin] that are accepted as alternative standards of care has not been studied in a prospective, randomized fashion.

Findings from the German noninterventional observational study HERMES studied trastuzumab in combination with cisplatin and 5-FU or capecitabine, as well as other regimens such as oxaliplatin and docetaxel. Although most patients did not receive the regimen described in the ToGA trial, the median progression-free survival (PFS) was comparable at 6.8 months.

Further studies of trastuzumab in combination with other regimens are ongoing, and this was 1 of the first targeted therapies to use in GI malignancies, prompting the search for additional biomarkers, and to understand further the drivers of resistance (escape pathways) and how to overcome resistance.

For example, there are some compelling data from the combination of trastuzumab plus lapatinib, which achieved positive results in patients with heavily pretreated, HER2-positive, metastatic colorectal cancer [CRC], according to the final results of the phase II HERACLES-A trial. The HERACLES-B trial is evaluating pertuzumab and ado-trastuzumab [T-DM1], and HERACLES-RESCUE is looking at T-DM1 monotherapy in metastatic CRC that has progressed on lapatinib and trastuzumab in HERACLES-A. It should be very interesting to learn how these trials perform in light of other biomarkers and therapies, such as MSI status and immunotherapy.

Ramucirumab, another mAb, targets VEGFR2. How has this precision medicine had an impact on how you treat patients with GI cancer?

Following the success that we just discussed about the ToGA trial and trastuzumab, there was a lot of hype looking for new biomarkers. Ultimately, that led to agents targeting the VEGF pathway. There were initial efforts with bevacizumab in the AVAGAST trial that unfortunately hampered initial enthusiasm, but also led to finding a subset of patients who might respond. The analysis also suggested that the difference when assessing overall survival data in GC could be explained by the higher use of third-line therapy following study discontinuation in Asian patients compared with non-Asian patients—nearly 70% vs nearly 40%.

Ramucirumab, by specifically binding to VEGF2, prevents all known VEGFs from binding to VEGF2, and therefore could lead to more complete inhibition of angiogenesis than agents directly binding to a single VEGF, demonstrating a significant survival benefit in the second-line setting. This was reported in the phase III REGARD trial, which investigated the agent as monotherapy, and the phase III RAINBOW trial, which investigated ramucirumab in combination with paclitaxel. The FDA and European Medicines Agency approval of this anti-angiogenic agent has led to its incorporation in the vast majority of second-line therapy for my patients.

What important considerations should be made in terms of combinations or sequencing for patients with GI cancer?

First, it's important to understand which mutations are the driving mutations. What biomarkers are we targeting in the precision medicine field? Second, we need to make rational decisions. A combination is either aimed at improving the previously detected signal when we use a single agent, or it's aimed at overcoming a resistance that was found in a specific drug. It's important to understand that some biomarkers may change over time; a patient's HER2 status may change, as well as many other biomarkers.

So, for example, a patient with CRC may show up with a *RAS* wild-type phenotype, and after you expose the patient to EGFR inhibitors, they may develop a resistance that is driven by a secondary mutation. In that area, then, we need to use agents that overcome that mutation resistance and potentially resensitize the tumor. Those are the key questions that we need to formulate in the future for the management of these patients.

An exciting advancement, in multiple cancer types, is inhibition of the PD-1/PD-L1 pathway. What role does checkpoint inhibition have in GI cancers?

Immune checkpoint inhibitors are the "new kid on the block." So, following very exciting successes in melanoma and lung cancer, basket trials based on PD-L1 positivity demonstrated that some of these patients had significant responses in GI cancers. When they looked further into why this response was happening, they noted that patients with a history of either Lynch syndrome or MSI, as well as those with high TMB [tumor mutational burden], are able to produce large amounts of epitopes that the immune system detects, and where potential biomarkers are predictive of response to PD-1 and PD-L1 inhibitors.

Recently, the FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic MSI-H or mismatch repair–deficient (dMMR) solid tumors that have progressed following prior treatment, and who have no satisfactory alternative treatment options, or with MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

In addition, the FDA granted accelerated approval to nivolumab for the treatment of patients 12 years and older with dMMR and MSI-H metastatic CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

Interestingly enough, compared with other cancers, such as lung cancer and melanoma, where the PD-L1 expression may predict response to treatment, in GI malignancies that has not been the case. We've seen multiple clinical trials of combination agents, actually sometimes using CTLA4 inhibitors plus immune checkpoint inhibitors or monotherapy with immune checkpoint inhibitors, where PD-L1 overexpression has not been a predictive biomarker of response. So, if these patients are going to respond, they will respond across the board. Something that will be interesting to find out is whether TMB has anything to do with the responses these patients showed regardless of PD-L1 overexpression. Additional studies will reveal those answers.

Other future potential targets in precision medicine include receptor tyrosine kinases, *RAS*, and PI3 kinase. Can you talk about the early-stage development of these targets in GI cancer so far?

Overall, the results of multiple phase II clinical trials targeting alterations of MET, EGFR, PI3 kinase, and the always elusive *RAS* mutations, have been quite disappointing in showing survival advantage in GI cancer. However, there are some promising results in certain subsets of patients. So, quite simply, *BRAF* V600-mutated CRC seems to be the most recent bearer of good news. It represents about 7% to 15% of CRCs that are a difficult-to-treat subtype. But there are some encouraging emerging data out from a phase II study presented by SWOG at the 2017 ASCO GI Cancers Symposium, which showed that patients who had the combination of vemurafenib, a BRAF inhibitor, and cetuximab plus irinotecan had improved PFS. That trial met its primary endpoint, and we will likely follow vemurafenib on further studies.

More recently, at the European Society for Medical Oncology [ESMO] 2017 annual meeting, the phase III BEACON CRC study showed that binimetinib (a MEK inhibitor) plus encorafenib (a BRAF inhibitor) and cetuximab in patients with *BRAF*-mutated disease and at least 2 prior regimens showed significant improvement in response rate, with good tolerability and good outcomes.

Personally, I have had success in the management of *BRAF* V600E-mutated cholangiocarcinoma using a combination of BRAF/MEK inhibitors.[21] Isocitrate dehydrogenase 1 and 2 (IDH1/2) may also be targetable with specific inhibitors or with cyclin inhibitors. Results from large basket studies, such as the TAPUR study and NCI-MATCH, will be crucial to identify which patients may be the most likely to respond to the currently available targeted therapies.

How will oncologists stratify treatment strategies based on the subtypes discussed earlier?

Given the ever-increasing number of biomarkers and therapies, it's important to make sure that we follow guidance from emerging and strong-evidence data. Consensus guidelines from well-established groups such as ASCO, ESMO, and the National Comprehensive Cancer Network will be very valuable and important. Personally, I have always been an advocate of institutional or virtual genomic tumor boards, because those efforts have proven to help allocate patients who undergo biomarker testing and NGS, and improve utilization of drugs and outcomes.[22] The enrollment of

patients in clinical trials will help us to find predictive signals of response, and will be essential in how we allocate these patients further. Continuous education and following guidelines and expertise is always essential, and aids collaboration between us physicians and pathologists.

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