The Promise of Immunotherapy in the Management of Gastrointestinal Cancers:

What Does Managed Care Need to Know About Checkpoint Inhibition and Biomarkers in Colorectal and Gastric Tumors?

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from June 1, 2019 to May 31, 2021.

A score of 70% must be achieved on the post-test to receive continuing education credits.

Read the monograph, answer the post-test, complete the evaluation form, and send the completed post-test and evaluation to:

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Learning Objectives:
1. Discuss the mechanisms of action of immune checkpoint inhibitors and the rationale for checkpoint inhibition in the treatment of GI cancers.
2. Examine the current guideline recommendations for MSI-H/dMMR testing, as well as implications for treatment selection for patients with metastatic MSI-H/dMMR GI cancer including CRC.
3. Analyze how current biomarkers for immunotherapy, including MSI-H/dMMR, PD-L1, TMB, and others across the spectrum of GI cancers, may inform treatment choices.
4. Evaluate the safety and efficacy data and evidence for the use of anti–PD-1 immunotherapy in GI cancers alone or in combination with other agents, and describe recent clinical data.
5. Explore strategies for the prevention and optimal management of immune-related adverse effects in advanced gastric cancer.
6. Discuss the managed care considerations of current and emerging immunotherapies by exploring where these agents fit into the current GI cancer management paradigm.
7. Apply methods to enable optimal cost management of immunotherapies to be realized by multiple GI cancer stakeholders, including managed care organizations.

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Post-Test Questions

1. Which of the following is the most rapidly increasing cancer in both men and women?

   a. Hepatocelluar carcinoma **b.** Gastroesophageal junction
   c. Colorectal **d.** Anal

2. Which of the following is a mechanism by which tumor cells dampen local T cell response?

   a. Upregulation of PD-1 secretion
   b. Downregulation of immunoglobulin production
   c. Upregulation of PD-L1 expression
   d. Decreased activity of CTLA-4

3. A combined positive score (CPS) is a measure of which biomarker for immunotherapy activity?

   a. Mismatchrepair (MMR) **b.** PD-L1
   c. CTLA-4 **d.** Microsatellite instability (MMR)

4. Pembrolizumab and nivolumab block the interaction of PD-1 on the tumor cells, which allows cells to migrate into the tumor.

   a. True **b.** False

5. Which of the following is the FDA approved indication for pembrolizumab and nivolumab in treating metastatic hepatocellular carcinoma?

   a. Second-line systemic therapy after progression on or after sorafenib.
   b. First-line in combination with radiation.
   c. Second-line in combination with platinum-based therapy.
   d. Third-line after sorafenib and lenvatinib.

6. Which of the following is a biomarker of response to checkpoint immunotherapy in colorectal cancer?

   a. CPS > 1% **b.** CTLA-4 expression
   c. MMR deficiency **d.** Tumor mutational load

7. For second-line treatment of advanced metastatic gastric cancer, median overall survival with pembrolizumab treatment is comparable with that seen with trials of combination chemotherapy.

   a. True **b.** False

8. Which type of gastroesophageal junction (GEJ) cancer is more likely to respond to anti-PD-1 immunotherapy?

   a. Squamous **b.** Epstein Barr virus related
   c. Chromosomal instability (CIN) **d.** Adenacarcinoma

9. Which of the following is an accurate statement about immune-related adverse effects of immunotherapy?

   a. Radiologic assessment is needed prior to start of therapy and approximately every four weeks after starting therapy.
   b. Assessments (including history, physical examination and laboratory analyses) can stop when immunotherapy is discontinued.
   c. Grade 1 immune adverse events are managed with holding therapy.
   d. Low-dose corticosteroids are usually required to manage Grade 2 events.

10. According to this monograph, drugs account for what percentage of cancer costs?

    a. 25% **b.** 40% **c.** 50% **d.** 75%

Activity Evaluation and Improvement Process

Please rate this activity on the following scale:
4 - Excellent   3 - Good   2 - Fair   1 - Poor

1. Based on the content presented, I am better able to:

   Discuss the mechanisms of action of immune checkpoint inhibitors and the rationale for checkpoint inhibition in the treatment of GI cancers.

   4   3   2   1

   Examine the current guideline recommendations for MSI-H/dMMR testing, as well as implications for treatment selection for patients with metastatic MSI-H/dMMR GI cancer including CRC

   4   3   2   1

   Analyze how current biomarkers for immunotherapy, including MSI-H/dMMR, PD-L1, TMB, and others across the spectrum of GI cancers, may inform treatment choices.

   4   3   2   1

   Evaluate the safety and efficacy data and evidence for the use of anti–PD-1 immunotherapy in GI cancers alone or in combination with other agents, and describe recent clinical data.

   4   3   2   1

   Explore strategies for the prevention and optimal management of immune-related adverse effects in advanced gastric cancer.

   4   3   2   1

   Discuss the managed care considerations of current and emerging immunotherapies by exploring where these agents fit into the current GI cancer management paradigm.

   4   3   2   1

   Apply methods to enable optimal cost management of immunotherapies to be realized by multiple GI cancer stakeholders, including managed care organizations.

   4   3   2   1

2. The activity and presenters were free of bias.

   4   3   2   1

3. The activity was applicable to my position.

   4   3   2   1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4   3   2   1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

Fold on this crease second

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Gastrointestinal Cancer Monograph

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The Promise of Immunotherapy in the Management of Gastrointestinal Cancers:

What Does Managed Care Need to Know About Checkpoint Inhibition and Biomarkers in Colorectal and Gastric Tumors?

Tanios S. Bekaii-Saab, MD, FACP; Minsig Choi, MD; Gary M. Owens, MD

Introduction

Gastrointestinal (GI) cancers affect more than 320,000 people in the United States (U.S.) annually and result in over 165,000 deaths per year.[1] Cancer can occur in any part of the gastrointestinal tract, but the most common are colorectal and liver. Although early stage GI cancers are amenable to surgical resection with curative intent, the overall five-year relapse rate remains high. The addition of neoadjuvant or adjuvant chemotherapy and radiation therapy for later stage disease only modestly improves overall long-term survival. Unfortunately, a large proportion of patients present with unresectable disease at the time of diagnosis and approximately 25 percent of GI cancers are diagnosed at advanced stage, whereas another 25 to 50 percent of patients will develop metastatic disease. Despite improvements in survival with metastatic disease through use of targeted agents (cetuximab, panitumumab, bevacizumab, aflibercept, regorafenib, trastuzumab, ramucirumab, and sorafenib for certain cancers), additional improvements in outcomes are sought. Using the immune system to target cancer has become a major focus of treatment for many cancers, including GI cancers. Immunotherapy is emerging as an effective and promising treatment option. Gastroesophageal junction (GEJ), gastric, colorectal, and hepatocellular cancers are the focus of this monograph because of the availability of immune checkpoint therapy for these cancers.

Gastroesophageal Junction Cancer

The gastroesophageal junction (GEJ) forms the border between the distal esophagus and the proximal stomach, and normally is where squamous epithelium of the esophagus transitions into columnar epithelium of the gastric cardia. Cancers of the GEJ are typically adenocarcinomas.[2] Tobacco use, gastroesophageal reflux disease (GERD), Barrett's esophagus, and obesity are all risk factors for GEJ cancers.[3] The incidence of GEJ cancer rose significantly between the 1970s and 1990s in the U.S., but it has stabilized since 1990.[3] The highest rates of this cancer are seen in white males.[3]

Gastric Cancer

An estimated 27,510 cases of gastric cancer and an estimated 11,140 deaths will occur in the U.S. in 2019.[1] More than 90 percent of stomach cancers are adenocarcinomas. In 1930, most cases originated in the distal stomach (gastric body and antrum). Since then, the incidence of distal gastric carcinoma has declined dramatically; however, the incidence of adenocarcinoma of the proximal stomach has increased at a significant rate.[4] Overall, the number of new cases of gastric cancer have decreased about 1.5 percent each year over the last 10 years, and the five-year survival rate is 31 percent.[5]

Colorectal Cancer

Colorectal cancer is the third most common cancer in the Western world. The lifetime risk of developing colorectal cancer is 5.42 percent, and it is the third leading cause of cancer deaths in the U.S. for men and women.[6] The overall five-year survival rate with colorectal cancer is 64 percent. Unfortunately, 20 percent of patients have metastatic disease at presentation, and only 10 percent of those patients live five years. Median survival of untreated patients with metastatic disease is six months and with chemotherapy is two years. Those with KRAS wild-type disease have the longest survival at a median of 30 months.

Hepatocellular Carcinoma

An estimated 42,030 new cases of liver cancer (including intrahepatic bile duct cancers) will be diagnosed in the U.S. during 2019, three-quarters of which will be hepatocellular carcinoma (HCC).[1] Liver cancer is the most rapidly increasing cancer in both men and women, with incidence rates more than tripling since 1980, and from 2006 to 2015, the rate increased by about 3 percent per year.[7] An estimated 31,780 liver cancer deaths will occur in 2019.[1] The death rate for liver cancer has more than doubled, rising from 2.8 (per 100,000) in 1980 to 6.7 in 2016, with an increase of 2.4 percent per year from 2007 to 2016.

Exhibit 1: Relationship Between Microsatellite Instability and Tumor-Associated Inflammatory Response[10]

MSI-H = microsatellite instability high
MMR = mismatch repair
PD-L1 = programmed death ligand one
PD-1 = programmed death one
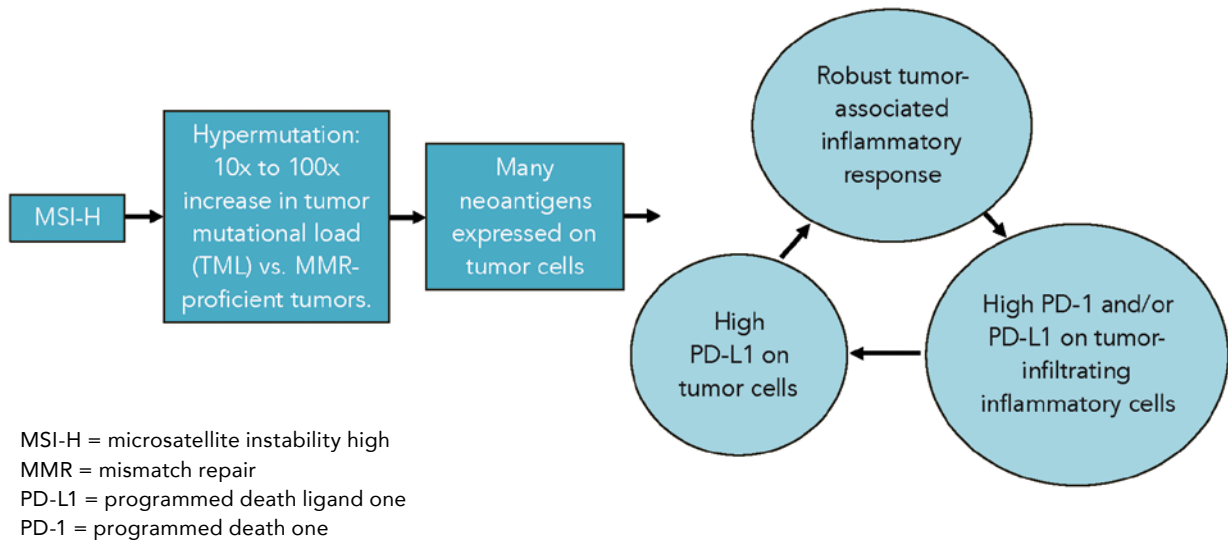
Immunotherapy in GI Cancers

The innate and adaptive immune system is able to identify and eliminate tumor cells that are identified as non-self. As a tumor grows and evolves, tumor cells can become increasingly genetically unstable as genetic mutations accumulate and the cells can adapt to evade the immune system through various cell surface proteins. For example, tumor cells of various cancers have been shown to upregulate programmed death ligand one (PD-L1) expression on the cell surface as a mechanism that dampens the local T cell response. In GI malignancies, PD-L1 upregulation has been demonstrated to occur in gastric and colorectal cancers. Immunotherapy in oncology acts to activate the immune system to destroy tumor cells. Cytotoxic T-lymphocyte associated protein four (CTLA-4) and programmed cell death one (PD-1) are critical immune checkpoint molecules that negatively regulate T cell activation via distinct mechanisms. CTLA-4 is a cell surface receptor on T cells that behaves as a negative regulator of the proliferation and the effector function of T cells. It prevents T cells from attacking normal body cells and cancer cells. Agents that target CTLA-4 and PD-1 are available for treating select GI cancers and are generically called checkpoint inhibitors. The ant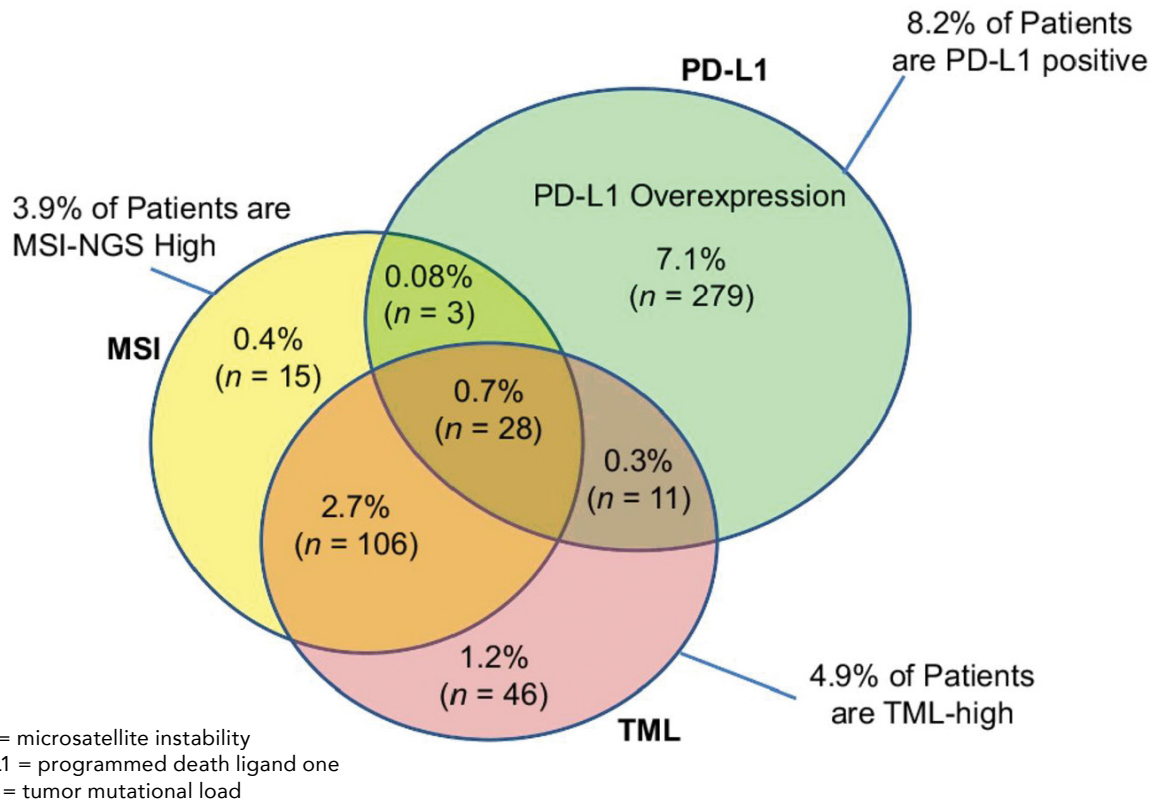i-PD-1 agents, pembrolizumab and nivolumab, block the interaction of PD-1 on the T cell with PD-L1 on the tumor cell surface, thus allowing T cells to remain active in the tumor microenvironment. Ipilimumab, an anti-CTLA-4 agent, blocks the activity of CTLA-4, which allows T cells to attack tumor cells.

Biomarkers for Immunotherapy Response in GI Cancers

Three biomarkers that are used to predict response to checkpoint inhibitors in GI cancers are mismatch repair, microsatellite stability, and PD-L1 expression. Mismatch repair (MMR) is one way that cells correct errors in DNA as cells divide. Cells can have mutations that lead to dysfunctional repair, which allows DNA errors to accumulate and lead to cancer. Mismatch repair deficiency (dMMR) occurs in about 8 percent of GI cancers.[8] It is most common in spontaneous colorectal cancer. MMR deficiency may also be found in people with Lynch syndrome, an inherited disorder that increases risk of colorectal, gastric, small intestine, liver, gallbladder duct, upper urinary tract, brain, skin, and prostate cancers, often before the age of 50.[9]

Genetic errors from dMMR result in accumulation of errors in genetic sequences that are normally repeated (called microsatellites). Cells with high levels of these errors have microsatellite instability (MSI-H). Exhibit 1 shows the relationship between MSI-H and tumor-associated inflammatory response.[10] Tumor mutational load (TML) is another way of measuring genetic errors in a cancer cell and correlates with MSI-H. Approximately 5 percent of GI cancers have high TML and 4 percent have MSI-H.[11] MSI-H, high TML, and dMMR all lead to an increased number of neoantigens, which increases immune recognition. Other factors than dMMR are drivers for developing cancer, such as infection with oncogenic viruses (human papillomavirus and Epstein Barr virus).

Exhibit 2: Overlap of PD-L1 overexpression, MSI–high, and TML-high in GI tumors[11]

8.2% of Patients are PD-L1 positive

PD-L1

PD-L1 Overexpression
7.1% (*n* = 279)

3.9% of Patients are MSI-NGS High

MSI

0.4% (*n* = 15)

0.08% (*n* = 3)

0.7% (*n* = 28)

0.3% (*n* = 11)

2.7% (*n* = 106)

1.2% (*n* = 46)

4.9% of Patients are TML-high

TML

MSI = microsatellite instability
PD-L1 = programmed death ligand one
TML = tumor mutational load

PD-1 expression on tumor cells is induced by gamma interferon. Activated T cells that could kill these tumor cells are specifically disabled by the tumor. Blockade of PD-1 binding to PD-L1 and PD-L2 revives T cells. PD-L1 expression is determined by a combined positive score (CPS), which is the number of PD-1 staining cells divided by the total number of viable tumor cells in the sample multiplied by 100. A specimen is considered to have positive PD-1 expression if the CPS is greater than or equal to 1 percent. Approximately 8 percent of GI cancers are PD-L1 positive.[11] Exhibit 2 shows the overlap of these three biomarkers of response to immunotherapy from trial testing biomarkers from 4,125 tumors from 14 different GI cancer sites.[11]

Overall, testing for MSI-H and dMMR is appropriate in all GI cancers. TML, done by next-generation sequencing, is a good predictor for activity of checkpoint inhibitors; however, it is not necessarily recommended by the current National Comprehensive Cancer Network (NCCN) guidelines. Testing for PD-L1 expression is important for selecting immunotherapy in gastric, GEJ, and esophageal cancers.

Treatment of Gastroesophageal Junction Cancer

Surgical removal is the treatment for local or early stage disease. Locally advanced unresectable and metastatic gastroesophageal cancers are not curable conditions. For locally advanced esophageal cancer, the addition of chemotherapy and/or radiation to surgery is considered the standard of care.[2] Chemotherapy remains the primary treatment for metastatic disease and improves survival over best supportive care. The goals of chemotherapy or radiation are to palliate symptoms, improve quality of life, and prolong survival. The prognosis for patients with GEJ cancers remains poor because of the emergence of chemoresistance and limited targeted therapeutic approaches.

Commonly activated oncogenes in esophageal adenocarcinoma and GEJ adenocarcinoma include, human epidermal growth factor receptor two (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), MET proto-oncogene, receptor tyrosine kinase (MET), and MSI. Each promotes oncogenesis through heterogeneous mechanisms. These oncogenes allow

Exhibit 3: Management of Advanced Esophageal or GEJ Cancer[17]

Patient with metastatic or unresectable esophageal or gastroesophageal junction adenocarcinoma

Line of treatment	HER2 positive	HER2 negative	PD-L1 positive	MSI-high
First-line	Platinum doublet (CF or FOLFOX) plus trastuzumab	Platinum doublet (CF or FOLFOX). If claudin positive, can consider clinical trial of anti-claudin antibody plus platinum-based chemotherapy	Platinum doublet (CF or FOLFOX)	Platinum doublet (CF or FOLFOX)
Second-line	Ramucirumab plus paclitaxel or clinical trial with agent such as DS-8201	Ramucirumab plus paclitaxel	Ramucirumab plus paclitaxel or clinical trial	Pembrolizumab
Third-line	Single agent chemotherapy or ramucirumab/paclitaxel depending if clinical trials was utilized in second-line setting	Clinical trial versus single agent chemotherapy	Pembrolizumab alone or clinical trial with combination immunotherapy such as nivolumab plus ipilimumab	Clinical trial with combination immunotherapy versus ramucirumab plus paclitaxel

GEJ = gastroesophageal cancer
HER2 = human epidermal growth factor receptor two
PD-L1 = programmed death ligand one
MSI-H = microsatellite instability high

for multiple intervention possibilities. For example, those with advanced or metastatic disease and HER2 overexpression are treated with trastuzumab.

One option for treatment at progression for patients with GEJ who have advanced tumors with dMMR, MSI-H, or overexpression of PD-L1 is immunotherapy with pembrolizumab or nivolumab. The KEYNOTE-028 trial evaluating the benefit of pembrolizumab (10 mg/kg every two weeks) in PD-L1-expressing advanced solid tumors included 23 patients with GEJ cancer.[12] Eighty-seven percent of the subjects had two or more prior therapies for metastatic disease, and both adenocarcinomas and squamous cell carcinomas were included. With GEJ, there were seven confirmed partial responses (overall response rate [ORR] 30 %). By histologic subtype, the objective response rate was higher for adenocarcinoma, and the median duration of response was 15 months. Similar results were noted in the Phase II KEYNOTE-180 study of 121 patients with advanced metastatic squamous or adenocarcinoma of the esophagus or GEJ that had progressed after two or more lines of systemic therapy.[13] The objective response was twofold higher among those with PD-L1-overexpressing tumors (14 % versus 6%). In KEYNOTE-181, pembrolizumab was associated with a statistically significant improvement in median OS compared with either paclitaxel, docetaxel, or irinotecan in patients with a PD-L1 combined positive score CPS ≥10, regardless of histology (9.3 vs 6.7 months).[14] The KEYNOTE-181 study evaluated pembrolizumab versus investigator's choice of chemotherapy as second-line therapy for patients with advanced or metastatic squamous and adenocarcinoma of the esophagus or Siewert type I adenocarcinoma of the esophagogastric junction.

Pembrolizumab is FDA indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 CPS ≥1 as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy. This indication was approved under accelerated approval based on tumor response rate

and durability of response. In May 2017, the FDA approved pembrolizumab for treatment of a variety of advanced solid tumors, including GEJ cancers that were MSI-H or dMMR, that had progressed following prior treatment, and for which there were no satisfactory alternative treatment options.

The CheckMate-032 trial evaluated nivolumab in 160 patients with disease progression on or intolerance of at least one systemic chemotherapy regimen for advanced gastric, esophageal, or GEJ cancer.[15] Nivolumab, with or without ipilimumab, led to durable responses and long-term overall survival, and responses were observed regardless of the tumor PD-L1 status. Twelve-month progression-free survival (PFS) with nivolumab alone was 8 percent and 10 percent for the combination of nivolumab plus ipilimumab, and 12-month overall survival (OS) rates were 39 percent and 24 percent, respectively. Grade 3 or worse treatment-related adverse events were reported in 17 percent and 27 percent of subjects, respectively. There is no FDA approval or NCCN Guideline recommendation for this use for nivolumab to date.[16] Exhibit 3 presents a management algorithm for advanced GEJ cancer based on biomarkers.[17]

Treatment of Gastric Cancer

As with GEJ cancer, surgical removal is the treatment for local or early stage gastric cancer. Locally advanced unresectable and metastatic gastric cancers are not considered curable. A number of controlled trials and meta-analyses provide evidence for the survival benefit of palliative systemic chemotherapy for patients with advanced gastric cancer. In one meta-analysis of three trials comparing chemotherapy with best supportive care, there was a significant benefit in OS in favor of chemotherapy compared with supportive care alone and an improvement in median OS from 4.3 to 11 months.[18]

Gastric cancer can be classified into four subtypes based on molecular phenotypes identified by utilizing integrative genomics –Epstein-Barr virus (EBV)–related, MSI-H, chromosomal instability (CIN), and genomically stable.[19] Among these, the EBV-related and MSI-H subtypes exhibit immune signatures and tumor microenvironments amenable to treatment with immunotherapy. The MSI-H subtype, which constitutes 22 percent of gastric cancers, has a high mutational burden.[20] PD-L1 is overexpressed in up to 42 percent of gastric cancer. However, there is a great variation in the PD-L1 positivity rate, between 12.3 and 64 percent.[20]

The KEYNOTE-012 trial tested the tolerability and safety of single-agent pembrolizumab as second-line treatment in patients with gastric cancer. The median OS of 11.4 months with pembrolizumab in this study is comparable with the nine to 10 months reported in trials of combination chemotherapy, and a definite improvement over the OS of four to five months achieved by single-agent chemotherapy in a second-line setting.[21] Pembrolizumab also demonstrated promising efficacy as third-line treatment in heavily pretreated patients with advanced-stage gastric cancer.[22] Based on these results and those of another trial, the FDA approved pembrolizumab for the treatment of patients with PD-L1-positive recurrent or advanced-stage gastric cancer, who have received two or more lines of chemotherapy.[12,21,22]

In a trial of pembrolizumab with paclitaxel in patients with PD-L1 positive advanced gastric or GEJ cancer that progressed on first-line chemotherapy with a platinum and fluoropyrimidine, pembrolizumab did not significantly improve OS compared with paclitaxel as second-line therapy (9.1 months vs 8.3).[23] Pembrolizumab is also being investigated as a single agent or in combination with standard chemotherapy, compared with standard chemotherapy alone for first-line therapy in advanced gastric and GEJ disease. In a preliminary finding report, monotherapy was noninferior to chemotherapy for OS in the entire intention-to-treat (ITT) population of patients whose tumors expressed PD-L1 CPS ≥1, but combination therapy did not improve OS or PFS compared to chemotherapy alone in the first-line setting.[24]

Nivolumab has also been studied in gastric cancer. Partial remission was observed in 11 percent of heavily treated patients, but the gain in OS for nivolumab was only 1.1 months.[25] However, it reduced the mortality risk by 37 percent compared with placebo. Moreover, the survival benefit with nivolumab persisted for more than 12 months. Nivolumab does not have an FDA approved indication for gastric cancer.

Treatment of Colorectal Cancer

Mutations in one of several MMR genes are found in Lynch syndrome related colorectal cancer, in 15 to 20 percent of sporadic colon cancers, and in 5 percent of metastatic cases.[26, 27] This subset of colorectal cancer is a target for immunotherapy. A Phase II study evaluating the clinical activity of pembrolizumab, in 41 patients with progressive metastatic carcinoma with or without dMMR, found an ORR of 40 percent and PFS of 78 percent in those with dMMR and 0 percent and 11 percent, respectively, in those whose tumors were MMR proficient.[10,28] The median PFS and OS were not reached in the cohort with dMMR colorectal cancer at the time of reporting.

In CheckMate-142, nivolumab, with or without ipilimumab, was studied in patients with dMMR (n =

Exhibit 4: Current Approval Status of anti-PD-1 Monoclonal Antibodies in GI Cancers		
	Pembrolixumab	**Nivolumab**
Gastric/Gastroespophageal cancer	Third-line, PD-L1+	
Colorectal	MSI-H/dMMR after fluoropyrimidine, oxaliplatin, and irinotecan	MSI-H/dMMR after fluoropyrimidine, oxaliplatin, and irinotecan (+/- Ipilumumab)
Hepatocellular carcinoma	Second-line after sorafenib	Second-line after sorafenib
Solid malignancy	MSI-H/dMMR in salvage setting	

MSI-H = microsatellite instability high
dMMR = mismatch repair deficiency
PD-L1 = programmed death ligand one
PD-1 = programmed death one

59) or MMR proficient (n = 23) metastatic colorectal cancer. The ORR was 39 percent with nivolumab monotherapy and 49 percent with combination therapy.[29] Combination therapy resulted in greater Grade 3 or 4 toxicity, relative to nivolumab alone. Clinical benefit was noted regardless of PD-L1 expression, or BRAF or RAS mutation status. With monotherapy, responses appeared to be durable. At a median follow-up of 12 months, 31 percent of subjects had achieved an investigator-assessed objective response and 69 percent patients had disease control for 12 weeks or longer.[30] At the end of the trial, the median duration of response was not yet reached, all responders were alive, and eight had responses lasting 12 months or longer.

Nivolumab and pembrolizumab are FDA approved for treating adult and pediatric patients with MSI-H or dMMR metastatic or unresectable colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Nivolumab is indicated as a single agent, or in combination with ipilimumab.

There are several questions to still be answered in treating metastatic colorectal cancer with immunotherapy. Whether additional biomarkers including PD-L1 expression levels or TML should be done in addition to MSI-H or dMMR to optimally select patients' needs to be determined. Preference of nivolumab monotherapy or combination with ipilimumab also needs to be delineated. The optimal duration of immunotherapy and the role of checkpoint inhibitors in the adjuvant setting are other open questions.

Several trials are ongoing with immunotherapy as first-line therapy for dMMR metastatic colorectal cancer (nivolumab), in combination with chemotherapy first-line therapy for dMMR metastatic colorectal (atezolizumab), and for Stage III disease compared to chemotherapy. Combination therapy with immunotherapy and targeted therapy is also under study. Combining anti-PD-1 agents and mitogen-activated protein kinase (MEK) inhibition is a rational combination. MEK inhibition alone can result in intratumoral T cell accumulation and synergizes with anti-PD-1 agents to promote durable tumor regression.[31] Atezolizumab and cobimetinib have been studied together and found to improve median OS (8.9 vs 7.1 months) compared with atezolizumab alone, but not compared to rografenib.[32] Other combination immunotherapy trials are ongoing.

Treatment of Hepatocellular Carcinoma
HCC is a classical inflammation-induced tumor type, which makes it a target for immunotherapy. Spontaneous immune responses are frequently observed and immunotherapy is eliminated from the body independent of liver function, so even patients with severe dysfunction could receive the treatment.

Both nivolumab and pembrolizumab have been studied in advanced HCC with fairly low response rates (14.3% and 17%, respectively).[33,34] Both agents have FDA approval for second- line systemic therapy in those who are Child Pugh Class A after progression on or after sorafenib. The NCCN guidelines suggest pembrolizumab as an option for first-line therapy for unresectable or metastatic disease with MSI-H or dMMR based on limited clinical data to support this use.[35]

Metastatic Anal Cancer
Approximately 80 to 95 percent of cases of squamous cell carcinoma of the anus (SCCA) are linked to

Exhibit 5: Immune-Related Adverse Events Can Affect Any Organ System
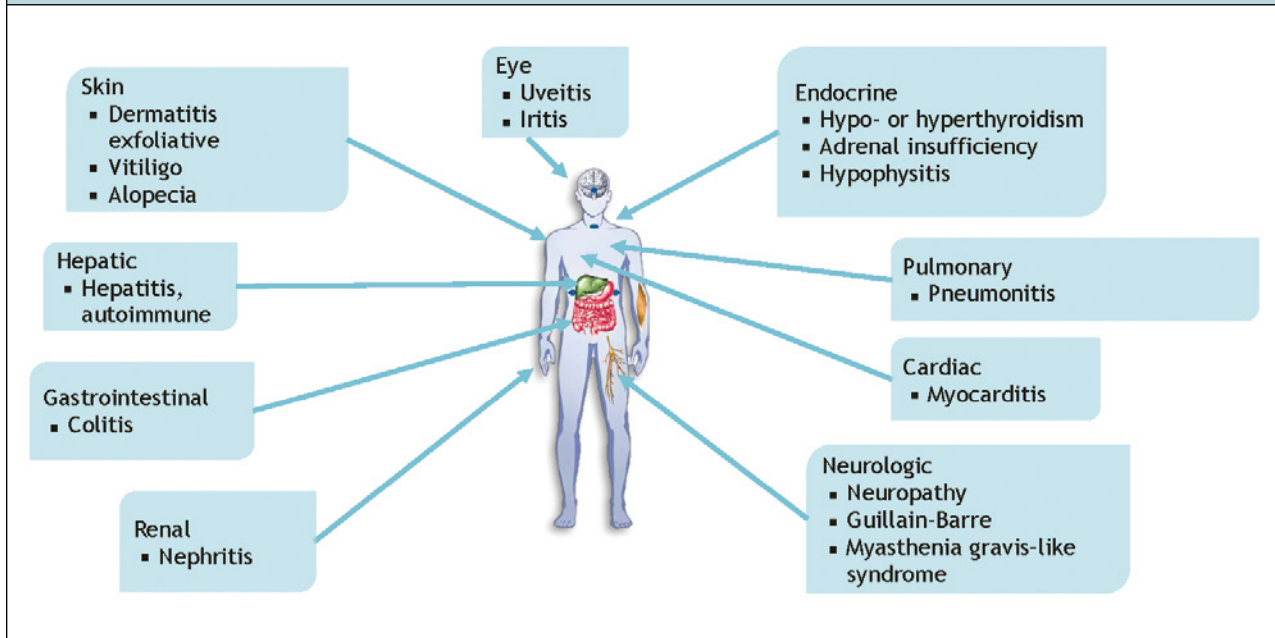
infection with human papillomavirus (HPV). The role of HPV in the tumorigenesis of SCCA provides rationale for the use of immune checkpoint blockade agents as a novel therapy for treatment of patients with a virally driven disease.[36] In a trial of nivolumab for previously treated unresectable metastatic SCCA, 24 percent of patients had responses. There were two complete responses and seven partial responses.[37] In a trial of pembrolizumab, among the 24 patients with SCCA and PD-L1-positive tumors, ORR was 17 percent with 42 percent with stable disease, for a disease control rate of 58 percent.[38] Based on these trials, nivolumab and pembrolizumab are included in the NCCN guidelines as an option for metastatic anal cancer for patients who have progressed on first-line chemotherapy.[39] The current FDA approvals for pembrolizumab and nivolumab are shown in Exhibit 4.

Adverse Events of Immunotherapy

Adverse events are very common in patients who are treated with immunotherapy and Grade 3 or 4 treatment-related adverse events occur in 10 to 20 percent of patients. Overall, the most common adverse events of any grade are diarrhea (22 percent, 2 percent severe), fatigue (18 percent, 2 percent severe), pruritus (17 percent, 2 percent severe), and pyrexia (15 percent, none severe). The most common laboratory adverse events are elevations in aspartate transaminase (AST at 8 percent) or alanine transaminase (ALT at 7 percent).

Immune-related adverse events (irAEs) are the most serious of the immunotherapy adverse events, can affect any organ system, and can be fatal (Exhibit 5). Clinicians have to be vigilant in monitoring for irAEs and must be quick to treat to prevent progression to more serious events. Prior to each dose, patients require careful and thorough clinical evaluation to assess for irAEs. Radiologic assessment is needed prior to start of therapy and approximately every eight to 12 weeks after starting therapy, and as needed to evaluate for pneumonitis. Assessments (including history, physical examination, and laboratory analyses) should continue even after cessation of therapy.

Grade 1 (asymptomatic to mild symptoms) irAEs are managed with observation only. Grade 2 (moderate symptoms) typically are treated with local or noninvasive intervention and withholding the medication until the toxicity resolves to Grade 1 or less. Low-dose corticosteroids are likely needed. Grade 3 events, which are medically significant but not immediately life-threatening, require stopping immunotherapy immediately. Hospitalization and high-dose steroids are indicated. Patients should receive a slow steroid taper over a month or more, once toxicity resolves to Grade 1 or less. Grade 4 events are life-threatening irAEs and require urgent intervention and permanent discontinuation of immunotherapy. Severe irAEs are rare but, if they are identified early, they can be controlled and reversed.

Exhibit 6: Current Cancer Management Approaches

Aggressive prior authorization

- To labeled indication at a minimum
- Restriction to populations studied in the clinical trials
- Restriction to selected genetic subtypes using genetic markers
- Limited use by only "approved" centers or groups

Risk shifting or sharing

- Increased contracting with ACOs and other risk-bearing entities
- Increased use of pathways by many organizations, but success has been variable with new agents
- Risk-based or value-based contracting with oncology groups
- Contracting with Centers of Excellence

Contracting strategies

- Aggressive contracting for preferred agent positioning
- Closed formularies even on the medical side
- Outcomes-based contracting

Payer Management Challenges

Managing costs related to immunotherapy and the overall costs of cancer treatment are a challenge for payers. The costs of cancer treatment have grown dramatically over the last 10 years. The total national expenditure for cancer in the U.S. for 2020 is estimated at over $157 billion.[40] Drug costs are a significant part of this increase. Almost every newly approved cancer drug has an annual cost greater than $120,000, and immunotherapy can cost over a million dollars per patient.[41] In one analysis of Medicare data, drug costs were found to account for 50 percent of cancer care costs.[42]
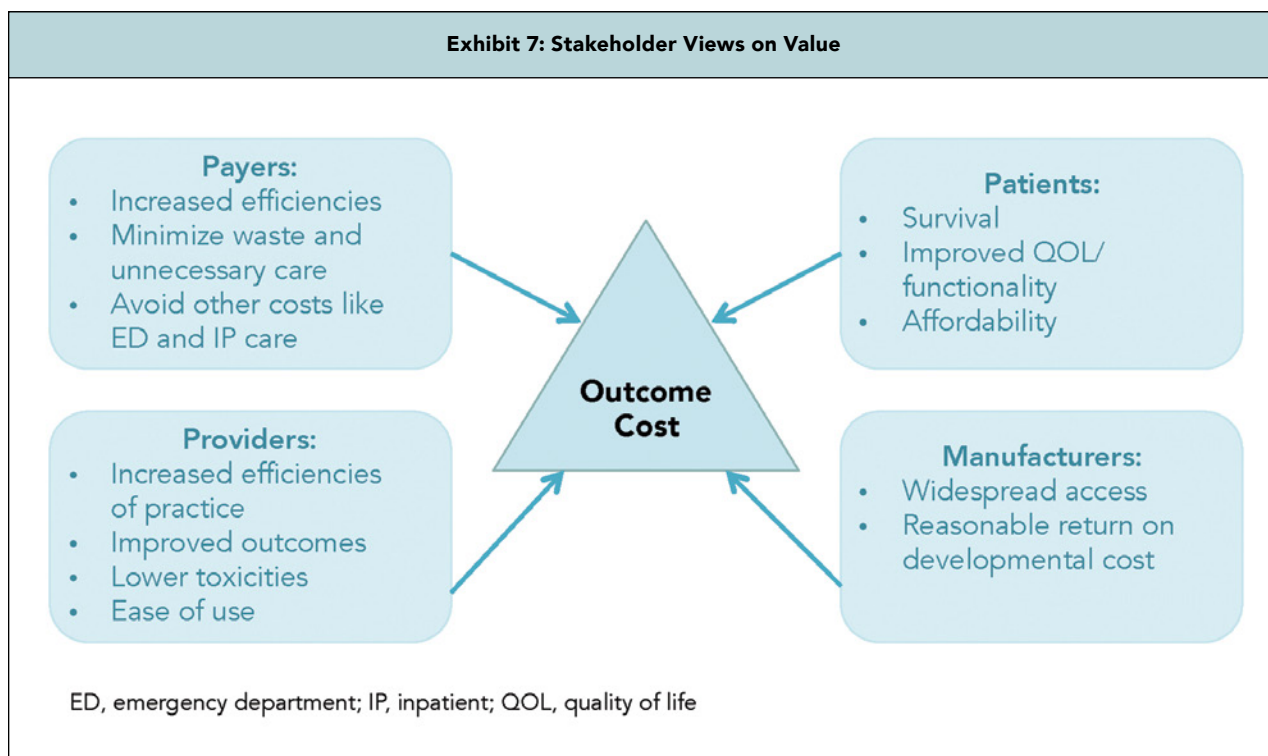
Employers are concerned about the rising costs and in turn pressure payers to reduce costs. The Integrated Benefits Institute sponsored research on the subject and came away with an estimate for cancer of $19,000 per year in lost working hours and medical treatments per 100 employees.[43] Although cancer strikes just 1.6 percent of the workforce, disease-related costs account for 10 percent of health care spending for employers and that number is rising due to the escalating cost of treatment.

Costs are concerning to payers, but it is also more than a cost issue for them. The field of immuno-oncology is changing almost weekly and payers are finding it hard to keep up. New issues include how to deal with biomarkers in selecting therapy, use of combination therapies, which line of therapy immunotherapy should be, and many more issues. Until the new century arrived, payer management of cancer care was limited to a few management activities. These included limited prior authorizations, case management of catastrophic cases, site-of-care shifts to outpatient treatment, and management of infusion therapy costs. Current cancer management strategies are outlined in Exhibit 6.

There has been much discussion in the payer community about the role of value-based or outcomes-based contracting for drugs. There are examples of this type of approach in diabetes, cardiovascular diseases, respiratory diseases, and a few other areas. Can this approach be used with cancer treatments and immunotherapies across multiple cancer types? There are numerous operational and legal issues that must be considered for a risk- or value-based contract. Legal considerations include 340B pricing issues, Medicaid best price, FDA regulations on economic claims, and anti-kickback statutes. Operational considerations include which outcomes should be used (OS, PFS, response, duration of response), whether the data is available at the level of detail necessary, and over what time frame is reasonable. Patient factors such as quality of life come into play in a disease where survival typically is not long. It is most likely that value-based contracting for immuno-oncology agents will cross

Exhibit 7: Stakeholder Views on Value

Payers:
- Increased efficiencies
- Minimize waste and unnecessary care
- Avoid other costs like ED and IP care

Patients:
- Survival
- Improved QOL/ functionality
- Affordability

Outcome Cost

Providers:
- Increased efficiencies of practice
- Improved outcomes
- Lower toxicities
- Ease of use

Manufacturers:
- Widespread access
- Reasonable return on developmental cost

ED, emergency department; IP, inpatient; QOL, quality of life

the spectrum of multiple cancer sites, rather than being specific to a certain cancer.

Because value means different things to different stakeholders, payers need to take these multiple views into consideration to develop agreements (Exhibit 7). Value-based contracts should target the triple aim of improve the experience of care, improve the health of populations, and reduce per capita costs of health care to help satisfy the different value needs. Types of value-based agreements include financial-based, performance-based, and coverage with evidence development. Financial-based agreements have reimbursement tied to financial considerations (e.g., cost caps, price-volume agreements). Performance-based contracts are tied to metrics related to patient performance, outcomes, quality of life, and tolerability. There may be outcomes and compliance guarantees. The last type, coverage with evidence development, is conditional coverage based on future population level outcomes.

There are numerous challenges to value-based contracting. Typical endpoints measured in clinical trials such as PFS and OS are not captured in medical claims at the present time. Those same endpoints may not be easily measurable in a time period required for a value-based contract. Patients treated with multiple lines of therapy can confound the ability to measure outcomes and tie those outcomes to a particular immunotherapy. Additionally, patients treated with combinations of therapies make it difficult to attribute outcomes to a particular therapy. There may be small numbers of patients with certain tumor types in a plan—this will become more complex as genetic markers (e.g., mutational burden) further stratify patients. Off-label use of the therapy under contract can confound results. Lastly, patients may leave the plan before outcomes can be measured.

The issue of having to manage expensive immunotherapy is only going to grow. There are over 240 immuno-oncology products in development, many in mid- to late-phase. Four examples in Phase III development for GI cancers are andecaliximab, an MMP9 inhibitor for gastric cancer; OncoVAX® and anti-interleukin-1-alpha for colorectal cancer; and pexastimogene devacirepvec (engineered strain of oncolytic vaccinia poxvirus) for liver cancer.

Conclusion

Many gastric cancers have genetic changes that make them good targets for immunotherapy. A number of trials provide evidence for benefit of immunotherapy for patients with certain advanced GI cancers. The role of immunotherapy is evolving for the treatment of various GI cancers as additional studies are done and new indications emerge. Expect the treatment guidelines to change to earlier use of these agents for many GI cancers.

The cost of cancer care is growing rapidly. Former

managed care cost management techniques are not adequate for the future—especially with costly immunotherapy agents. New reimbursements and value-based approaches will be one way to handle the cost. However, these approaches are still in their relative infancy for oncology and face significant operational, legal and patient/provider challenges.

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