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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gastrointestinal cancer

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ABSTRACT

Gastrointestinal (GI) cancers, including esophageal, gastroesophageal junction, gastric, duodenal and distal small bowel, biliary tract, pancreatic, colon, rectal, and anal cancer, comprise a heterogeneous group of malignancies that impose a significant global burden. Immunotherapy has transformed the treatment landscape for several GI cancers, offering some patients durable responses and prolonged survival. Specifically, immune checkpoint inhibitors (ICIs) directed against programmed cell death protein 1 (PD-1), either as monotherapies or in combination regimens, have gained tissue site-specific regulatory approvals for the treatment of metastatic disease and in the resectable setting. Indications for ICIs in GI cancer, however, have differing biomarker and histology requirements depending on the anatomic site of origin. Furthermore, ICIs are associated with unique toxicity profiles compared with other systemic treatments that have long been the mainstay for GI cancer, such as chemotherapy. With the goal of improving patient care by providing guidance to the oncology community, the Society for Immunotherapy of Cancer (SITC) convened a panel of experts to develop this clinical practice guideline on immunotherapy for the treatment of GI cancer. Drawing from published data and clinical experience, the expert panel developed evidence- and consensus-based recommendations for healthcare professionals using ICIs to treat GI cancers, with topics including biomarker testing, therapy selection, and patient education and quality of life considerations, among others.

INTRODUCTION

Colorectal, liver, stomach, esophageal, and pancreas cancer account for more than one-third of cancer-related deaths worldwide. In the year 2022, there were an estimated 151,030 new cases of and 52,580 deaths due to colorectal cancer (CRC) in the US alone, making it the third most common cause of cancer-related death in this country.[1] Stomach cancer led to an estimated 769,000 deaths worldwide in 2020 and was the leading cause of cancer-related death in some Asian countries.[2] While surgery, radiation, chemotherapy, liver-directed therapy, monoclonal antibodies, and targeted therapy offer some patients a meaningful response, many gastrointestinal (GI) tumors harbor mechanisms of resistance that will eventually overcome these conventional treatments and prevent patients from achieving long-term survival. In recent years, immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis as monotherapies or in combination with anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) ICIs have been demonstrated to improve survival in biomarker selected GI tumors involving both the upper and lower tract[3–5] and therefore, regimens including these agents have become standard of care (SOC). However, not all patients benefit from ICIs, and their use requires a highly nuanced consideration of biomarker positivity, histology, and the anatomical site of cancer origin.

Anatomic origin contributes to the innate immunogenicity of these GI tumors and the degree to which known biomarkers are likely to predict response to ICIs. For example, PD-L1 expression, which is useful and validated to predict response to ICIs for esophagogastric cancers,[6] does not predict response to ICIs for advanced CRC[7] (refer to box 1 for the definitions of 'advanced' and 'esophagogastric' throughout this guideline).

Even within biomarker-selected subgroups of the same tumor, the response to ICIs is highly variable between individual patients, highlighting a need for future research into

Box 1 Terminology definitions

Advanced: any tumor that is surgically unresectable or metastatic.
Esophagogastric: tumors of esophageal, gastroesophageal junction, or gastric origin.

immunotherapy biomarkers. The histology of the primary tumor also influences response to ICIs, with certain histologies strongly associated with specific patient populations. For example, the more immune-responsive squamous cell category of esophageal carcinoma is fueling prospective studies of immune checkpoint blockade in China,[8 9] where this histology predominates.[10]

To aid the oncology community in clinical decision-making with the overall goal to improve patient care, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary expert panel to develop a clinical practice guideline (CPG) including evidence- and consensus-based recommendations on the optimal use of immunotherapy for patients with esophagogastric, colorectal, anal, small bowel, and pancreaticobilliary cancer. Immunotherapy for the treatment of hepatocellular carcinoma is covered in a separate standalone SITC CPG.[11] The expert panel developed recommendations on immunotherapy-related biomarkers, recommended immunotherapy agents, response monitoring, patient education, and patient quality of life (QOL) support. Ongoing clinical trials are also highlighted throughout this guideline, particularly to address areas of unmet need such as microsatellite stable (MSS) CRC and pancreatic cancer. It is imperative for clinical trials to maintain a high ethical standard of research, with patient and caregiver education central to informed consent. Recommendations on the management of ICI-related complications, such as immune-related adverse events (irAEs), may be found in SITC's CPG on ICI-related adverse events.[12]

SITC CPGs are provided by SITC to assist providers in clinical decision making and do not mandate a particular course of treatment or medical care. The CPGs are not intended to supplant sound judgment by the treating physician with respect to particular patients or special clinical situations and cannot always account for individual variations among patients. SITC considers adherence to the guidance to be voluntary, with the ultimate determination for the selected course of action to be made by the physician in light of each patient's individual circumstances.

GUIDELINE DEVELOPMENT METHODS

This CPG was developed by the SITC GI Cancer Immunotherapy Guideline Expert Panel, under the governance of the SITC Cancer Immunotherapy Guidelines Oversight Committee. The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model for guideline development.

Expert panel composition

The guideline development group was multidisciplinary and balanced. Members were selected based on their expertise and experience in the field, including medical oncology, nursing, and patient advocacy, as well as other specialties as-needed to support recommendation development.

Conflict of interest management

Disclosures of all financial relationships that might result in actual, potential, or perceived conflicts of interest were individually reported prior to the onset of manuscript development as well as at all key decision points during manuscript development. Those with significant financial connections that may compromise the ability to fairly weigh evidence (either actual or perceived) were not eligible to participate in guideline development. Any non-disqualifying conflicts of interests among members of the SITC GI Cancer Immunotherapy Guideline Expert Panel were managed as outlined in SITC's disclosure and conflict of interest resolution policies.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Recommendation development

Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate. Literature searches in relevant databases were performed and publications were screened for inclusion in the evidence base for the guideline recommendations. Recommendations herein were developed based both on literature review and expert opinion presented during open communication and scientific debate. Subsequently, recommendations were refined through a modified Delphi process as described by the RAND/ University of California, Los Angelas (UCLA) Appropriateness Method, expert panel consensus discussions, and review and editing of manuscript drafts.

Evidence rating

The level of evidence (LE) for a given consensus recommendation is expressed in parentheses following the recommendation (eg, LE:1). Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group 'The Oxford Levels of Evidence 2'.[13] A summary of the OCEBM grading scale may be found in box 2.

External review

A draft of this CPG was made publicly available to provide an opportunity for stakeholders potentially affected by the guideline to review and comment on the content. All comments were evaluated by the expert panel and considered for inclusion into the final manuscript.

Box 2 Summary of 'The Oxford Levels of Evidence 2' (adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence working group)

Level 1
Systematic review or meta-analysis.

Level 2
Randomized trial or observational study with dramatic effect.

Level 3
Non-randomized, controlled cohort, or follow-up study.

Level 4
Case series, case-control, or historically controlled study.

Level 5
Mechanism-based reasoning.

TISSUE-AGNOSTIC INDICATIONS FOR IMMUNOTHERAPY IN THE TREATMENT OF GI CANCER

Some patients with advanced GI cancer may be eligible for treatment with ICIs based on tissue-agnostic approvals rather than organ- or histology-specific indications. Eligibility for treatment with ICIs based on the tissue-agnostic indications is determined by the presence of biomarkers that suggest tumor antigenicity. For some of the rarer GI malignancies, these tissue-agnostic indications are the only US Food and Drug Administration (FDA)-approved uses for immunotherapy.

Tissue-agnostic biomarkers: high microsatellite instability/mismatch repair deficiency, tumor mutational burden, and *POLE/POLD1* status

Tumor detection and eradication by the immune system relies, in large part, on expression of neoantigens, which may arise due to non-synonymous mutations in protein-coding genes. Therefore, the tumor mutational burden (TMB) is generally accepted as a surrogate measure for a tumor's neoantigen load. Increased mutational load may arise due to genomic instability in cancer cells, including defects in one or more cell cycle checkpoints and/or DNA repair pathways. One specific phenotype of genomic instability in cancer, mismatch repair deficiency (dMMR), may lead to increased point mutation frequency as well as an amplification of short tandem repeats known as high microsatellite instability (MSI-H). MSI-H, dMMR, and high tumor mutational burden (TMB-H) are all approved as biomarkers for patient selection for treatment with ICIs, however, TMB should only be used in select circumstances. Available biomarkers that may be used to determine eligibility for ICI therapy are summarized in box 3.

The levels of tumor-infiltrating lymphocytes (TILs) and memory T cells have been observed to increase concomitantly with TMB in CRC[14] and multiple other malignancies. While higher mutational load is associated with clinical benefit from immune checkpoint blockade for some cancers, it is not sufficient to fully predict response.[15]

Box 3 Utility of available tissue-based biomarkers to determine eligibility for immune checkpoint inhibitors (ICIs)

Microsatellite instabilty (MSI)/mismatch repair deficiency (dMMR): all gastrointestinal (GI) cancers.
Tumor mutational burden (TMB)*: all GI cancers.
Programmed death-ligand 1 (PD-L1)†: esophagogastric cancers only.
HER2 (ICI indications)‡: esophagogastric adenocarcinomas only.

*TMB can be used to determine eligibility for immunotherapy-naïve patients who have progressed on prior therapy. The level of evidence for use of TMB to determine ICI eligibility is lower for GI malignancies in the absence of a *POLE/POLD1* mutation.
†Combined positive score (CPS) is the validated scoring system for adenocarcinoma, while CPS or tumor proportion score (TPS) are both validated in esophageal squamous cell carcinoma (ESCC). Cut-off values for PD-L1 testing depend on the assay used, cancer histology, and line of therapy. See the **'Diagnostic tests and biomarkers for upper GI cancers'** section for a detailed discussion of appropriate PD-L1 thresholds.
‡Although HER2 status is important for treatment selection for other GI cancers, the only Food and Drug Administration (FDA)-approved indication including ICIs at the time of publication was for esophagogastric cancers.

Microsatellite instability and mismatch repair deficiency

Whole exome sequencing (WES) demonstrates that MSI-H/dMMR tumors have a significantly higher number of mutations than MSS/mismatch repair proficient (pMMR) tumors.[7] MSI predicts response to immune checkpoint blockade for all tumor types, regardless of PD-L1 expression.[16 17] In May 2017, the FDA granted the first tissue-agnostic approval for the use of pembrolizumab for all pretreated, advanced solid MSI-H/dMMR tumors based on a pooled analysis of the KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158 studies. In August 2021, the FDA granted a similar approval for the use of the PD-1 inhibitor dostarlimab for all pretreated, advanced solid dMMR tumors based on the tissue-agnostic GARNET study. Notably, the approval for pembrolizumab includes MSI-H and dMMR tumors whereas dostarlimab is only indicated for dMMR tumors, per the FDA label. This has implications for selection of diagnostic tests as immunohistochemistry (IHC) assays for dMMR will not detect MSI-H. Next-generation sequencing (NGS)-based genomic assays often include assessment of TMB and MSI status, however.

Assays for detecting MSI and dMMR

A number of commercial assays are available to assess MSI status. Polymerase chain reaction (PCR) assays evaluate instability by comparing the size of amplification fragments across known tandem repeat regions from tumor tissue to amplicons from non-tumor tissue.[18 19] Newer PCR assays do not require matched non-tumor tissue in some cases.[20] As there are numerous microsatellite regions throughout the genome, either WES or targeted gene panel-based NGS can also be used to assess microsatellite stability.[21 22] As NGS becomes more widely available, it will likely become the preferred microsatellite stability test given its improved accuracy and sensitivity[23] and the

need to examine multiple targets in a single broad platform. As an example, the FDA approved the FoundationOne CDx MSI assay as a companion diagnostic for the tissue-agnostic approval for pembrolizumab for MSI-H tumors in February 2022.

Mismatch repair deficiency occurs with loss of function or expression of any one of the MLH1, MSH2, MSH6, or PMS2 proteins, which collectively make up the mismatch repair machinery. A deletion of the terminal end of the *EPCAM* gene can result in MSH2 silencing and thus dMMR. Nuclear IHC staining is used to identify MLH1, MSH2, MSH6, and PMS2, with the tumor labeled 'dMMR' if one or more of these mismatch repair proteins cannot be detected. IHC assays may be performed with in-house antibodies and staining protocols. Commercial dMMR assays are available, however, such as the VENTANA MMR RxDx Panel, which is the companion diagnostic approved for use with dostarlimab.

Circulating tumor DNA (ctDNA) offers a potential alternative method for obtaining tumor microsatellite status, particularly when tissue acquisition is unsafe or unfeasible or when the tumor sample is inadequate for tissue-based testing. Although this blood-based technique was not FDA-approved for MSI-H detection at the time of publication of this guideline, excellent concordance with reference tissue-based pentaplex assays has been reported for ctDNA assays for MSI-H,[24] with sensitivities and specificities ranging from 91.8%–98% to 100%, respectively.[25] Furthermore, ctDNA may detect response to ICI therapy 6–10 weeks earlier than standard imaging.[26] Different ctDNA assays have different minimum sample ctDNA thresholds, although one study reported a sensitivity and specificity for MSI-H detection of 94.1% and 100%, respectively, for samples with >0.4% ctDNA obtained from 87 patients with CRC.[25]

Additional considerations for MSI-H/dMMR tumors

On diagnosis of MSI-H/dMMR GI cancers, it is important to distinguish the origin of the tumor's genomic instability (ie, somatic vs germline mutations). For example, only about 12% of sporadic CRCs are MSI-H versus >90% of Lynch syndrome-associated CRCs.[27] Consideration for referral for genetic testing and counseling is particularly pertinent in CRC, pancreatic cancer, any GI cancer occurring as a rare subtype or in the context of a DNA mismatch repair or tumor suppressor gene mutation, patients with a family history of cancer, or for those patients diagnosed with cancer at a young age. Identification of a familial cancer syndrome may affect management and can guide future cancer screening for the affected patient and their family. Several national organizations have published guidelines for genetic risk assessment.[28 29] For example, the US Multi-Society Task Force on Colorectal Cancer strongly recommends mismatch repair testing (either an MSI or MMR assay) for patients with newly diagnosed CRC and genetic evaluation for Lynch syndrome for all patients with a dMMR tumor without MLH1 promoter hypermethylation.[30] If a tumor sample is not available, then germline testing for variants in mismatch repair (or *EPCAM*) genes can be considered.

Tumor mutational burden

In June 2020, the FDA granted a second tissue-agnostic approval for the use of pembrolizumab in the treatment of advanced, pretreated, TMB-H (defined as ≥10 mutations per megabase [mut/Mb] solid tumors, as determined by the FoundationOne CDx assay companion diagnostic test. This approval was based on an analysis of the phase II KEYNOTE-158 study, which enrolled patients with advanced, pretreated solid tumors (n=790 evaluable patients with tissue available for TMB testing). Pembrolizumab demonstrated an improved objective response rate (ORR) in the TMB-H versus TMB-low (TMB-L) population (29% vs 6%) in KEYNOTE-158.[31] However, the study included only 10 (rare) tumors. Importantly, no patients with CRC, esophagogastric cancer, small bowel adenocarcinoma (SBA), pancreatic ductal adenocarcinoma (PDAC), or biliary tract cancer (BTC) were included in the registrational data leading to the approval. For the 14 patients with TMB-H anal cancer included in the efficacy population of KEYNOTE-158, the response rate was only 7%.[32] Furthermore, at the time of the approval, there was controversy about the appropriate TMB cut-off to define the indication. Notably, while the ORR for tumors with TMB >13 mut/Mb in KEYNOTE-158 was 37%, the ORR for tumors with TMB ≥10 mut/Mb to <13 mut/Mb was only 13%.[32] The MyPathway phase IIa, open-label, multicenter basket study demonstrated a similar trend with response rates to atezolizumab (an anti-PD-L1 ICI) of 38.1% (n=42; 95% CI 23.6 to 54.4) and 2.1% (n=48; 95% CI 0.1 to 11.1) for tumor TMB cut-offs of ≥16 mut/Mb and 10–16 mut/Mb, respectively, in 91 immunotherapy-naïve patients with 19 advanced solid tumor types (including CRC, gastroesophageal cancer, BTC, and pancreatic cancer).[33] An analysis including data from 14 different solid tumors demonstrated highly variable means and ranges of TMB across tumor subsites as well as improved neoantigen load prediction with a cancer-specific versus pan-cancer TMB threshold.[34]

Subsequent studies, including a retrospective analysis that included 1,662 patients with advanced solid tumors of multiple tissue origins and histologies who received a variety of ICIs, have demonstrated an association between higher TMB and improved overall survival (OS) after anti-PD-(L)1-based therapy.[35] Notably, the cut-off threshold for high TMB varied across tumor types in this analysis, although the tumors in the top quintile of TMB levels for each histology consistently showed OS benefit with ICIs (with the exception of glioma). Postmarketing studies to evaluate the predictive role of TMB in additional tumor types as well as the most appropriate 'TMB-H' cut-off were ongoing at the time of publication of this manuscript.

TMB assays

Tumor mutational burden is most accurately measured by WES of tumor tissue matched to non-tumor tissue. However,

assessment by NGS of targeted gene panels is a more time-effective and cost-effective method to assess TMB. The number of genes included in targeted panels varies widely, with some including as few as 324 and others as many as 607.[36] Certain cancers, including colon cancer, tend to have greater TMB variability between different NGS panels, but overall TMB assessments from WES and targeted gene panels have correlated well. The Friends of Cancer Research (FOCR) Consortium is working to establish uniform measurement and reporting of TMB as targeted NGS gene panels become more widely available. In phase II of the FOCR Consortium TMB harmonization project, panel sizes >667 kb that had pathogenic variants and potential germline variants filtered out produced the most accurate TMB results based on 29 clinical tumor samples (including colorectal and gastric cancer) and 10 human-derived matched tumor-normal cell lines that were processed for WES at a central laboratory and distributed for TMB estimation across 16 sites.[37] The online, publicly available tmbLab calibration tool derived from The Cancer Genome Atlas (TCGA) data and created as part of the FOCR study may help improve the reproducibility and comparability of TMB panel assays.[38] The FoundationOne CDx test is an NGS panel that was formally approved by the FDA for the assessment of TMB, among other clinically significant genomic biomarkers.[39] Additionally, the FDA has allowed accredited third parties to review and make clearance recommendations to authorize NGS-targeted panels performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.[40]

Although TMB can be obtained from ctDNA and blood samples may be more readily available than tumor tissue, this technique likely overestimates TMB compared with standard tissue sampling. One study reported an 80th percentile blood-based TMB of ≥16 mut/Mb tissue equivalency for most solid tumors studied, which is much higher than historical tissue-based TMBs.[41] The threshold to predict benefit with ICI therapy has also been shown to be higher for blood-based TMB compared with tissue-based methods in non-small cell lung cancer (NSCLC)[42] and advanced, refractory MSS CRC.[43] As such, blood-based TMB assessment was not recommended for patient selection for ICIs outside of a clinical trial at the time of manuscript publication.

GI cancers in pivotal trials for tissue-agnostic indications for ICIs

Patients with GI cancers were variably represented in the pivotal registrational trials leading to tissue-agnostic approvals for ICIs. Although these tissue-agnostic indications may be the only FDA-approved options for using immunotherapy to treat some biomarker-positive GI malignancies, expected response rates are not predictable for tumor types that were under-represented or omitted entirely from these registrational studies. All rare GI tumors that have a high TMB or are MSI-H/dMMR and are lacking treatment options should be considered for ICI therapy regardless of their representation in tissue-agnostic studies, however, outcomes reported for small cohorts must be interpreted with caution. Furthermore, it is important to note that distinct from many other tumors, high TMB in GI cancer is often driven by MSI[44 45] and limited data are available on outcomes with ICIs in tumors that are TMB-H in the absence of MSI. A summary of the data supporting tissue-agnostic approvals for ICIs, including the numbers of patients with GI cancers enrolled, is provided in table 1.

DNA polymerase epsilon and delta (*POLE/POLD1*)

Mutations in *POLE/POLD1* have been associated with an excellent response to ICI therapy even in the absence of MSI.[46 47] Tumors with pathogenic *POLE/POLD1* mutations tend to have a TMB well above 10 mut/Mb,[45 48] which will likely be apparent on TMB testing. At the time of publication, reports have cited TMBs of 31 mut/Mb for *POLE*-mutated cancers with known genomic alterations[48] and 122–303 mut/Mb for *POLE*-associated cancers.[45] In one retrospective cohort analysis of advanced solid tumors with non-synonymous *POLE/POLD1* mutations, the median OS for patients receiving ICI therapy for *POLE/POLD1*-mutant tumors was 34 vs 18 months for patients with *POLE/POLD1*-intact tumors (p=0.004).[46] A prospective study of patients with pMMR solid tumors found that only *POLE* mutations affecting proofreading (eg, mutations in DNA binding or the catalytic site of the exonuclease domain) predicted response to nivolumab monotherapy.[49] These proofreading mutations were associated with high tumor mutational load and increased TILs. One retrospective analysis of 458 tumors with *POLE* mutations demonstrated that 15.0% of these mutations were pathogenic, 15.9% were benign, and 69.1% were variants of unknown significance.[47] Patients who received PD(L)-1-based ICI therapy and whose tumors contained pathogenic *POLE* mutations had an improved clinical benefit rate (82.4% vs 30.0%; p=0.013), median progression-free survival (PFS; 15.1 vs 2.2 months; p<0.001), OS (29.5 vs 6.8 months; p<0.001), and longer duration of response (DOR; median 15.5 vs 2.5 months; p<0.001) compared with those with tumors with benign variants. The efficacy of anti-PD-1 therapy for immunotherapy-naïve patients with non-MSI-H *POLE/POLD1*-mutated advanced solid tumors is being prospectively evaluated in a phase II trial (NCT03810339) in China.

Panel recommendations

- For all patients with a GI cancer, MSI/MMR status and TMB testing (for MSS/pMMR tumors) should be performed on tumor tissue in a CLIA-certified lab (LE:3). MSI status and TMB may be obtained by NGS. MMR status may be obtained by IHC.
- TMB testing should be performed on tumor tissue. At the time of guideline writing, TMB assessment using ctDNA is strictly investigational and may overestimate mutational load (LE:4).
- At the time of guideline writing, PD-L1 expression is not a validated biomarker of response to ICIs for GI cancers outside of esophagogastric cancers (LE:3).

Table 1 FDA tissue-agnostic approvals for immunotherapy

Tissue-agnostic immunotherapy approval	Supporting studies	Biomarker-positive population	Biomarker-positive patients with GI cancers included	Outcome measures for biomarker-positive study population	FDA-approved companion diagnostic
Pembrolizumab for unresectable/ metastatic, MSI-H/dMMR solid tumors that have progressed on prior treatment without satisfactory treatment alternatives (May 23, 2017)	KEYNOTE-016 (NCT01876511) KEYNOTE-164 (NCT02460198) KEYNOTE-012 (NCT01848834) KEYNOTE-028 (NCT02054806) KEYNOTE-158 (NCT02628067)[225]	N=149 patients with MSI-H/ dMMR tumors 15 different tumor types	▶ CRC (n=90) ▶ Biliary (n=11) ▶ Gastric/GEJ (n=9) ▶ Pancreatic cancer (n=6) ▶ Small intestinal cancer (n=8) ▶ Esophageal cancer (n=1)	ORR=39.6% (95% CI 31.7 to 47.9) with 7% CR and 32% PR Responses lasting ≥6 months: 78% (of responding patients)	FoundationOne CDx (for MSI -H)* VENTANA MMR RxDx Panel (for MMR)
Pembrolizumab for unresectable/ metastatic, TMB-H (≥10 mut/Mb) solid tumors that have progressed following prior treatment without satisfactory treatment alternatives (June 16, 2020)	KEYNOTE-158 (NCT02628067)[31]	N=102 patients with TMB-H (≥10 mut/Mb) tumors	Anal cancer (n=14)	ORR=29% (95% CI 21 to 39) with 4% CR and 25% PR Responses lasting ≥12 months: 57% (of responding patients) Responses lasting ≥24 months: 50% (of responding patients)	FoundationOne CDx
Dostarlimab-gxly for recurrent or advanced dMMR solid tumors progressed on or following prior treatment with no satisfactory treatment alternatives (August 17, 2021)	GARNET (NCT02715284)[110]	N=209 patients with dMMR tumors	▶ CRC (n=69) ▶ Small intestine cancer (n=12) ▶ Gastric cancer (n=8) ▶ Pancreatic carcinoma (n=4) ▶ Liver cancer (n=2) ▶ Biliary neoplasm (n=1) ▶ Esophageal cancer (n=1) ▶ Gallbladder cancer (n=1) ▶ Unknown origin possibly GI tract (n=1)	ORR=41.6% (95% CI 34.9 to 48.6) with 9.1% CR and 32.5% PR Median DOR=34.7 months (range 2.6–35.8+) Responses lasting ≥6 months: 95.4% of responding patients	VENTANA MMR RxDx Panel

Data presented in this table are based on data available at the time of each corresponding FDA approval.
*Original FDA approval did not specify a companion diagnostic. Approval was granted to the FoundationOne CDx for assessment of MSI status on February 21, 2022.
CI, confidence interval; CR, complete response; CRC, colorectal cancer; dMMR, mismatch repair deficiency; DOR, duration of response; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; GI, gastrointestinal; MSI-H, high microsatellite instability; mut/Mb, mutations/megabase; ORR, objective response rate; PR, partial response; TMB-H, high tumor mutational burden.

- For all patients with advanced GI cancer, tumor tissue evaluation by NGS is recommended, if feasible. NGS testing is particularly encouraged for tumors known to have actionable mutations or when results may determine clinical trial eligibility.

ESOPHAGEAL/GASTROESOPHAGEAL JUNCTION/GASTRIC CANCER

In 2022, there were an estimated 20,640 new cases of and 16,410 deaths due to esophageal cancer in the US alone.[1] For all stages combined, the 5-year relative survival rate for esophageal cancer diagnosed in the US between 2010 and 2016 was just 20%. Until recently, the mainstay of esophageal cancer treatment was chemotherapy, with some additional survival benefit with the addition of VEGF or HER2 inhibitors in select patients.[50 51] In 2021, the FDA approved multiple new indications for the use of ICIs to treat esophageal (and gastroesophageal junction [GEJ]) cancer in both the adjuvant and metastatic settings. When used in combination with chemotherapy (esophageal adenocarcinoma or esophageal squamous cell carcinoma [ESCC]) or CTLA-4 inhibitors (ESCC) in the first line or as monotherapy in the second line (ESCC), PD-1 inhibitors significantly prolong survival.[52–55]

In 2022, gastric cancer accounted for an estimated 26,380 new cases and 11,090 deaths in the US alone.[1] The 5-year relative survival rates for gastric cancer are just 32% for all stages combined, and 5.5% for distant metastatic disease.[56] In 2021, PD-1 inhibitors gained FDA-approved indications for the frontline treatment of gastric (and GEJ) adenocarcinoma in combination with chemotherapy and anti-HER2 agents (when indicated).[53 57] However, global studies of anti-PD-(L)1 monotherapy in untreated and pretreated gastric cancer and as maintenance following induction chemotherapy have all failed to demonstrate a survival benefit versus chemotherapy.[58–60] In the ATTRACTION-2 study, which enrolled patients only from Japan, South Korea, and Taiwan with advanced, pretreated (≥2 prior lines of chemotherapy) gastric or GEJ adenocarcinoma, survival benefit was observed with nivolumab monotherapy versus placebo (median OS 5.26 vs 4.14 months; HR 0.62; 95% CI 0.51 to 0.76; p<0.0001).[61] In the US, however, there was a voluntary withdrawal of the indication for third-line pembrolizumab monotherapy for advanced gastric cancer based on an April 2021 FDA Oncologic Drugs Advisory Committee (ODAC) recommendation.[62]

Diagnostic tests and biomarkers for upper GI cancers

Upper GI malignancies that are MSI-H/dMMR have demonstrated superior survival outcomes in response to ICIs in tissue-agnostic studies,[7] and in subgroup analyses of registration trials enrolling all molecular subtypes.[53] A post hoc analysis of patients with MSI-H gastric and GEJ cancer enrolled in KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 demonstrated a survival benefit for pembrolizumab with or without chemotherapy, regardless of line of treatment.[63] Although all pretreated, unresectable or metastatic TMB-H gastric and esophageal cancers are included in the FDA tissue-agnostic indication for pembrolizumab monotherapy, neither cancer was among the 10 tumor types included in KEYNOTE-158.[31] For more details on assays and indications based on MSI-H/dMMR and TMB-H, refer to the **'Tissue-agnostic indications for immunotherapy in the treatment of GI cancer'** section.

Histology

While squamous cell carcinoma is the most common histology of esophageal cancer worldwide, adenocarcinomas account for about 80% of esophageal cancers in the US.[10] ESCCs are enriched for PD-L1 expression,[64] but this subgroup of tumors has been historically understudied in the US due to trial inclusion of exclusively adenocarcinomas or a combination of both histologies.[65] In recent years, however, squamous histology has gained increasing representation in clinical trials in the US. The KEYNOTE-590 trial evaluating first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer included 749 patients, 76% of whom had ESCC. In this study, HRs for survival and ORRs for ESCC versus esophageal adenocarcinoma were comparable.[52] Furthermore, the CheckMate 648 and ESCORT-1st studies enrolled exclusively for ESCC and demonstrated benefit for PD-1 inhibitor combinations in the first-line.[6 8] Although not directly compared, the HR for survival for nivolumab plus chemotherapy versus chemotherapy alone was comparable for ESCC in CheckMate 648 compared with the analogous CheckMate 649 study of (HER2-positive excluded) upper GI adenocarcinomas.[6 53]

PD-L1 expression

PD-L1 expression is an important biomarker for upper GI malignancies. While some pivotal studies have demonstrated improved outcomes for upper GI tumors with higher PD-L1 expression, benefit is often maintained in the all-comers populations.[6 52 53 57 58] However, the survival benefit demonstrated for PD-L1-unselected study populations is likely driven by tumors with higher PD-L1 expression. For example, although the OS benefit for the addition of nivolumab to chemotherapy was significant for all patients with esophagogastric adenocarcinoma randomized in the CheckMate 649 study (HR 0.80; 95% CI 0.71 to 0.90), this survival advantage did not achieve statistical significance in an exploratory subgroup analysis of combined positive score (CPS) <5 tumors (unstratified HR 0.94; 95% CI 0.78 to 1.13).[53] And while the FDA has approved the use of frontline anti-PD-1 plus chemotherapy regimens for esophagogastric cancers regardless of PD-L1 expression, the European Commission has limited the indication to only tumors with CPS ≥5 (for esophagogastric adenocarcinomas) or tumor proportion score (TPS) ≥1 (for ESCC).

ICI trials of upper GI cancers have used a variety of PD-L1 antibodies and assay platforms. For example, the Dako PD-L1 IHC 28-8 pharmDx TPS assay was

used in CheckMate 648 whereas the Dako PD-L1 IHC 22C3 pharmDx CPS assay was used in KEYNOTE-590 and KEYNOTE-181 and was later FDA-approved as a companion diagnostic for determining PD-L1 status for the use of pembrolizumab for advanced, pretreated ESCC. Furthermore, international studies have used PD-L1 assays not commonly used in the US. For example, the ESCORT-1st study used the Chinese-based 6E8 antibody TPS assay (Shuwen Biotech).[65] As more ICIs are approved and their application to upper GI malignancies is broadened, it is imperative to further characterize and reconcile these PD-L1 assays. Lack of harmonization of PD-L1 expression assays is problematic. The Blueprint Programmed Death Ligand 1 Immunohistochemistry Comparability Project is a collaborative effort to assess the feasibility of harmonizing commercially available PD-L1 immunohistochemical assays: 22C3, 28-8, VENTANNA PD-L1 (SP142), VENTANNA PD-L1 (SP263), and Dako PD-L1 IHC 73-10. The Blueprint phase II analysis of 81 lung cancer specimens stained with all five of these assays revealed a high level of staining concordance between the 22C3, 28-8, and SP263 antibodies.[66] Among an international panel of pathologists, there was strong reliability in tumor cell PD-L1 scoring (intraclass correlation coefficient [ICC] 0.86–0.93) but poor reliability for immune cell PD-L1 scoring (ICC 0.18–0.19); agreement in PD-L1 assessment from cytological cell blocks was good (ICC 0.78–0.85). The Blueprint phase II data have demonstrated some concordance between assays in lung cancer, however, PD-L1 is a dynamic biomarker and small, comparative PD-L1 assay concordance studies for gastric cancer are conflicting. For example, in one analysis of 226 patients with gastric adenocarcinoma who underwent curative-intent gastrectomy, concordance between the 22C3 and 28-8 assays was good (Cohen's kappa=0.881) using a CPS cut-off of 5 but did vary with different CPS cut-offs (Cohen's kappa=0.735 with CPS cut-off 1; Cohen's kappa=0.837 with CPS cut-off 10).[67] In a more recent analysis of 362 biopsy and resection samples taken from patients with stage I–IV gastric cancer, however, the paired CPS scores obtained with the 28-8 assay were much higher than those obtained with the 22C3 assay (CPS ≥1: 70.3% vs 49.4%, p<0.001; CPS ≥5: 29.1% vs 13.4%, p<0.001; CPS ≥10: 13.7% vs 7.0%, p=0.004), with only moderate concordance (Gwet's kappa=0.598) between these two assays at a CPS cut-off of ≥5.[68] At the time of publication, the 22C3 assay was validated for esophagogastric adenocarcinomas, while both the 22C3 and 28-8 assays were validated for ESCC.

Human epidermal growth factor receptor 2 (HER2) expression

HER2 overexpression occurs in about 20% of advanced gastric and GEJ adenocarcinomas and about 26% of esophageal adenocarcinomas.[69 70] The KEYNOTE-811 study demonstrated that anti-HER2 agents can be safely and effectively used with chemo-immunotherapy, leading to FDA accelerated approval for this combination in the first line (for a detailed discussion of KEYNOTE-811, refer to the **'Immunotherapy for treatment-naïve disease'** section). In fact, synergy may exist between HER2 inhibition and ICIs as trastuzumab has been shown to upregulate PD-1 and PD-L1 expression, as well as increase TILs.[57] However, there are no data to suggest that HER2 overexpression itself correlates with PD-L1 expression.[71]

Epstein-Barr virus (EBV) status

EBV infection is another characteristic of some upper GI malignancies that may play a role in predicting response to ICIs. Specifically, EBV-positive gastric cancers are characterized by enhanced immune cell infiltration and often amplification of genes encoding PD-L1 and PD-L2, and these viral-associated cancer cells exhibit higher PD-L1 expression on tumor and immune cells.[72] In a study of 57 evaluable Korean patients with advanced, pretreated gastric cancer, the ORR to pembrolizumab monotherapy was 24.6%. However, the ORR for the six patients with EBV-positive gastric cancer was 100%, with a median DOR of 8.5 months.[73] Of note, all of the EBV-positive tumors had high PD-L1 expression by CPS. In an analysis of patients with advanced gastric cancer who received subsequent-line anti-PD-1 therapy, the median PFS and ORRs were 3.7 months and 33% vs 1.9 months and 13% for patients with EBV-positive (n=6) vs EBV-negative tumors (n=78), respectively.[74] Of note, this PFS advantage demonstrated by patients with EBV-positive cancers did not achieve statistical significance (HR 0.48; 95% CI 0.22 to 1.05; p=0.064). Therefore, based on the limited available data for EBV-positive gastric tumors, and the overlap with PD-L1 expression, routine EBV testing is not recommended.

Intrapatient biomarker heterogeneity

Available data suggest that there is imperfect concordance between TMB assessment from tissue-based versus blood-based samples (for more details on TMB in blood versus tissue samples, see the **'Tissue-agnostic indications for immunotherapy in the treatment of GI cancer'** section). Spatial and temporal differences in biomarker expression have been observed as well. A retrospective analysis of 211 patients with stage II–IV gastroesophageal adenocarcinoma demonstrated a concordance of just 61% between PD-L1 expression obtained from paired intrapatient baseline primary tumor and a metastatic site (median time between biopsies 14.5 days).[75] The concordance between paired primary and metastatic site was similarly low (69%) for TMB level (median time between biopsies 17 days). Furthermore, heterogeneity in tumor PD-L1 expression and TMB were observed before versus after treatment with chemotherapy (57%–63% concordance for PD-L1, 73%–75% concordance for TMB). The number of patients treated with ICIs in this cohort was too small to determine if changes in PD-L1 or TMB-H status correlated with response. Although data suggest that PD-L1 and TMB results differ depending on where and when biopsy tissue was obtained, there are no data to inform treatment with ICIs when these biomarkers

demonstrate heterogeneity within the same patient. In general, higher PD-L1 expression likely predicts a greater likelihood of benefit with ICIs and there is equipoise to giving ICIs when a positive and negative PD-L1 score exist on different tissue samples for the same patient. However, intrapatient biomarker heterogeneity needs to be considered on a case-by-case basis accounting for the timing of the biopsies, the degree of biomarker positivity, and patient comorbidities.

Panel recommendations

- All patients with esophagogastric cancers should undergo tumor testing for PD-L1 expression (LE:2) and MSI-H/dMMR status (LE:3). TMB (LE:3) should also be considered. For patients with esophagogastric adenocarcinomas, tumor tissue should also be tested for HER2 expression (LE:2).
- For patients with esophagogastric cancers, PD-L1 expression testing should be performed using a validated antibody. At the time of writing, the 22C3 and 28-8 antibodies are both validated.
- For patients with esophagogastric adenocarcinoma, CPS is the most established scoring system used to quantify PD-L1 expression (LE:2). For ESCC, both CPS and TPS are valid approaches to determine eligibility for ICI therapy (LE:2).
- For patients with esophagogastric cancers, routine EBV testing is not currently recommended for ICI treatment determination.

Immunotherapy in the management of resectable upper GI cancer

Neoadjuvant chemotherapy and radiation have improved esophageal cancer survival outcomes following curative-intent esophagectomy,[76] however, pathological complete response (pCR) rates following neoadjuvant therapy remain low and recurrence rates remain higher among those who do not achieve a pCR.[77] The addition of adjuvant ICIs is becoming the new SOC for upper GI malignancies. In the double-blind CheckMate 577 phase III trial evaluating adjuvant nivolumab for resected (R0) stage II or III esophageal or GEJ cancer, 794 patients who had received neoadjuvant chemoradiation and had residual pathological disease at the time of esophagectomy were randomized 2 to 1 to nivolumab or placebo for up to 1 year.[78] After a minimum follow-up of 14 months, median disease-free survival (DFS), the primary study end point, was significantly longer for the nivolumab group compared with the placebo group (22.4 vs 10.4 months; HR 0.67; 95% CI 0.55 to 0.81).[78] This trend was observed across multiple subgroups, however, benefit seemed to be higher in tumors with a PD-L1 CPS ≥5 vs PD-L1 CPS <5 (HR 0.62 vs 0.89) in a post hoc analysis of DFS.[79] Furthermore, the median distant metastases-free survival was 29.4 vs 16.6 months for the nivolumab group compared with the placebo group (HR 0.71; 95% CI 0.58 to 0.87). Median time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death (PFS2) was also improved for the nivolumab versus placebo group (not reached vs 32.1 months).[80] Grade 3–4 treatment-related adverse events (TRAEs) were slightly higher in the nivolumab arm (14%) compared with the placebo arm (6%), however, there were no treatment-related deaths in either arm.

In May 2021, CheckMate 577 was the basis of the FDA approval for the use of adjuvant nivolumab for patients with completely resected esophageal/GEJ cancer who do not achieve a pCR following neoadjuvant chemoradiation. Adjuvant nivolumab plus ipilimumab versus chemotherapy is being evaluated for high risk (R1 or ypN1 to 3) resected esophageal, GEJ, and gastric cancer in the European Organisation for Research and Treatment of Cancer (EORTC) VESTIGE study, with results pending at the time of manuscript publication.[81] Other studies are evaluating the efficacy and safety of perioperative ICI strategies, including the phase III KEYNOTE-585 study of neoadjuvant plus adjuvant pembrolizumab or placebo plus chemotherapy for GEJ and gastric cancer.[82]

Panel recommendations

- For all patients with resectable esophagogastric cancers, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with resected (R0) stage II or III esophageal or GEJ cancers who received neoadjuvant CRT and have residual pathological disease, adjuvant nivolumab is a SOC option (LE:2).

Immunotherapy in the management of unresectable/metastatic upper GI cancer

ICIs, specifically anti-PD-1-based regimens, are approved as upfront treatments as well as subsequent-line options for esophagogastric cancers. Data supporting FDA approvals are summarized in this manuscript and an algorithm to support clinical decision-making for the treatment of stage IV esophagogastric cancers is provided in figure 1.

Immunotherapy for treatment-naïve disease

Five checkpoint inhibitor indications were approved by the FDA specifically for the first-line treatment of advanced, esophagogastric cancers at the time of manuscript publication. Distinctions in indication based on tumor location, histology, and HER2 expression status are included in the label due to differences in the enrolled populations in the registrational trials. Data from pivotal trials supporting these approvals as well as approvals for pretreated disease are summarized in table 2 and table 3, respectively.

In March 2021, the FDA approved the frontline use of pembrolizumab in combination with platinum plus fluoropyrimidine chemotherapy for the treatment of locally advanced or metastatic esophageal (adenocarcinoma or squamous cell carcinoma) and Siewert type 1 GEJ (epicenter of tumor 1–5 cm above the GEJ) cancers that are not amenable to chemoradiation or surgery. This

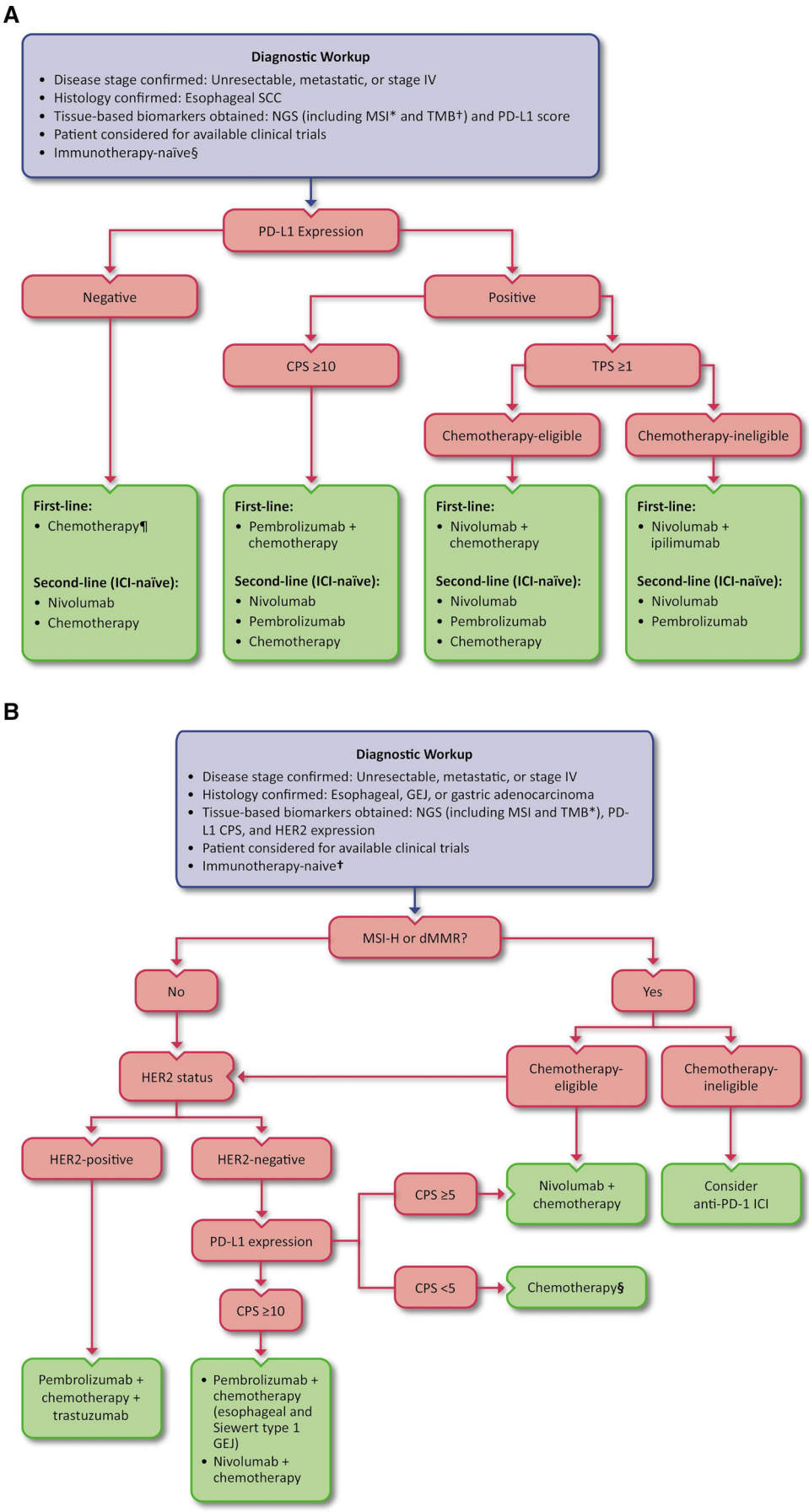

Figure 1 (Continued)

Figure 1 Advanced esophagogastric diagnostic testing and treatment algorithm. (A) Advanced esophageal squamous cell carcinoma. *ESCC is rarely reported as MSI-H/dMMR in global studies.[226] However, the reported frequency of ESCC that is MSI-H/dMMR in studies of Asian patients is much higher.[227 228] All patients who are chemotherapy eligible with advanced, MSI-H/dMMR ESCC should receive chemotherapy plus an anti-PD-1 inhibitor in the first line and should be considered for pembrolizumab monotherapy or dostarlimab monotherapy (for dMMR disease only) following progression of disease on a non-immunotherapy regimen. †Patients with advanced ESCC that is TMB-H (≥10 mut/Mb) may be considered for pembrolizumab monotherapy following progression of disease on a non-immunotherapy regimen. §For patients whose disease progresses on a regimen containing immunotherapy, consideration for clinical trial is preferred. If clinical trial enrollment is not feasible, then guidelines-directed subsequent therapy is recommended. ¶Although the FDA-approved frontline nivolumab+chemotherapy and pembrolizumab+chemotherapy for ESCC regardless of tumor PD-L1 expression, outcomes from CheckMate 648 and KEYNOTE-590 suggest that superiority compared with chemotherapy is most pronounced in patients with tumors with a TPS ≥1 or a CPS ≥10, respectively. (B) Advanced esophageal adenocarcinoma, GEJ, or gastric carcinomas. *Patients with tumors that are MSI-H/dMMR may be considered for pembrolizumab monotherapy or dostarlimab monotherapy (for dMMR disease only) following progression of disease on a non-immunotherapy regimen. Patients with tumors that are TMB-H (≥10 mut/Mb) may be considered for pembrolizumab monotherapy following progression of disease on a non-immunotherapy regimen. †For patients whose disease progresses on a regimen containing immunotherapy, consideration for clinical trial is preferred. If clinical trial enrollment is not feasible, then guidelines-directed subsequent therapy is recommended. §Although the FDA has approved nivolumab+chemotherapy for esophageal, GEJ, or gastric adenocarcinoma regardless of tumor PD-L1 expression, data from CheckMate 649 suggest that this benefit is driven by tumors with a CPS ≥5. Use of an ICI in combination with chemotherapy for patients with esophagogastric adenocarcinomas with CPS <5 may be considered on a case-by-case basis. CPS, combined positive score; dMMR, mismatch repair deficiency; ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; ICI, immune checkpoint inhibitor; MSI-H, high microsatellite instability; mut/Mb, mutations per megabase; NGS, next-generation sequencing; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; TMB-H, high tumor mutational burden.

approval was based on improved survival with the addition of pembrolizumab to chemotherapy in the phase III, double-blind KEYNOTE-590 study.[52] A total of 749 patients with untreated, advanced/unresectable esophageal and GEJ carcinoma were randomized 1:1 to receive pembrolizumab plus chemotherapy (cisplatin plus fluoropyrimidine) versus placebo plus chemotherapy, and were stratified according to geographical location, histology, and performance status. Primary survival end points differed between subgroups. OS alone was evaluated in patients with ESCC and PD-L1 CPS ≥10, while OS and PFS were evaluated in patients with ESCC, patients with PD-L1 CPS ≥10, and all randomized patients. With a median follow-up of 22.6 months, median OS was significantly improved with pembrolizumab plus chemotherapy versus placebo plus chemotherapy in all subgroups: 13.9 vs 8.8 months with a HR of 0.57 for ESCC and PD-L1 CPS ≥10 (95% CI 0.43 to 0.75; p<0.0001); 12.6 vs 9.8 months with a HR of 0.72 for esophageal SCC (95% CI 0.60 to 0.88; p=0.0006); 13.5 vs 9.4 months with a HR of 0.62 for carcinomas with a PD-L1 CPS ≥10 (95% CI 0.49 to 0.78; p<0.0001); and 12.4 vs 9.8 months with a HR of 0.73 for all randomized patients (95% CI 0.62 to 0.86; p<0.0001). The addition of pembrolizumab to chemotherapy also demonstrated a significant improvement in median PFS for the prespecified subgroups in which it was evaluated: 6.3 vs 5.8 months with a HR of 0.65 for esophageal SCC (95% CI 0.54 to 0.78; p<0.0001); 7.5 vs 5.5 months with a HR of 0.51 for PD-L1 CPS ≥10 (95% CI 0.41 to 0.65; p<0.0001); and 6.3 vs 5.8 months with a HR of 0.65 for all randomized patients (95% CI 0.55 to 0.76; p<0.0001). Grade ≥3 TRAE rates were similar for pembrolizumab plus chemotherapy (72%) and placebo plus chemotherapy (68%).

A significant OS and PFS benefit was demonstrated with the addition of pembrolizumab to chemotherapy (5-FU plus cisplatin or capecitabine plus oxaliplatin) in KEYNOTE-859, a placebo-controlled study that enrolled 1,579 treatment-naïve patients with HER2-negative, locally advanced, unresectable or metastatic gastric or GEJ adenocarcinoma.[83] Randomization was stratified by region, PD-L1 CPS (<1 vs ≥1), and chemotherapy regimen. With a median follow-up of 31.0 months, median OS (the study's primary end point) was 12.9 vs 11.5 months (HR 0.78; 95% CI 0.70 to 0.87; p<0.0001), median PFS was 6.9 vs 5.6 months (HR 0.76; 95% CI 0.67 to 0.85; p<0.0001), and ORR was 51.3% vs 42.0% (p=0.00009). Responses were notably consistent across PD-L1 subgroups. Grade ≥3 TRAEs occurred in 59.4% vs 51.1% of patients treated with chemotherapy plus pembrolizumab versus chemotherapy plus placebo, respectively. These data were presented in February 2023 at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium. First-line chemotherapy plus pembrolizumab was not FDA-approved for advanced gastric adenocarcinoma at the time of guideline publication. In April 2021, the FDA approved nivolumab plus fluoropyrimidine-containing and platinum-containing chemotherapy for advanced/metastatic gastric, GEJ, and esophageal adenocarcinoma based on the phase III, double-blind Checkmate 649 study, which randomized 1,581 patients with untreated, advanced, non-HER2-positive, unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma 1:1:1 to receive nivolumab plus chemotherapy (capecitabine and oxaliplatin or leucovorin, fluorouracil, and oxaliplatin), nivolumab plus ipilimumab, or chemotherapy alone.[53] With a median follow-up of 13.1 months (interquartile range [IQR] 6.7–19.1) for nivolumab plus chemotherapy

Table 2 Landmark trials leading to FDA approvals for ICIs used to treat unresectable/metastatic, *treatment-naïve* esophagogastric cancers

Trial	Study arms	Study population	Stratification factors	Outcome measures used for FDA approval*
KEYNOTE-590 NCT03189719 (phase III, double-blind)	Pembrolizumab plus chemo (n=373) vs chemo (5-FU+cisplatin) (n=376)	E, GEJ Siewert type 1; SCC or AC; HER2 testing not required	Geographical region (Asia vs non-Asia), PS, histology	Median OS for all randomized: 12.4 vs 9.8 mo; HR 0.73 (0.62 to 0.86); p<0.0001 Median PFS for all randomized: 6.3 vs 5.8 mo; HR 0.65 (0.55 to 0.76); p<0.0001
CheckMate 649 NCT02872116 (phase III, open-label)	Nivolumab plus chemo (n=789)† vs chemo (XELOX or FOLFOX) (n=792)	E, GEJ, G; AC; HER2-negative or unknown	PD-L1 status assessed by 28-8 pharmDx assay with primary population amended from TPS ≥1 to CPS ≥5 during enrollment, geographical region (Asia vs USA and Canada vs rest of world), PS (0 vs 1), and type of chemotherapy (XELOX vs FOLFOX)	Median OS for CPS ≥5: 14.4 vs 11.1 mo (HR 0.71 (98.4% CI 0.59 to 0.86); p<0.0001) PFS by RECIST V.1.1 BICR for CPS ≥5: 7.7 vs 6.0 mo (HR 0.68 (0.58 to 0.79); p<0.0001) Median OS for all randomized: 13.8 vs 11.6 mo (HR 0.80 [0.71 to 0.90]; p=0.0002)
KEYNOTE-811 NCT03615326 (phase III, double-blind)	Pembrolizumab plus chemo plus trastuzumab (n=217) vs chemo (5-FU/cisplatin or capecitabine/ oxaliplatin) plus trastuzumab (n=217)	GEJ, G; AC; HER2-positive	Geographic region (Australia/ Europe/Israel/North America vs Asia vs rest of world), PD-L1 CPS (≥1 vs <1), and ICC (5-FU plus cisplatin vs capecitabine plus oxaliplatin)	ORR by RECIST V.1.1 BICR: 74.4% vs 51.9%; one-sided p<0.0001
CheckMate 648 NCT03143153 (phase III, open-label)	Nivolumab plus chemo (n=321) Nivolumab plus ipilimumab (n=325) Chemo (5-FU+cisplatin) (n=324)	ESCC (including adenosquamous cell carcinoma)	Tumor cell PD-L1 status (≥1% vs <% or indeterminate), geographical region (East Asia (Japan, Korea, Taiwan) vs rest of Asia vs rest of world), ECOG PS (0 vs 1), and number of organs with metastases (≤1 vs ≥2)	Nivolumab plus chemo versus chemo: Median OS for PD-L1 ≥1%: 15.4 vs 9.1 mo (HR 0.54 [99.5% CI 0.37 to 0.80]; p<0.001) Median OS for overall population: 13.2 vs 10.7 mo (HR 0.74 [99.1% CI 0.58 to 0.96]; p=0.002) Median PFS for PD-L1 ≥1%: 6.9 vs 4.4 mo (HR 0.65 [98.5% CI 0.46 to 0.92]; p=0.002) Median PFS for overall population: 5.8 vs 5.6 mo (HR 0.81 [98.5% CI 0.64 to 1.04]; p=0.04) Nivolumab plus ipilimumab versus chemo: Median OS for PD-L1 ≥1%: 13.7 vs 9.1 mo (HR 0.64 [98.6% CI 0.46 to 0.90]; p=0.001) Median OS for overall population: 12.7 vs 10.7 mo (HR 0.78 [98.2% CI 0.62 to 0.98]; p=0.01) Median PFS for PD-L1 ≥1%: 4.0 vs 4.4 mo (HR 1.02 [98.5% CI 0.73 to 1.43]; p=0.90) Median PFS for overall population: not tested

CIs are 95% unless stated otherwise.
*Outcomes for the experimental arm are always presented first.
†CheckMate 649 also included a nivolumab plus ipilimumab arm, which did not meet its end point.
AC, adenocarcinoma; BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; E, esophageal; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; 5-FU, 5-fluorouracil; G, gastric; GEJ, gastroesophageal junction; HR, hazard ratio; ICC, investigator's choice chemotherapy; mo, months; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance status; RECIST, Response evaluation criteria in solid tumors; SCC, squamous cell carcinoma; XELOX, capecitabine and oxaliplatin.

Table 3 Landmark trials leading to FDA approvals for ICIs used to treat unresectable/metastatic, *previously treated* esophagogastric cancers

Trial	Study arm(s)	Study population*	Stratification factors	Outcome measures used for FDA approval†
KEYNOTE-059‡ NCT02335411 (phase II, single-arm, multicohort) Indication withdrawn	Pembrolizumab monotherapy, cohort 1 (n=143)§	Patients with tumors that are: ▶ Progressed after ≥2 prior lines of therapy, including prior 5-FU plus platinum doublet ▶ GEJ Siewert types II and III and G AC, HER2-negative or HER2-positive and previously treated with trastuzumab ▶ PD-L1 CPS ≥1 ▶ MSS or unknown MSI/MMR status	Not applicable	ORR: 13.3% (8.2, 20.0) DOR for responders: ranged from 2.8+ to 19.4+ mo; DOR ≥6 mo 58%; DOR ≥12 mo 26%
KEYNOTE-180 NCT02559687 (phase II, single-arm)	Pembrolizumab monotherapy (n=121)	Patients with tumors that are: ▶ ≥2 prior lines of therapy ▶ E SCC or AC, GEJ Siewert type I AC ▶ HER2 status not specified	Not applicable	ORR for ESCC and CPS ≥10: 20% (8, 37) DOR for ESCC and CPS ≥10: range 4.2 to 25.1+ mo; DOR ≥6 mo 71%; DOR ≥12 mo 57%
KEYNOTE-181 NCT02564263 (phase III, open-label)¶	Pembrolizumab monotherapy (n=314) vs ICC (paclitaxel, docetaxel, or irinotecan) (n=314)	Patients with tumors that are: ▶ 1 prior line of therapy ▶ ESCC or AC, GEJ Siewert type I AC ▶ HER2-negative for GEJ	Histology and geographic region (Asia vs rest of world)	Median OS for ESCC and CPS ≥10: 10.3 vs 6.7 mo (HR 0.64 [0.46 to 0.90]) Median OS ESCC: 8.2 vs 7.1 mo (HR 0.78 [0.63 to 0.96]; p=0.0095) Median OS CPS ≥10: 9.3 vs 6.7 mo; (HR 0.69 [0.52 to 0.93]; p=0.0074) Median OS all randomized: 7.1 vs 7.1 mo (HR 0.89 [0.75 to 1.05]; p=0.0560)
ATTRACTION-3 NCT02569242 (phase III, open-label)	Nivolumab monotherapy (n=210) vs ICC (paclitaxel or docetaxel) (n=209)	Patients with tumors that are: ▶ 1 prior line of therapy, including prior 5-FU and platinum ▶ E, GEJ SCC, adenosquamous	Geographical region (Japan vs rest of the world), number of organs with metastases (≤1 vs ≥2), PD-L1 expression (<1% vs ≥1%)	Median OS: 10.9 vs 8.4 mo (HR 0.77 [0.62 to 0.96]; p=0.0189) ORR (investigator-assessed): 19.3% (nivolumab) vs 21.5% (chemo) Median DOR: 6.9 mo (5.4 to 11.1) vs 3.9 mo (2.8 to 4.2)

CIs are 95% unless stated otherwise.
*No patients in the study populations had prior treatment with ICIs in earlier lines of therapy.
†Outcomes for the experimental arm are always presented first, when applicable.
‡The FDA approval for third-line pembrolizumab monotherapy for PD-L1-positive, unresectable/metastatic G/GEJ AC was withdrawn following an ODAC review of data from the phase II KEYNOTE-061 and KEYNOTE-062 studies along with consideration of the changing landscape of gastric cancer treatment.
§Total study enrollment for KEYNOTE-059 was n=259, however, the FDA approval in 2017 was based on outcomes observed for cohort 1 (n=143).
¶The FDA approval was based on results of both the phase II KEYNOTE-180 and phase III KEYNOTE-181 studies.
AC, adenocarcinoma; CI, confidence interval; CPS, combined positive score; DOR, duration of response; E, esophageal; ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; 5-FU, 5-fluorouracil; G, gastric; GEJ, gastroesophageal junction; HR, hazard ratio; ICC, investigator's choice of chemotherapy; MMR, mismatch repair deficiency; MSS, microsatellite stable; ODAC, Oncologic Drugs Advisory Committee; ORR, objective response rate; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma.

and 11.1 months (IQR 5.8–16.1) for chemotherapy alone, the addition of nivolumab to chemotherapy significantly improved median OS (HR 0.71; 98.4% CI 0.59 to 0.86; p<0.0001) and PFS (HR 0.68; 98% CI 0.56 to 0.81; p<0.0001) for patients with a PD-L1 CPS ≥5. With a minimum follow-up of 24 months, the benefit of adding nivolumab to chemotherapy continued for both median PFS (HR 0.75; 95% CI 0.67 to 0.84)) and median OS (HR 0.66; 95% CI 0.56 to 0.77) for the CPS ≥10 subgroup.[84] The rate of grade 3–4 TRAEs was 59% for nivolumab plus chemotherapy and 44% for chemotherapy alone. With an additional 12 months of follow-up, the median OS benefit with the addition of nivolumab to chemotherapy persisted for patients with PD-L1 CPS ≥5 (14.4 vs 11.1 months; HR 0.70; 95% CI 0.61 to 0.81) and for all randomized patients (13.8 vs 11.6 months; HR 0.79; 95% CI 0.71 to 0.88).[85] Although the FDA approval for this indication did not stipulate a CPS cut-off, the efficacy of frontline nivolumab plus chemotherapy may be lower for adenocarcinomas with a CPS <5. While the addition of nivolumab to chemotherapy for patients with a tumor PD-L1 CPS <5 resulted in a numerically higher ORR (55% vs 46%), the addition of nivolumab did not improve the OS or PFS for this subgroup in exploratory analyses (unstratified HRs for OS 0.94 [95% CI 0.78 to 1.13] and PFS 0.93 [95% CI 0.76 to 1.12]).[53] The nivolumab plus ipilimumab arm stopped enrollment early due to higher rates of toxicity compared with the other arms, and with a minimum follow-up of 35.7 months, the OS end point for this group was not met (11.7 months for nivolumab plus ipilimumab vs 11.8 months for chemotherapy alone; HR 0.91; 95% CI 0.77 to 1.07). Notably, while median OS for

nivolumab plus ipilimumab versus chemotherapy alone was not significantly different for patients with PD-L1 CPS ≥5 (11.2 vs 11.6 months), a trend toward increased survival was observed in the subgroup of patients with MSI-H tumors. The results of CheckMate 649 contrast slightly with the phase II/III ATTRACTION-4 study, in which the addition of nivolumab to chemotherapy (oxaliplatin with either S-1 or capecitabine) demonstrated a PFS benefit (HR 0.68; 98.51% CI 0.51 to 0.90; p=0.0007) but not an OS benefit (HR 0.90; 95% CI 0.75 to 1.08; p=0.26; median follow-up 26.6 months) for 724 patients in Japan, South Korea, and Taiwan with untreated HER2-negative gastric and GEJ adenocarcinoma.[86]

Providers are faced with a choice between either nivolumab or pembrolizumab in combination with chemotherapy for advanced, HER2-negative, esophageal or GEJ adenocarcinoma. A survival benefit with anti-PD-1 in combination with chemotherapy was demonstrated in both CheckMate 649 and KEYNOTE-590, and there are no data indicating that checkpoint inhibitors of the same class and target have differing efficacy. Therefore, this expert panel recommends that the choice between nivolumab plus chemotherapy versus pembrolizumab plus chemotherapy be determined by the availability of each agent and the corresponding PD-L1 assay.

In May 2021, the FDA granted accelerated approval for the frontline use of pembrolizumab in combination with trastuzumab and chemotherapy for advanced/metastatic HER2-positive gastric and GEJ adenocarcinoma based on the results of KEYNOTE-811.[57] In this phase III, double-blind study patients with previously untreated, HER2-positive, unresectable/metastatic gastric and GEJ adenocarcinomas were randomized 1:1 to receive pembrolizumab or placebo in addition to SOC trastuzumab plus chemotherapy (5-fluorouracil [5-FU] and cisplatin or capecitabine and oxaliplatin). At first interim analysis (264 patients enrolled, median follow-up 12.0 months), the ORR (secondary end point) was 74.4% for pembrolizumab plus SOC vs 51.9% for placebo plus SOC (22.7% difference; 95% CI 11.2 to 33.7; p=0.00006), including complete response (CR) rates of 11.3% vs 3.1%, respectively. At the time of data cut-off, 433 of 434 enrolled patients were treated with grade ≥3 TRAE rates of 57.1% (including death in 3.2%) for pembrolizumab plus SOC vs 57.4% (including death in 4.6%) for placebo plus SOC. Notably, the accelerated approval from the FDA for this combination was based on ORR in KEYNOTE-811, as the survival primary end points were still maturing at the time of this publication. This combination was not approved by the European Medicines Agency at the time of manuscript publication.

In May 2022, the FDA granted approvals for two additional first-line ICI-based combinations for the treatment of advanced or metastatic ESCC regardless of tumor PD-L1 expression. The first indication is for the use of nivolumab plus fluoropyrimidine-based and platinum-based chemotherapy and the second is for nivolumab plus ipilimumab in this population. These approvals were based on the global, phase III CheckMate 648 study, which randomized 970 patients with advanced ESCC to first-line nivolumab plus chemotherapy (5-FU plus cisplatin) versus nivolumab plus ipilimumab versus chemotherapy alone.[6] With a minimum of 13 months follow-up, both the nivolumab plus chemotherapy and the nivolumab plus ipilimumab arms demonstrated improved OS compared with chemotherapy alone for patients with PD-L1 ≥1% (HR 0.54 with p<0.001 and HR 0.64 with p=0.001, respectively). This survival benefit compared with chemotherapy alone persisted when PD-L1-negative patients were included in the analysis (nivolumab plus chemotherapy HR 0.74 [p=0.002] vs nivolumab plus ipilimumab HR 0.78 [p=0.01]). However, while the addition of nivolumab to chemotherapy increased the ORR for patients with tumor PD-L1 TPS <1% (42% vs 34%), there was no significant difference in OS or PFS between the nivolumab-containing regimens and chemotherapy alone, and the greatest benefits of a nivolumab-containing regimen are anticipated to be seen in patients with a tumor TPS ≥1%. A significant PFS benefit was also seen for patients with PD-L1 ≥1% with nivolumab plus chemotherapy versus chemotherapy alone (HR 0.65; 98.5% CI 0.46 to 0.92; p=0.002), however, this benefit was not observed for nivolumab plus ipilimumab versus chemotherapy.[87] Response rates reported for the nivolumab plus ipilimumab arm were also lower than those observed for the nivolumab plus chemotherapy arm (PD-L1 ≥1%–53% vs 35%; overall population 47% vs 28%, respectively). While nivolumab or pembrolizumab plus chemotherapy remain the preferred first-line treatment options for ESCC, nivolumab plus ipilimumab is another approved option that may be considered in select patients. For example, some patients who are not chemotherapy candidates may be able to tolerate dual checkpoint blockade. However, although the spectrum of toxicity for each regimen is unique, the overall incidence of high-grade adverse events associated with nivolumab plus ipilimumab may be comparable to rates associated with chemotherapy. For example, in CheckMate 648, the rate of grade 3–4 TRAEs was 47% for nivolumab plus chemotherapy, 32% for nivolumab plus ipilimumab, and 36% for chemotherapy alone.[87] It is important to note that the side-effect profile of nivolumab plus ipilimumab is distinct—unlike with chemotherapy, treatment-related neutropenia is rare, whereas dermatological toxicity is common. Furthermore, different mechanisms underlie similar toxicity presentations that are common to both regimens (eg, immune-mediated diarrhea/colitis vs chemotherapy-induced diarrhea), which has important implications for management. As such, the potential need for immunosuppression should be anticipated for all patients being considered for nivolumab plus ipilimumab.

Negative trials evaluating ICI monotherapy in the frontline and maintenance setting

KEYNOTE-590, CheckMate 649, KEYNOTE-811, and CheckMate 648 demonstrated that anti-PD-1 combined

with either chemotherapy (with or without trastuzumab) or anti-CTLA-4 improves outcomes in the frontline treatment of advanced esophagogastric cancers while maintaining acceptable safety profiles. However, the efficacy of ICI monotherapy in the frontline is less clear. KEYNOTE-062 was a phase III, partially blinded trial including patients with untreated, HER2-negative, PD-L1-positive (CPS ≥1) advanced gastric or GEJ adenocarcinoma that randomized 763 participants 1:1:1 to receive pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine), or chemotherapy alone.[58] At final analysis with a median follow-up of 29.4 months, the median OS for patients with CPS ≥1 for pembrolizumab monotherapy versus chemotherapy alone was non-inferior (10.6 vs 11.1 months; HR 0.91; 99.2% CI 0.69 to 1.18). Pembrolizumab monotherapy was also better tolerated than chemotherapy alone, with grade ≥3 TRAE rates of 17% and 69%, respectively. However, pembrolizumab monotherapy was not superior to chemotherapy alone for patients with PD-L1 CPS ≥1 (HR 0.91; 95% CI 0.74 to 1.10). Additionally, although the median OS was numerically longer in the PD-L1 CPS ≥10 subgroup (17.4 months with pembrolizumab vs 10.8 months with chemotherapy; HR 0.69; 95% CI 0.49 to 0.97), this difference was not statistically tested as superiority in the CPS ≥1 group was not demonstrated. Median PFS for pembrolizumab monotherapy versus chemotherapy alone, respectively, was 2.0 vs 6.4 months (HR 1.66; 95% CI 1.37 to 2.01) for the PD-L1 CPS ≥1 subgroup and 2.9 vs 6.1 months (HR 1.10; 95% CI 0.79 to 1.51) for the PD-L1 CPS ≥10 subgroup. Analysis of secondary end points (for the PD-L1 CPS ≥1 group) revealed worse ORRs for pembrolizumab monotherapy compared with chemotherapy alone (14.8% vs 37.2%) but improved DOR (13.7 vs 6.8 months). Furthermore, the median OS for pembrolizumab plus chemotherapy versus chemotherapy alone was not significantly different (12.5 vs 11.1 months; HR 0.85; 95% CI 0.70 to 1.03; p=0.05), nor was it significant for the PD-L1 CPS ≥10 subgroup (12.3 vs 10.8 months; HR 0.85; 95% CI 0.62 to 1.17; p=0.16). At the time of manuscript writing, ICI monotherapy is not FDA-approved for the frontline treatment of advanced esophageal, GEJ, or gastric cancer.

ICI monotherapy has also been evaluated as maintenance treatment following first-line induction chemotherapy, with similarly non-significant survival benefits. In the phase III, open-label JAVELIN Gastric 100 study, 805 patients with untreated, HER2-negative, locally advanced/metastatic gastric or GEJ carcinoma without progressive disease after 12 weeks of first-line chemotherapy (oxaliplatin plus a fluoropyrimidine) were randomized 1:1 to receive maintenance treatment with avelumab monotherapy versus chemotherapy.[59] The median OS among the prespecified PD-L1-positive group (≥1% of tumor cells; 73–10 assay) was 16.2 months in the avelumab arm vs 17.7 months in the chemotherapy arm (HR 1.13; 95% CI 0.57 to 2.23; one-sided p=0.6352). Furthermore, there was no survival benefit for avelumab within the Asian subgroup or in an exploratory analysis of tumors with CPS ≥10 as measured by the 22C3 assay.

Immunotherapy for previously treated disease

Studies have demonstrated benefit for ICI monotherapy use for previously treated, immunotherapy-naïve esophagogastric cancers. Use of ICI monotherapy in this setting may be considered for tumors with a high CPS score, however, data to support this practice are marginal. Furthermore, as ICI use becomes more common in the frontline, patients with immunotherapy-naïve pretreated disease will become less common.

In July 2019, the FDA approved the use of pembrolizumab monotherapy for the treatment of recurrent, locally advanced, or metastatic ESCC with PD-L1 CPS ≥10 progressing after one or more lines of therapy. Approval was based on the phase II KEYNOTE-180 study, in which patients with pretreated, advanced ESCC and adenocarcinoma treated with pembrolizumab monotherapy had an ORR of 9.9%. However, the ORR was 14.3% for the squamous cell carcinoma subgroup and 13.8% for the PD-L1-positive (CPS ≥10) subgroup.[88] The open-label phase III KEYNOTE-181 study randomized 628 patients with pretreated, advanced/metastatic ESCC and adenocarcinoma and Siewert type 1 GEJ adenocarcinoma 1:1 to receive second-line pembrolizumab monotherapy versus investigator's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan).[89] At the time of final analysis, the median OS in the CPS ≥10 subgroup (a co-primary end point) was 9.3 months for pembrolizumab vs 6.7 months for chemotherapy, meeting the prespecified boundary for superiority (HR 0.69; 95% CI 0.52 to 0.93; p=0.0074).[54] Among prespecified subgroups with CPS ≥10, the survival benefit was greatest among those with SCC and those from Asia. The co-primary end points of OS for patients with SCC and for all patients were not met within prespecified boundaries for significance.

Nivolumab monotherapy was approved by the FDA for the treatment of advanced ESCC following fluoropyrimidine-based and platinum-based chemotherapy in June 2020. The open-label, phase III ATTRACTION-3 study randomized 419 patients with advanced ESCC refractory or intolerant to one previous line of fluoropyrimidine plus platinum chemotherapy 1:1 to receive either nivolumab monotherapy or investigator's choice of taxane chemotherapy.[90] With a minimum follow-up of 17.6 months, median OS (primary end point) was significantly better for nivolumab monotherapy versus chemotherapy (10.9 vs 8.4 months; HR 0.77; 95% CI 0.62 to 0.96; p=0.019). Nivolumab monotherapy was also better tolerated, with a grade 3–4 TRAE rate of 18% compared with 63% in the chemotherapy group. At 3 years follow-up, the median OS remained superior for nivolumab monotherapy versus taxane chemotherapy (10.91 vs 8.51 months; HR 0.79; 95% CI 0.64 to 0.97), including for those patients whose best overall response was stable disease (17.38 months for nivolumab vs 9.36

months for chemotherapy; HR 0.45; 95% CI 0.26 to 0.78) and progressive disease (10.91 months for nivolumab vs 6.18 months for chemotherapy; HR 0.56; 95% CI 0.33 to 0.95).[55]

Accelerated approval for the use of pembrolizumab monotherapy for the third-line treatment of advanced PD-L1-positive (CPS ≥1) gastric or GEJ adenocarcinoma was initially granted by the FDA in September 2017 based on an ORR of 21.3% among patients with PD-L1-positive tumors and two prior lines of therapy in the phase II KEYNOTE-059 study.[91] The indication was voluntarily withdrawn in July 2021 after an industry-wide review of accelerated approvals for ICIs by the FDA ODAC in early 2021. At a public meeting of ODAC to review the indication, concerns were cited regarding a lack of superiority of pembrolizumab monotherapy compared with chemotherapy seen in the KEYNOTE-061 and KEYNOTE-062 studies, as well as the changing landscape of treatment for gastric cancer.[92] Although pembrolizumab monotherapy was not associated with statistically significant improvements in OS in KEYNOTE-061, updated exploratory analyses at 2 years of follow-up showed some trends for improved HRs for death and 24-month survival rates for pembrolizumab versus paclitaxel with increasing CPS scores (CPS ≥1: HR 0.81, 24-month OS rates 19.9% vs 8.5%; CPS ≥5: HR 0.72, 24-month OS rates 24.2% vs 8.8%; CPS ≥10: HR 0.69, 24-month OS rates 32.1% vs 10.9%). DOR also increased apace with increasing CPS score (CPS ≥1: 19.1 vs 5.2 months; CPS ≥5: 32.7 vs 4.8 months; CPS ≥10: not reached vs 6.9 months), however, these analyses were also exploratory.[92]

Panel recommendations

- For all patients with advanced esophagogastric cancers, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with untreated, advanced, MSS/pMMR esophagogastric cancers, single-agent ICIs are not recommended. Single-agent anti-PD-1 therapy may be an option for patients with untreated, advanced, MSI-H/dMMR esophagogastric cancers who are not eligible for chemotherapy (LE:3).
- For patients with untreated, advanced, TPS ≥1 ESCC, nivolumab in combination with fluoropyrimidine-based and platinum-based chemotherapy is a preferred SOC option (LE:2).
- For patients with untreated, advanced, CPS ≥10 ESCC, chemotherapy plus pembrolizumab is a preferred SOC option (LE:2).
- For patients with untreated, advanced, TPS ≥1 ESCC, nivolumab in combination with ipilimumab is also an approved option (LE:2).
- For patients with untreated, advanced, CPS ≥10, HER2-negative esophageal or Siewert type I GEJ adenocarcinoma, chemotherapy plus pembrolizumab is a SOC option (LE:2).
- For patients with untreated, advanced, HER2-negative esophageal/GEJ/gastric adenocarcinomas with CPS ≥5 or that are MSI-H/dMMR, chemotherapy plus nivolumab is a SOC option (LE:2).
- For patients with untreated, HER2-positive, advanced esophagogastric adenocarcinoma, chemotherapy plus trastuzumab plus pembrolizumab is recommended (LE:2).

Emerging data on immunotherapies for the treatment of esophageal, GEJ, and gastric cancer

The following studies are discussed because of their potential to be impactful, however, at the time of manuscript publication, FDA evaluation was ongoing for all of these ICIs, and these data should not be used to guide treatment decisions outside of a clinical trial or forthcoming FDA approval.

Although the role of neoadjuvant or potentially even definitive immunotherapy for the treatment of resectable, MSI-H/dMMR gastric cancer was still an area of ongoing investigation at the time of this guideline's publication, emerging data will determine the optimal treatment strategy for these patients. A retrospective meta-analysis of several trials of resectable gastric cancer demonstrated no benefit for the addition of perioperative chemotherapy to surgery for patients with MSI-H, resectable gastric cancer.[93] In the randomized, phase IIb DANTE study of patients with resectable adenocarcinoma of the stomach and GEJ (≥cT2 and/or N+), the addition of perioperative atezolizumab to 5-FU-leucovorin-oxaliplatin-docetaxel (FLOT) chemotherapy increased pathological regression rates for the 25 enrolled patients with MSI-H tumors.[94] Results of the phase III MATTERHORN study (NCT04592913) of the addition of perioperative durvalumab to FLOT chemotherapy for patients with stage II or higher, resectable gastric or GEJ adenocarcinoma were pending at the time of publication.[95] In cohort 1 of the phase II INFINITY trial, 9 of 15 (60%) patients with MSI-H/dMMR resectable cT2-4 and N gastric or GEJ adenocarcinoma who received neoadjuvant durvalumab plus tremelimumab followed by resection achieved a pCR.[96] The phase II GERCOR/NEONIPIGA study is evaluating the efficacy of neoadjuvant nivolumab plus ipilimumab, followed by adjuvant nivolumab (for Becker tumor regression grade [TRG] <3), in patients with resectable, MSI-H/dMMR, T2–T4 NxM0 gastric and esophagogastric adenocarcinoma.[97] With a median follow-up of 14.9 months, 29 of the 32 participants had undergone surgery with a pCR (pathological T0N0) rate of 58.6%, postoperative morbidity of 55% (Clavien-Dindo classification), and one postoperative death occurred due to a cardiovascular adverse event. Of the three patients who did not undergo resection, two refused surgery and had CR on endoscopic biopsy, and one had metastatic progression of disease prior to surgery. At the time of data lock, no patients had relapsed and one patient had died without relapse.[98]

Several ongoing studies are evaluating first-line ICI strategies for unresectable esophagogastric cancers as

well. Many of these studies include anti-PD-1 ICIs developed in regions outside the US, most predominantly in Asia. The expected benefit of adding an anti-PD-1 agent to chemotherapy in the first line has been maintained with these newer agents, with one agent demonstrating activity as a monotherapy in the second line. If and how these emerging anti-PD-1 agents will be integrated into the SOC in the US and other regions remains to be determined.

ESCORT-1st is a phase III trial randomizing 596 patients with advanced, untreated ESCC recruited from 60 hospitals in China to receive chemotherapy (paclitaxel plus cisplatin) with or without the PD-1 inhibitor camrelizumab.[8] The addition of camrelizumab in the first line improved median OS (HR 0.70; 95% CI 0.56 to 0.88; one-sided p=0.001) as well as median PFS (HR 0.56; 95% CI 0.46 to 0.68; one-sided p<0.001). In another study from China, the phase III JUPITER-06 trial, 514 patients with advanced ESCC were randomized to receive chemotherapy (paclitaxel plus cisplatin) with or without the anti-PD-1 toripalimab.[99] Again, the addition of toripalimab to chemotherapy in the front line resulted in a significant improvement in OS (17.0 vs 11.0 months; HR 0.58; 95% CI 0.43 to 0.78; p=0.00037) and PFS (HR 0.58; 95% CI 0.46 to 0.74; p<0.00001), with these survival benefits maintained across PD-L1 expression subgroups.

The PD-1 inhibitor sintilimab is being evaluated in combination with chemotherapy (cisplatin plus either paclitaxel or 5-FU) as first-line therapy for advanced ESCC in the ORIENT 15 study, a global, phase III trial (NCT03748134) with 659 patients enrolled at the time of interim analysis.[100] Primary study end points will be OS in the randomized population and for patients with PD-L1-positive (CPS ≥10) tumors. Another trial evaluating sintilimab, the phase III ORIENT 16 study, has randomized 650 Chinese patients with advanced gastric and GEJ adenocarcinoma to receive first-line chemotherapy (oxaliplatin plus capecitabine) with or without sintilimab.[101] At interim analysis, it was announced that ORIENT 16 had met its primary end point of improved OS in both the intention-to-treat (ITT) and PD-L1-positive subgroups.[102]

Tislelizumab, an anti-PD-1 antibody that binds with higher affinity than pembrolizumab and is engineered for reduced Fc gamma receptor affinity, was studied in the first-line setting in the global RATIONALE 305 study, which enrolled patients with previously untreated, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma.[103] After a median follow-up of 11.8 and 11.7 months for the tislelizumab plus chemotherapy and placebo plus chemotherapy arms, respectively, the addition of tislelizumab provided a significant median OS improvement (17.2 vs 12.6 months; HR 0.74; 95% CI 0.59 to 0.94; one-sided p=0.0056) for 546 PD-L1-positive patients (primary end point). The tislelizumab arm also achieved a longer median PFS, higher ORR, longer median DOR, and improved health-related quality of life (HRQOL) with no new safety signals.

Tislelizumab has also demonstrated improved OS compared with investigator's choice chemotherapy when administered as a second-line monotherapy in the global phase III RATIONALE 302 study, which enrolled 512 patients with ESCC.[104] With a median follow-up of 8.5 months for the tislelizumab arm and 5.8 months for investigator's choice chemotherapy arm, the median OS was significantly greater for the tislelizumab arm in the ITT population at 8.6 vs 6.3 months (HR 0.70; 95% CI 0.57 to 0.85; p=0.0001). Even greater benefit was observed in the CPS ≥10 subgroup, with median OS of 10.3 vs 6.8 months (HR 0.54; 95% CI 0.36 to 0.79; p=0.0006). In the ITT population, tislelizumab was also associated with an improved ORR (20.3% vs 9.8%), more durable responses (median DOR 7.1 vs 4.0 months; HR 0.42; 95% CI 0.23 to 0.75), and fewer grade ≥3 TRAEs (19% vs 56%) compared with investigator's choice chemotherapy.

DUODENAL AND DISTAL SMALL BOWEL CANCERS

Small bowel tumors are rare, representing just 3% of all GI tract cancers.[105] SBA comprises 59% of duodenal, 42% of jejunal, and 15% of ileal tumors.[106] Genetic testing and counseling should be considered for all patients diagnosed with SBA. Microsatellite status and TMB should be obtained as well, particularly in the setting of advanced disease, for which there are multiple biomarker-specific immunotherapy indications, as described in the preceding sections. No patients with SBA were included in the analysis of KEYNOTE-158 that led to FDA approval for pembrolizumab for the treatment of TMB-H tumors. However, in the phase II KEYNOTE-158 study, 19 of the 233 patients with advanced, pretreated, MSI-H/dMMR non-colorectal solid tumors enrolled to receive pembrolizumab monotherapy had small intestine cancer.[107] The ORR for the patients with MSI-H/dMMR small intestine cancer in KEYNOTE-158 was 42.1% (compared with 34.3% in all evaluable patients). Median PFS and OS were 9.1 months and not reached, respectively, for the small intestine cancer subgroup, compared with 4.1 and 23.5 months for all evaluable patients. However, the study was not powered or designed to compare between subgroups. The subsequent phase II ZEBRA study, which exclusively enrolled patients with advanced, pretreated SBA to receive pembrolizumab monotherapy, failed to meet the primary efficacy end point of an ORR ≥30%.[108] However, study participants were not selected for MSI status, with 32 pMMR/non-MSI-H tumors, 4 MSI-H tumors, and 4 microsatellite unknown tumors represented, further emphasizing the importance of biomarker testing for patients with SBA being considered for immunotherapy. Among the 32 patients with pMMR/non-MSI-H disease, only one patient achieved a confirmed partial response (PR) and 10 patients achieved stable disease (SD).[109] The median DOR was just 2.6 months (range 1.3–16.7 months) for the 10 patients with a pMMR/non-MSI-H tumor who achieved SD.

The phase I GARNET study supported a tissue-agnostic FDA approval for the PD-1 inhibitor dostarlimab for the treatment of recurrent or advanced, pretreated dMMR solid tumors in August 2021. Data for cohort F, which was composed mainly (93.4%) of GI cancers, was presented in January 2021.[110] For the 106 patients with dMMR non-endometrial cancers pretreated with up to two prior lines of therapy for advanced disease who received dostarlimab monotherapy, an ORR of 38.7% (95% CI 29.4 to 48.6) was observed, including on ORR of 33.3% (95% CI 9.9 to 65.1) for the 12 patients with small intestinal cancer. With a median follow-up of 12.4 months, the median DOR was not reached for the cohort. Serious TRAEs were reported in 5.5% of patients and no deaths were attributed to dostarlimab.[111]

PANCREATIC ADENOCARCINOMA

In 2022, there were 62,210 new cases of PDAC and 49,830 deaths due to the disease in the US alone.[1] With a median survival of <1 year and a 5-year OS rate of <10%, metastatic PDAC remains one of the deadliest cancers in the world.[2 112] Chemotherapy and poly-ADP ribose polymerase inhibition (PARPi) have demonstrated only a modest PFS benefit for PDAC,[113] which is often diagnosed at an unresectable, late stage. Unfortunately, most cases of PDAC have remained largely unresponsive to immunotherapy as well.[114 115] Numerous strategies have been employed in an attempt to augment responses, including the use of granulocyte-macrophage colony-stimulating factor (GM-CSF)[116] and peptide vaccine[117] combinations, cytokine-induced natural killer cells,[118] mesothelin-specific chimeric antigen receptor (CAR) T-cell therapy,[119] CD40 agonist antibodies,[120] and combining stereotactic body radiotherapy (SBRT) with single or dual checkpoint blockade.[121] Despite exploration of these novel strategies, pembrolizumab for MSI-H/dMMR or TMB-H PDAC and dostarlimab for dMMR PDAC were the only FDA-approved immunotherapies for this disease at the time of publication of this manuscript based on the KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158 studies[31 107] and the GARNET study,[110] respectively. Although not FDA-approved, ICI therapy may also be considered for patients with PDAC harboring a pathogenic *POLE/POLD1* mutation with an associated ultramutated TMB. However, *POLE/POLD1* mutations are rare for this tumor, occurring at an estimated frequency of <2%.[46]

BILIARY TRACT CANCERS

In 2022, there were an estimated 12,130 new cases and 4,400 deaths due to BTCs in the US.[1] For the purposes of this CPG, BTCs include intrahepatic and extrahepatic cholangiocarcinoma as well as gallbladder cancer. Refer to SITC's CPG on immunotherapy for the treatment of hepatocellular carcinoma for expert panel recommendations on ICIs in liver cancer.[11] Relatively uncommon, BTCs have a substantial unmet medical need for improved therapies, with a 5-year survival rate of just 10%.[122] BTC has proven to be relatively unresponsive to ICI monotherapy,[123] and rates of MSI and *POLE/POLD1* mutations have been reported at just 1%–2% and 5.2%, respectively, in cholangiocarcinoma.[46 124] In September 2022, however, the anti-PD-L1 ICI durvalumab gained FDA approval in combination with chemotherapy for first-line treatment of advanced BTC. Superior efficacy of chemotherapy plus durvalumab was demonstrated in the global, phase III TOPAZ-1 trial, which randomized 685 patients with advanced, untreated BTC to receive gemcitabine and cisplatin with or without durvalumab.[5] In TOPAZ-1, the addition of durvalumab to chemotherapy significantly improved both OS (median 12.8 vs 11.5 months; HR 0.80; 95% CI 0.66 to 0.97; p=0.021) and PFS (HR 0.75; 95% CI 0.63 to 0.89; p=0.001), with a higher ORR observed for the durvalumab arm (26.7% for durvalumab plus chemotherapy vs 18.7% for chemotherapy alone).[5] Although this FDA approval applies to surgically unresectable BTC, patients who receive gemcitabine plus cisplatin plus durvalumab for locally advanced disease may be reconsidered for eligibility for resection on response to therapy in multidisciplinary discussion.

Emerging data on immunotherapy for the treatment of BTC

Based on TOPAZ-1, there is now an FDA-approved front-line immunotherapeutic treatment option for BTC.[5] Other prospective studies of immunotherapy in the front-line treatment of BTC were ongoing at the time of guideline publication, including the phase III KEYNOTE-966 study (NCT04003636) evaluating patients with advanced, treatment-naïve BTC,[125] which demonstrated a statistically significant improvement in OS with the addition of pembrolizumab to gemcitabine plus cisplatin. Nivolumab in combination with gemcitabine plus cisplatin was compared with nivolumab plus ipilimumab in the phase II BilT-01 trial, which enrolled 71 patients with advanced, untreated BTC.[126] The 6-month PFS rates were 70% for the nivolumab plus chemotherapy arm and 18.6% in the dual immunotherapy arm. Median PFS was 8.8 and 4.1 months in the immunotherapy plus chemotherapy and dual immunotherapy arms, respectively. OS data were maturing at the time of manuscript preparation. An open-label, single-center phase II trial including 121 patients with chemotherapy-naïve, advanced BTC demonstrated efficacy and tolerable safety of gemcitabine plus cisplatin plus durvalumab with or without the anti-CTLA-4 ICI tremelimumab and described markers of response in a dedicated biomarker cohort.[124] The ORRs for gemcitabine plus cisplatin plus durvalumab (n=47 evaluable patients) and gemcitabine plus cisplatin plus durvalumab plus tremelimumab (n=47 evaluable patients), were 72% and 70%, respectively.[127] Finally, the randomized, placebo-controlled phase II IMbrave 151 study of treatment-naïve patients with advanced BTC demonstrated a numerically higher but not statistically significant improvement in median PFS (primary end

point) with the addition of bevacizumab to atezolizumab plus gemcitabine plus cisplatin (8.3 vs 7.9 months; HR 0.76; 95% CI 0.51 to 1.14).[128] And although the ORRs were similar between the two arms (24.1% vs 25.3%), the addition of bevacizumab prolonged the DOR with 88.5% vs 47.4% of responders having a response lasting at least 6 months in the bevacizumab versus placebo arms, respectively.

Several studies are also exploring ICIs to address the unmet need for second-line treatment of MSS/pMMR BTC following progression on first-line chemotherapy. However, given the FDA approval for frontline durvalumab plus chemotherapy based on TOPAZ-1, the future generalizability of these studies may be limited as fewer patients will receive chemotherapy alone as first-line treatment. A phase II study that enrolled 54 patients (46 of whom were evaluated for an objective response with imaging) with advanced, pretreated BTC for treatment with nivolumab monotherapy[129] demonstrated an investigator-assessed ORR of 22% with a DCR of 59%. All of the responders had pMMR disease. The median PFS in the ITT population was 3.68 months and higher tumor PD-L1 expression was associated with improved PFS (HR 0.23; 95% CI 0.10 to 0.51; p<0.001 with PD-L1 cut-off ≥1%; HR 0.37; 95% CI 0.17 to 0.84); p=0.02 with PD-L1 cut-off >10%). A subgroup analysis of 39 patients with previously treated, advanced MSS BTC from the non-randomized phase II CA209-538 study demonstrated an ORR of 23% and a DCR of 44% with nivolumab plus ipilimumab treatment.[130] The median PFS was 2.9 months and the median DOR was not reached.

In the open-label, multicohort, non-randomized phase II LEAP-005 study evaluating the anti-angiogenic multikinase inhibitor lenvatinib combined with pembrolizumab for patients with pretreated solid tumors, 31 patients were enrolled in the BTC cohort.[131] With a median follow-up of 9.5 months, the ORR was 10% while the DCR was 68%. Median DOR was 5.3 months, median PFS was 6.1 months, and median OS was 8.6 months. A total of 48% of patients experienced a grade ≥3 TRAE. There were no treatment-related deaths. The most frequent TRAE was hypertension (42%). Enrollment into the BTC cohort of LEAP-005 has been expanded to 100 patients based on these results. Another single-arm study evaluating lenvatinib plus pembrolizumab in 32 patients with previously treated, advanced BTC in China demonstrated an ORR of 25% and a DCR of 78.1%, with a median PFS and OS of 4.9 and 11.0 months, respectively.[132]

The combination of the anti-PD-L1 atezolizumab with the MEK inhibitor cobimetinib met its primary end point of PFS (median PFS 3.65 months for combination vs 1.87 months for atezolizumab monotherapy; HR 0.58; 90% CI 0.35 to 0.93; one-tail p=0.027) in patients with pretreated, metastatic BTC.[133] The combination of atezolizumab and the anti-CD27 antibody varlilumab with or without cobimetinib is now being evaluated for previously treated, unresectable BTC (NCT04941287).

Panel recommendations

- For all patients with SBA, PDAC, and BTC, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with previously treated, advanced MSI-H/dMMR SBA, PDAC, or BTC, pembrolizumab monotherapy is a recommended treatment option (LE:3) and dostarlimab monotherapy is a recommended treatment option for dMMR tumors only (LE:3).
- For patients with previously treated TMB-H (≥10 mut/Mb) SBA, PDAC, or BTC, anti-PD-1 ICI monotherapy may be considered if no other treatment options are available (LE:3); however, at the time of guideline publication, there were insufficient data on efficacy in these tumor types.
- For patients with MSS/pMMR, TMB-L (<10 mut/Mb) SBA or PDAC, ICIs should not be used outside of a clinical trial (LE:3).
- For patients with untreated, advanced BTC, treatment with combination gemcitabine/cisplatin/durvalumab (LE:2) is recommended (LE:2) unless a contraindication to immunotherapy exists.
- For patients with treatment-refractory, immunotherapy-naïve, advanced MSS/pMMR BTC, treatment with combination lenvatinib plus pembrolizumab (LE:3) or nivolumab with (LE:3) or without (LE:3) ipilimumab may be considered if a suitable clinical trial is not available.

IMMUNOTHERAPY FOR THE TREATMENT OF COLORECTAL AND ANAL CANCER

CRC causes a substantial global burden, with an estimated 1.9 million incident cases per year worldwide.[134] The incidence is highest in China and the US and the burden is projected to continue rising, including an increase in the number of early onset cases. Although squamous cell carcinoma of the anal canal (SCCA) is relatively uncommon in the US (only about 9,000 cases per year),[135] the incidence has been rising by 2.7% per year accompanied by a 3.1% per year increase in mortality.[136] Furthermore, SCCA impacted 50,685 people globally in 2020 alone.[137] Unfortunately, like many other rare cancers, SCCA is understudied and lacks effective treatment options. Checkpoint inhibitors may be used to treat certain patients with CRC and SCCA, however, response rates are low for non-biomarker selected tumors. An algorithm describing immunotherapy treatment for advanced CRC is provided in figure 2.

Diagnostic tests and biomarkers for immunotherapy for colorectal and anal cancer

Many disease features and biomarkers are used to guide treatment of advanced CRC and SCCA and recommendations on non-immunotherapy-specific diagnostics may be found in other published guidelines.[138 139] MSI-H/dMMR (CRC and SCCA) or a pathogenic *POLE/POLD1* mutation with an associated ultramutated TMB (CRC) are the only biomarkers that can determine eligibility for ICI use

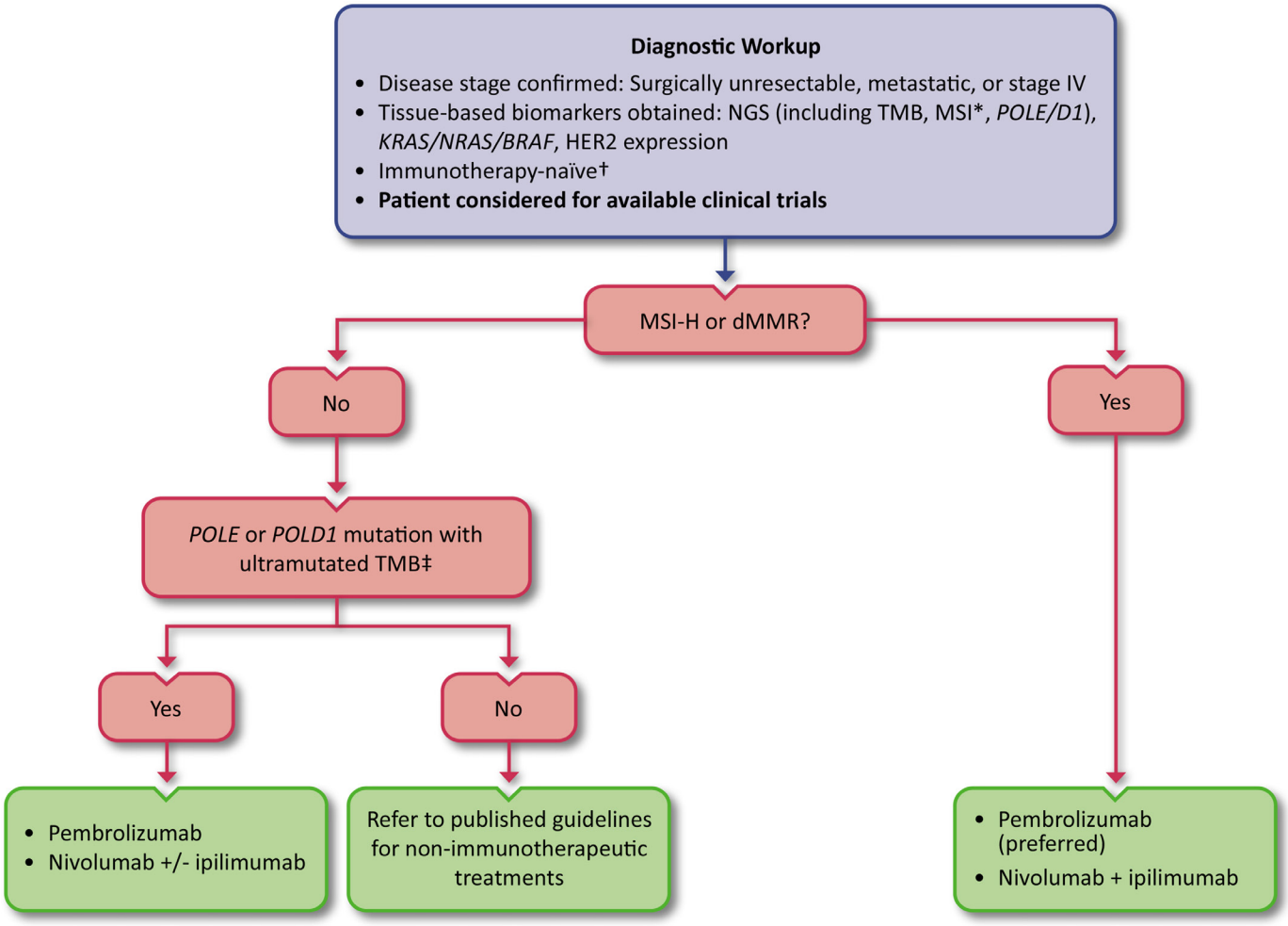

Figure 2 Advanced CRC testing and treatment algorithm. *Patients with tumors that are MSI-H/dMMR may be considered for pembrolizumab monotherapy or nivolumab with or without ipilimumab following progression of disease on a non-immunotherapy regimen. Dostarlimab monotherapy may be considered in this instance for dMMR disease only. †For patients whose disease progresses on a regimen containing immunotherapy, consideration for clinical trial is preferred. If clinical trial enrollment is not feasible, then guideline-directed subsequent therapy is recommended. ‡Patients with tumors with *POLE/POLD1* mutations and associated ultramutated TMB may be considered for treatment with ICIs. While there are no widely accepted TMB cut-offs to define the 'ultramutated' phenotype, these tumors typically have TMB values well above 10 mut/Mb, with reports citing TMBs of 31 mut/Mb for *POLE*-mutated cancers with known genomic alterations[48] and 122–303 mut/Mb for *POLE*-associated cancers.[45] CRC, colorectal cancer; dMMR, mismatch repair deficiency; ICI, immune checkpoint inhibitor; MSI-H, high microsatellite instability; mut/Mb, mutations per megabase; NGS, next-generation sequencing; TMB-H, high tumor mutational burden.

in lower GI tract tumors. Importantly, PD-L1 expression status does not predict response to immunotherapy for CRC.[7 140] While there may be some correlation between PD-L1 expression and response to ICIs for advanced SCCA (discussed in the **'Immunotherapy for the treatment of colorectal and anal cancer'** section), these data are based on small studies. As such, PD-L1 expression should not be used to inform treatment decisions for either CRC or SCCA. Distinct from the tissue-agnostic indications for these biomarkers, patients with MSI-H/dMMR CRC are eligible for first-line treatment with ICIs. Although dMMR is characteristic of Lynch syndrome (formerly known as hereditary non-polyposis CRC), it can also be found in about 15% of sporadic cases of CRC,[141] and all patients with newly diagnosed CRC should be considered for MSI or MMR testing.

Although MSI is a common driver of high mutational burden in CRC, at least 4% of TMB-H tumors are MSS/MSI-L[45] and around 1%–2% of MSS tumors have an ultramutated TMB.[45] Pathogenic *POLE/POLD1* mutations resulting in an 'ultramutated' tumor phenotype are another driver of high mutational burden and, although reports vary, may occur with a relatively high frequency in CRC (7.4%).[46] As pathogenic *POLE/POLD1* mutations are associated with an excellent response to ICI therapy, even in the absence of MSI, patients with advanced MSS/pMMR CRC should be considered for *POLE/POLD1* mutation testing in the absence of other indications for

immunotherapy.[47] See the **'Tissue-agnostic biomarkers: high microsatellite instability/mismatch repair deficiency, tumor mutational burden, and *POLE/POLD1* status'** section for further discussion of this biomarker.

Patients with CRC were well-represented in the studies leading to tissue-agnostic approvals of ICIs based on dMMR and/or MSI-H.[142] However, no patients with CRC were included in the KEYNOTE-158 study that led to the TMB-H indication for pembrolizumab and only 21 patients with CRC were included in the MyPathway study. Emerging evidence suggests that the etiology of a tumor's hypermutated state may influence response to checkpoint blockade. A single-institution retrospective analysis that included 137 patients with advanced CRC who were treated with ICIs found that although OS was longer for patients whose tumors were TMB-H compared with TMB low (HR 0.40; 95% CI 0.24 to 0.65), this survival benefit disappeared if patients were stratified by mismatch repair or *POLE/POLD1* pathogenic mutation status (HR 1.17; 95% CI 0.59 to 2.32).[143] Furthermore, the ORRs for the patients with anal cancer in KEYNOTE-158 were similar regardless of TMB status (11% for TMB low [n=75] vs 7% for TMB-H [n=14]). The data from KEYNOTE-158 and the MyPathway study are not adequate to support the use of ICI monotherapy for pretreated MSS/pMMR CRC or SCCA based on TMB elevation in the absence of a known driver such as MSI or a pathogenic *POLE/POLD1* mutation. Further discussion of the KENOTE-158 and MyPathway data, along with assay considerations for evaluation of TMB, MSI and MMR status, may be found in the **'Tissue-agnostic indications for immunotherapy in the treatment of gastrointestinal cancer'** section.

Panel recommendations

- All patients with metastatic CRC should have tumor tissue evaluated by NGS.
- For all patients with CRC and SCCA, PD-L1 expression does not currently inform treatment decisions for ICIs.
- For patients with CRC, MSI/MMR status (LE:2) and a *POLE/POLD1* mutation with an associated ultramutated TMB (LE:3) are the primary biomarkers that should be used to inform ICI treatment decisions.

Immunotherapy for the treatment of colorectal cancer

CRC that is MSS/pMMR does not generally respond to anti-PD-(L)1 antibodies, regardless of PD-L1 expression.[7] Although numerous strategies using immunotherapy to treat MSS/pMMR CRC are being explored, none of these studies have led to FDA approvals, and immunotherapy should not be used in this setting outside of a clinical trial (except for *POLE/POLD1* mutated CRC with an associated ultramutated TMB). While some patients with MSI-H/dMMR CRC benefit from ICI therapy in the first and subsequent lines, a proportion of these patients will have primary or secondary resistance to immunotherapy and further studies are needed to identify additional biomarkers of response.

Initial trials of immunotherapy for advanced MSI-H/dMMR CRC were performed in the setting of pretreated disease. In the phase II KEYNOTE-164 study of 124 patients with metastatic, MSI-H/dMMR CRC, pembrolizumab monotherapy was associated with an ORR of 33% (as measured by RECIST v1.1) for patients who had received at least one prior line of treatment or two or more previous lines including fluoropyrimidine, oxaliplatin, and irinotecan.[144] The median PFS was 2.3 months for patients with two or more prior lines of treatment and 4.1 months for patients with one or more prior lines of treatment. Median OS was 31.4 months (median follow-up 31.3 months) for patients with two or more prior lines of treatment and not reached (median follow-up 24.2 months) for patients with one or more prior lines of treatment. In May 2017, KEYNOTE-164 was one of five studies leading to the first tissue-agnostic FDA approval of pembrolizumab for the treatment of unresectable or metastatic, MSI-H/dMMR cancers that have progressed on prior therapy with no satisfactory alternative treatment options. The indication was extended specifically to MSI-H/dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[16]

Nivolumab monotherapy was evaluated in the treatment of patients with metastatic, pretreated, MSI-H/dMMR CRC in one arm of the phase II CheckMate 142 study. Among the 74 enrolled patients, most (54.1%) had received three or more prior lines of therapy.[145] With a median follow-up time of 12.0 months, the investigator-assessed ORR was 31.1%, with 68.9% of patients achieving disease control for ≥12 weeks and 34.8% maintaining a response for ≥12 months. The OS rates at 9 and 12 months were 78% and 73%, respectively. This cohort of CheckMate 142 led to the accelerated approval of nivolumab in July 2017 for the treatment of metastatic, MSI-H/dMMR CRC that has progressed following fluoropyrimidine, oxaliplatin, and irinotecan treatment.

In a separate cohort of CheckMate 142, 119 patients with pretreated, metastatic, MSI-H/dMMR CRC received nivolumab with four doses of ipilimumab.[4] With a median follow-up time of 13.4 months, the investigator-assessed ORR was 55%, with 80% of patients achieving disease control for ≥12 weeks. PFS rates at 9 and 12 months were 76% and 71%, respectively, with OS rates at 9 and 12 months of 87% and 85%, respectively. Notably, 82 of the 119 patients in this study arm had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan, and the ORR for this subgroup was 46%, with 89% of patients still responding to treatment at 6 months.[146] For the 58 patients pretreated with fluoropyrimidine, oxaliplatin, and irinotecan in the nivolumab monotherapy arm of Checkmate 142, the ORR was 28% with 67% of these patients maintaining a response at ≥6 months.[146 147] Formal statistical comparisons between cohorts were not performed. Accelerated approval of nivolumab plus ipilimumab for the treatment of metastatic, MSI-H/dMMR CRC that has progressed following fluoropyrimidine,

oxaliplatin, and irinotecan treatment was granted in July 2018 based on the 82 heavily pretreated patients in this cohort, and this combination is recommended in the second line.

Most recently, in August 2021, the FDA granted accelerated approval for use of dostarlimab-gxly for pretreated, recurrent/advanced, dMMR tumors. This approval was based on data from the ongoing phase I GARNET study, which evaluated 106 patients with pretreated (or prior treatment intolerant) dMMR non-endometrial solid tumors.[111] The ORR as assessed by RECIST v1.1 was 38.7% for the overall cohort, which included 69 patients with CRC, with median DOR not yet reached after a median follow-up time of 12.4 months.

ICIs have demonstrated safety and efficacy in patients with MSI-H/dMMR CRC following progression of disease on chemotherapy. However, data supporting the use of dual immune checkpoint blockade with nivolumab plus ipilimumab following disease progression on single agent anti-PD-(L)1 therapy for this disease are limited. Case studies[148 149] and a small case series[150] have described patients with advanced, MSI-H/dMMR CRC who achieved a response to dual checkpoint blockade following anti-PD-(L)1 monotherapy. However, at the time of manuscript writing, prospective data to support the use of nivolumab plus ipilimumab to treat advanced, MSI-H/dMMR CRC that has progressed on a prior line of ICI therapy were lacking.

Pembrolizumab monotherapy for the first-line treatment of unresectable or metastatic MSI-H/dMMR CRC (regardless of PD-L1 expression) was approved by the FDA in June 2020. Approval was based on the phase III open-label KEYNOTE-177 trial, in which 307 patients with advanced, untreated MSI-H/dMMR CRC were randomized 1:1 to receive either pembrolizumab monotherapy or SOC chemotherapy (with or without bevacizumab or cetuximab).[3] At second interim analysis, with a median follow-up of 32.4 months, the pembrolizumab arm met the co-primary PFS end point with significant improvement compared with chemotherapy (median PFS 16.5 vs 8.2 months; HR 0.60; 95% CI 0.45 to 0.80; p=0.0002). Additionally, the radiographic ORR was 43.8% (including a 17% CR rate) and 33.1% (including a 6% CR rate) for the pembrolizumab and chemotherapy arms, respectively. At time of final analysis 12 months later, OS (the second co-primary end point) demonstrated a trend toward reduced risk of death for the pembrolizumab arm (HR 0.74; 95% CI 0.53 to 1.03; p=0.0359), however, the difference was not statistically significant according to the prespecified alpha of 0.0246 (one-sided). Potentially confounding the analysis was a high crossover rate with 60% of participants in the ITT population receiving subsequent anti-PD-(L)1 therapies.[151] Although nivolumab monotherapy does not have a corresponding FDA indication for the treatment of metastatic, untreated, MSI-H/dMMR CRC, data from an arm of the phase II CheckMate 142 study evaluating nivolumab plus ipilimumab in the first-line setting for metastatic, MSI-H/dMMR have demonstrated promising results.[152] For the 45 patients treated with nivolumab plus ipilimumab who were followed for a median of 29.0 months in CheckMate 142, the ORR was 69% (including a 13% CR rate) and the DCR was 84%. With a minimum follow-up of 24.2 months, neither median PFS nor median OS were reached. The confirmatory, randomized phase III CheckMate 8HW study (NCT04008030), designed to compare the efficacy and safety of nivolumab plus ipilimumab versus chemotherapy or nivolumab monotherapy in patients with MSI-H/dMMR metastatic CRC is ongoing. Pending results from CheckMate 8HW, however, the phase III data supporting pembrolizumab monotherapy in the frontline setting for MSI-H/dMMR CRC are more robust than the phase II data for nivolumab plus ipilimumab.

While the efficacy of ICI therapy has been well-established in both the first and subsequent lines of treatment for advanced, MSI-H/dMMR CRC, there have been no head-to-head trials comparing anti-PD-1 monotherapy with combination ICI therapy (eg, nivolumab plus ipilimumab). For example, anecdotal comparisons of ORR and DCR from separate cohorts of CheckMate 142 suggest that nivolumab plus ipilimumab is more effective than nivolumab monotherapy for pretreated, advanced MSI-H/dMMR CRC, including for patients pretreated with a fluoropyrimidine, oxaliplatin, and irinotecan.[4 145 146] An indirect, interstudy web-based statistical comparison suggested a small (1 month) restricted mean survival time benefit of nivolumab plus ipilimumab versus pembrolizumab monotherapy for pretreated, advanced MSI-H/dMMR CRC.[153] Long-term follow-up has demonstrated that responses to nivolumab plus ipilimumab were durable, with 4-year OS rates of 93% (95% CI 82% to 97%) in patients with CR/PR, 66% (95% CI 49% to 78%) in patients with SD, and 71% (95% CI 61% to 78%) overall.[154]

Emerging data on immunotherapy for the treatment of colorectal cancer

The phase III, multicenter COMMIT study (NCT02997228) is evaluating the efficacy of chemotherapy plus bevacizumab with or without atezolizumab and atezolizumab monotherapy for patients with metastatic, MSI-H/dMMR CRC. Other studies are evaluating ICI therapy in the resectable and metastatic settings for tumors both deficient and proficient in MMR. Clinical trial enrollment should be considered for all patients with CRC regardless of disease stage and biomarker status.

Several trials are evaluating the role of perioperative ICI therapy for both dMMR and pMMR colon cancer. Pathological response is a common end point for neoadjuvant ICI studies; however, it is not yet known whether this biomarker corresponds to improvements in EFS or OS for colon cancer. Because of the lack of randomized evidence, perioperative immunotherapy for this disease should not be administered outside of a clinical trial until more safety and efficacy data are available. However, if an R1 resection is anticipated and appropriate clinical

trial enrollment is not feasible, then administration of neoadjuvant ICIs with multidisciplinary oversight could be considered for resectable MSI-H/dMMR colon cancer given data for disease response, although in the metastatic setting. Encouraging early results are emerging, however. The exploratory, randomized phase II NICHE study (NCT03026140) evaluated patients with early stage, dMMR and pMMR colon cancer who received 1 month of neoadjuvant nivolumab plus ipilimumab (with or without celecoxib for pMMR disease).[155] Pathological response was observed in all 20 evaluable dMMR tumors (including 12 pCRs). Four of the 15 evaluable pMMR tumors demonstrated a pathological response, with $CD8^{+}PD\text{-}1^{+}$ T-cell infiltration predictive of response in these tumors. The NICHE-2 study, which enrolled exclusively for patients with dMMR non-metastatic colon cancer, demonstrated unprecedented 95% major pathologic response (MPR) and 67% pCR rates (secondary end points) for 107 patients following one dose of neoadjuvant ipilimumab and two doses of neoadjuvant nivolumab.[156] Although the primary end point of 3-year DFS has yet to be reported, no patients had experienced a recurrence of their disease at a median follow-up time of 13 months. Furthermore, the primary end point of safety was met, with just three patients experiencing a grade 3 or 4 irAE and three patients experiencing a delay in surgery. Patients with resectable, early stage (T3–T4), MMR unselected colon cancer received neoadjuvant nivolumab in the NICOLE study, which resulted in a MPR (<10% viable tumor) in 3 of 19 patients with pMMR disease and 0 out of 3 patients with dMMR disease.[157] Neoadjuvant nivolumab also resulted in a higher TIL immunoscore compared with a control cohort (p=0.028). Results of the phase III ATOMIC trial (NCT02912559), in which patients with stage III dMMR colon cancer were randomized to receive adjuvant leucovorin, fluorouracil, and oxaliplatin (FOLFOX) with or without atezolizumab, were pending at the time of manuscript publication.

Perioperative ICI therapy is also being explored in trials enrolling exclusively for MSI-H/dMMR rectal cancer. In a report on 12 of the first patients with untreated, stage II–III, MSI-H/dMMR rectal cancer enrolled in one pilot single-institution phase II study (NCT04165772), single-agent dostarlimab administered every 3 weeks for 6 months prior to planned surgery resulted in a 100% complete clinical response rate (95% CI 74% to 100%) at a median follow-up time of 12 months (range 6–24 months).[158] In addition, patients were able to defer radiation therapy and surgery. While these data are provocative, this Expert Panel cannot endorse routine use of PD-1 inhibitors as definitive therapy for MSI-H/dMMR rectal cancer without longer follow-up data. The therapeutic landscape is evolving quickly, however. On February 9, 2023, the FDA ODAC voted eight to five in favor of data from two proposed single-arm trials enrolling a total of 130 patients being sufficient to characterize the benefits and risks of dostarlimab in the curative intent setting for patients with dMMR/MSI-H locally advanced rectal cancer.[159] Rationale in support of this approach included a discussion of the highly morbid multimodality SOC treatment for patients with this disease, as well as proposed trial end points including clinical CR at 12 and 36 months. The ongoing multicenter EA2201 trial (NCT04751370) is evaluating the role of dual immune checkpoint blockade combined with short-course radiation in locally advanced MSI-H/dMMR rectal cancer.

Other trials investigating perioperative ICI therapy for CRC include a phase II study (NCT04082572), which demonstrated a pCR of 79% among 14 patients with localized unresectable or high-risk resectable (defined as ≥20% recurrence risk) MSI-H/dMMR CRC who underwent surgery following treatment with neoadjuvant pembrolizumab.[160] A randomized phase II trial of pre-operative PD-1 inhibitor toripalimab with or without celecoxib enrolled 34 patients with clinical stage II or III MSI-H/ dMMR CRC.[161] The pCR rate was 65% with toripalimab and 88% with toripalimab plus celecoxib.

Several ongoing clinical trials are also evaluating novel ICI combinations to address the significant unmet need for immunotherapy treatments for metastatic MSS/pMMR CRC. In the open-label, phase II comparative AtezoTRIBE trial, 218 patients with MMR-unselected, metastatic CRC were randomized 1:2 to first-line treatment with FOLFOXIRI plus bevacizumab without (arm A) or with (arm B) atezolizumab, followed by maintenance 5-FU plus bevacizumab with (arm B) or without (arm A) atezolizumab.[162 163] With a median follow-up time of 19.9 months, the ORR was similar for the two arms (64% for patients receiving atezolizumab vs 59% for the chemotherapy plus bevacizumab alone group; p=0.412). However, the study did meet its primary end point, as median PFS was significantly longer for the atezolizumab group (13.1 vs 11.5 months; HR 0.69; 80% CI 0.56 to 0.85; p=0.012). Furthermore, although the effect size was smaller, the addition of atezolizumab to chemotherapy plus bevacizumab demonstrated activity in the subgroup of 199 patients with pMMR tumors, with a median PFS of 12.9 vs 11.4 months (HR 0.78; 80% CI 0.62 to 0.97); p=0.071). In the phase II, open-label MAYA study of metastatic MSS and O-6-methylguanine-DNA methyltransferase (MGMT) silenced CRC, patients received two cycles of temozolomide priming followed by nivolumab plus ipilimumab in the absence of disease progression.[164] Acquired MMR deficiency is a well-characterized resistance mechanism to temozolomide, providing rationale for the combination approach. Although 135 patients started temozolomide priming, only 33 patients moved on to receive the dual ICI treatment. With temozolomide priming, the 8-month PFS rate (primary end point) was 32%, with a median PFS of 7.1 months and a median OS of 18.5 months. The rate of severe irAEs was relatively low at 6% for grade ≥3 events. The phase II CheckMate 9X8 study randomized 195 patients with treatment-naïve, MSI-unselected metastatic CRC 2:1 to receive FOLFOX plus bevacizumab with or without nivolumab.[165] The median PFS and OS did not differ significantly between

the two treatment arms with considerably greater toxicity observed for the nivolumab group.

The addition of a tyrosine kinase inhibitor (TKI) to ICIs is one strategy being explored in clinical trials to overcome primary immunotherapy resistance in MSS/pMMR CRC, although these data are conflicting, with some studies showing a lack of efficacy for liver metastases and other studies suggesting a benefit in *RAS*-wild-type (WT) tumors. The combination of lenvatinib (a multikinase TKI) and pembrolizumab was evaluated for safety and efficacy in multiple cohorts of MSS/pMMR solid tumors in the open-label, phase II LEAP-005 study.[166] The CRC cohort included 32 patients with unresectable/metastatic, MSS/pMMR CRC that had progressed on separate prior lines of oxaliplatin and irinotecan.[167] The ORR (the study's primary end point) for the CRC cohort was 22%, with a DCR of 47%. Grade ≥3 TRAEs occurred in 50% of patients, including one treatment-related death due to intestinal perforation. Enrollment in the CRC cohort has been expanded to 100 patients. Other prospective clinical trials of anti-PD-(L)1 ICIs in combination with TKIs inclusive of patients with MSS/pMMR CRC are ongoing and include the REGONIVO (phase Ib),[168] COSMIC-021 (phase Ib),[169] and CAMILLA (phase II)[170 171] trials, with positive efficacy signals for patients with *RAS*-WT disease reported for small numbers of patients in the COSMIC-021 and CAMILLA studies. The liver is generally considered immunologically cold and patients with hepatic metastases have experienced poor outcomes with ICI treatment.[172] A retrospective cohort study including 95 patients with pretreated, MSS/pMMR metastatic CRC receiving PD(L)-1-targeting agents with or without a variety of investigational agents including TKIs demonstrated improved efficacy for patients without liver metastases (ORR 19.5%; median PFS 4.0 months) compared with those with disease metastatic to the liver (ORR 0%; median PFS 1.5 months).[173] Liver metastases were the most predictive variable for progression of disease after controlling for age, Eastern Cooperative Oncology Group (ECOG) performance status, *RAS* and *BRAF* status, TMB, metastatic sites, and primary tumor location. Improved efficacy for patients with metastatic CRC without liver involvement was also observed in the REGONIVO study,[174] and data from the expanded CRC cohort of LEAP-005 were pending at the time of publication. While promising responses have been noted in some studies of ICI plus TKI combinations, patient heterogeneity, sample size, and lack of mature data from phase III trials continue to make this approach strictly investigational and not to be used outside of a clinical trial.

Ongoing studies are also investigating the optimal duration of ICI therapy for patients with advanced MSI-H/dMMR CRC. While the standard label indication for anti-PD-1 therapy duration is up to 2 years or until disease progression or dose-limiting toxicity, new data suggest that 1 year of ICI therapy may be sufficient for some patients. Furthermore, a CR may be difficult to determine in the setting of persistent but stable radiographic findings. With a median of 34.5 months follow-up, the GERCOR NIPICOL study demonstrated 1-year, 2-year, and 3-year PFS rates of 75.4%, 70.0%, and 70.0%, respectively, for 57 patients with chemotherapy-pretreated metastatic, MSI-H/dMMR CRC receiving 4 doses of nivolumab plus ipilimumab followed by nivolumab monotherapy for a total treatment duration of 1 year.[175] Furthermore, two of three patients with stable disease at 12 months who later developed progressive disease achieved a PR with a second course of nivolumab.

Panel recommendations

- For all patients with CRC, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with untreated, metastatic, MSI-H/dMMR CRC, pembrolizumab monotherapy is recommended (LE:2). Treatment with combination nivolumab plus ipilimumab may be considered for this indication as well (LE:3), although there are no randomized data to suggest that this regimen is superior to pembrolizumab monotherapy.
- For patients with untreated, metastatic, MSS/pMMR CRC, treatment with ICIs is not recommended outside of a clinical trial. This applies to patients with tumors that are TMB-H while being MSS/pMMR (LE:3), except for patients with *POLE/POLD1* mutations with an associated ultramutated TMB (LE:3).
- For patients with previously treated, metastatic, MSI-H/dMMR CRC who have not received prior ICI therapy, pembrolizumab monotherapy (LE:3) or nivolumab with (LE:3) or without (LE:3) ipilimumab are all recommended options. Dostarlimab monotherapy is a recommended treatment option for dMMR disease only (LE:3).
- For patients with resected pathological stage I–III MSI-H/dMMR colon cancer, ICIs should not be used in the adjuvant setting outside of a clinical trial. A non-randomized multicenter study of neoadjuvant ICI therapy for patients with resectable dMMR colon cancer demonstrated a pCR (ypT0N0) in 67% of patients (LE:3), but longer follow-up is needed to address survival outcomes. Clinical trial participation is preferred.
- For patients with MSI-H/dMMR resectable rectal cancer, phase II data from a single group study of neoadjuvant ICI therapy suggest remarkable activity (LE:3), but longer follow-up is needed to address the DOR. Clinical trial participation is preferred.

Immunotherapy for the treatment of anal cancer

For patients with SCCA who present with metastatic disease or progression beyond chemoradiation without an option for salvage surgery, there are no FDA-approved treatment options following near certain progression on first-line platinum-based chemotherapy.[176] About 70% of SCCA cases are caused by the human papillomavirus genotype 16 (HPV16) virus genotype, and many patients

with SCCA have HIV.[177] Other HPV-related cancers, including cervical carcinoma and head and neck squamous cell carcinoma, have demonstrated a response to PD-(L)1 inhibition, which invokes reactivation of HPV-specific T cells.[178 179]

While there are no SCCA-specific FDA approvals for immunotherapy, patients with advanced SCCA were included in the KEYNOTE studies leading to some of the tissue-agnostic FDA approvals. Small, early phase immunotherapy studies have suggested some benefit with checkpoint blockade for advanced, pretreated SCCA, particularly for PD-L1-expressing tumors. The phase Ib KEYNOTE-028 study demonstrated a DCR of 58% (17% PR, 42% SD) with pembrolizumab monotherapy in 24 patients with PD-L1-positive (CPS ≥1%) advanced SCCA, with a median PFS of 3.0 months and median OS of 9.3 months.[180] The open-label, phase II KEYNOTE-158 study included multiple cohorts of patients with previously treated, biomarker-unselected, advanced solid tumors, including 112 patients with SCCA.[181] Pooled results from the anal cancer cohorts of the KEYNOTE-028 and KEYNOTE-158 studies (n=137) demonstrated an ORR of 14.0% for PD-L1-positive patients and 3.3% for PD-L1-negative patients.[182] With a median follow-up time of 11.7 months, the 12-month PFS and OS rates were 14.5% and 47.4%, respectively. With further follow-up for a median time of 34.7 months, the ORR was 11% (15% for PD-L1-positive tumors and 3% for PD-L1-negative tumors).[183] In the phase II multicenter NCI9673 (part A) study of 37 patients with treatment-refractory, metastatic SCCA, nivolumab monotherapy was associated with an ORR of 24%, including two CRs.[184] Although only a limited number of patients had pretreatment PD-L1 expression available (four responders and five non-responders), tumor cell PD-L1 expression was higher for patients with responding disease (p=0.0056). Median PFS was 4.1 months and median OS was 11.5 months at a median follow-up time of 10.1 months. While these studies suggest that low or negative PD-L1 expression in SCCA may negatively impact response to ICIs, patients should *not* be selected for ICI treatment based on PD-L1 expression.

Emerging data on immunotherapy for the treatment of anal cancer

The phase III EA2176 study (NCT04444921) is randomizing patients with advanced SCCA 2:1 to first-line carboplatin/paclitaxel with or without nivolumab for 6 months followed by maintenance nivolumab, with a primary end point of PFS.[185] This will be the first phase III randomized trial dedicated to studying advanced, treatment-naïve SCCA, with a target enrollment of 205 patients to be stratified by HIV status and history of prior chemoradiation. The double-blind, phase III POD1UM-303/InterAACT 2 study (NCT04472429) is similarly recruiting patients with unresectable/metastatic SCCA to evaluate the efficacy and safety of adding the anti-PD-1 ICI retifanlimab to frontline carboplatin and paclitaxel.

There are several ongoing studies for SCCA in the second-line/treatment-refractory setting as well. Results of part B of the phase II NCI9673 study (NCT02314169) comparing nivolumab with or without ipilimumab for metastatic, treatment-refractory SCCA are pending. The phase II POD1UM-202 study of retifanlimab enrolled 94 patients with advanced SCCA pretreated with platinum-based chemotherapy, including 9 patients with well-controlled HIV infection. Treatment resulted in an ORR of 14% for retifanlimab, with responses observed regardless of PD-L1 status, presence of liver metastases, age, or HIV status.[186] Furthermore, with a median follow-up time of 7 months, observed responses were durable (median DOR 9.5 months). The use of retifanlimab for pretreated, advanced SCCA was granted orphan drug and fast track designation by the FDA and received priority review status. However, in June 2021, the ODAC deferred approval of retifanlimab for this indication due to concerns that an ORR as low as 14% may not reasonably predict clinical benefit, particularly as many of the responders did not have bulky or non-lymph node (LN) target lesions.[187]

Studies evaluating immunotherapy for early stage SCCA are ongoing as well. The phase III EA2165 study (NCT03233711), for example, is recruiting patients to receive adjuvant nivolumab versus placebo following combined modality treatment for high-risk stage II–IIIB SCCA (T >4 cm; LN-positive), with a primary end point of DFS.

Special patient populations

Patients with Lynch syndrome are uniquely poised to benefit from ICIs as their disease arises from germline dMMR. However, ICI therapy does not appear to confer an increased benefit for patients with Lynch syndrome compared with patients with sporadic MSI-H/dMMR CRC. For example, an analysis of 86 patients with MSI-H/dMMR tumors (including CRC) treated with ICIs showed no significant difference in ORR (46% vs 59%; p=0.27), PFS (HR 1.2; 95% CI 0.582 to 2.512; p=0.61), or OS (HR 1.71; 95% CI 0.697 to 4.196; p=0.24) between Lynch and non-Lynch syndrome-associated disease, respectively.[188] A systematic review of large cohort studies of ICI therapy demonstrated ORRs between 46% and 71% for Lynch-associated CRC compared with 48% to 100% for sporadic MSI-H/dMMR CRC—essentially no difference in response, but as the authors concluded, sample sizes were limited and CIs were wide.[189]

Patients living with HIV (PLWH) have commonly been excluded from clinical trials evaluating immunotherapy due to presumed immune compromise. Substantial unmet need exists for effective anticancer treatments for PLWH, however, especially for SCCA. As many as 1% of women and 28% of men with SCCA are living with HIV.[177] Although not specific to GI malignancies, two studies have demonstrated acceptable safety and no notably reduced efficacy with PD-(L)1 blockade for a small number of patients with advanced solid tumors and HIV.[190 191] Examination of SCCA specimens from 23 PLWH and 17

HIV-negative patients revealed that PD-L1 expression, immune cell density, and interferon-gamma gene expression did not differ significantly based on HIV status.[192] Increasing numbers of clinical trials evaluating immunotherapy for SCCA are now including PLWH. For example, the phase II POD1UM-202 study of retifanlimab for previously treated, advanced SCCA enrolled 9 (9.6%) PLWH and found that HIV status affected neither the efficacy nor the safety of this PD-1 inhibitor.[186] At the time of manuscript publication, the National Cancer Institute (NCI) was specifically recruiting PLWH with SCCA to receive chemoradiation with or without nivolumab according to disease risk (NCT04929028). The FDA recommends that PLWH with a CD4 count <350 cells/µL should 'generally' be eligible for clinical trials only in the setting of a potentially curable malignancy or for interventions 'in a later stage of development that have demonstrated prior activity'.[193] However, there are no data to suggest that immunotherapy for PLWH should be adjusted based on CD4 count, and many HIV-negative patients may also have low CD4 counts due to prior cancer therapies. In fact, a retrospective cohort study of 84 patients with relapsed/refractory cancers who received ICIs in two NCI clinical trials found no significant difference in the proportion of patients with a CD4 count <350 cells/µL between PLWH and HIV-negative patients (p=0.5).[194] Furthermore, 3-year survival rates for patients with HPV-related malignancies did not differ significantly for patients with a CD4 count <350 cells/µL (32.2%) vs ≥350 cells/µL (21.2%; p=0.7). All-in-all, PLWH and cancer should have the opportunity to receive treatment with ICIs under FDA-approved indications and through clinical trial enrollment, regardless of CD4 count.

Patients with inflammatory bowel disease (IBD) have also been excluded from clinical trials of immunotherapy for GI cancer, and data-driven guidelines are lacking for this patient population. A phase Ib basket study of nivolumab for patients with advanced malignancies and an autoimmune disease (NCT03816345) is enrolling patients with IBD, although many clinical trials continue to exclude this population due to risk of toxicity. For additional discussion of patients with IBD, please refer to the **'Patient education and QOL support for patients with gastrointestinal cancer receiving immunotherapy'** section.

Panel recommendations

- For all patients with SCCA, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with treatment-naïve, metastatic SCCA with any MSI/MMR status and/or TMB, there are insufficient data to recommend first-line ICI therapy.
- For patients with previously treated, metastatic SCCA, nivolumab (LE:3) or pembrolizumab (LE:3) are recommended treatment options regardless of MSI/MMR, TMB, and PD-L1 status.

PATIENT EDUCATION AND QOL SUPPORT FOR PATIENTS WITH GASTROINTESTINAL CANCER RECEIVING IMMUNOTHERAPY

Immunotherapy offers some patients with cancer long-term disease control or even a cure. However, immunotherapy is distinct from other anticancer treatments in many ways, including the expected response kinetics, toxicity profile, and cost. To safely and effectively administer these potentially lifesaving agents, providers need to be well-informed about the unique features of immunotherapy and proactively communicate with their patients to provide necessary education and QOL support.

Patient education for immunotherapy for GI cancers

Providing timely education to patients about their cancer care can improve anxiety and self-care decisions and enhance QOL. As immunotherapy gains more indications and its use becomes more widespread, emerging data are demonstrating that patient education also plays a key role in early recognition and reporting of irAEs.[195] A mismatch still persists, however, between the education that providers offer and the content that patients desire. In a Cancer Support Community needs assessment conducted at nine oncology centers across the US, 46% of healthcare providers reported that patient education should go 'quite a bit' in depth into the science of immunotherapy, while only about one-third of patients and caregivers (31% and 38%, respectively) reported a need for this knowledge.[196] Patients and caregivers were far more interested in education about managing immunotherapy-related side effects (55% and 85%, respectively).

There are few published data to inform healthcare providers about the best practices for educating patients about immunotherapy. For example, 50% of patients and 73% of healthcare providers reported difficulty in obtaining information about how to cope with side effects of ICIs.[195] Barriers to educating patients about irAEs include the following: a constant need to update educational materials as more data become available, the high level of organization required to coordinate multidisciplinary team involvement (eg, medical subspecialists), and the unique presentation of irAEs compared with traditional chemotherapy side effects. *Immunotherapy & Me* (NCT03347058) is one patient education program in development that aims to identify and implement the most meaningful resources to improve outcomes and decrease cost for patients receiving immunotherapy treatment for their cancer.

Extrapolation of data from studies of patients receiving chemotherapy suggests that cancer treatment education is most effective when provided prior to treatment initiation in a quiet environment by the primary oncology team, and education should be tailored to the patient's individual learning preference.[195] Furthermore, education regarding irAEs should be reinforced periodically throughout treatment, with emphasis on the importance of notifying the treatment team promptly at the first sign of a potential irAE. It is helpful to provide patients with a handout or card with the name(s) of their oncologic

drug(s) clearly written out in order to avoid confusion, for example, if they were to seek emergency care outside of their designated institution. Additionally, there are several credible online educational resources available to patients and clinicians through the National Cancer Institute (NCI), the American Cancer Society, and SITC. Downloadable resources that may be provided directly to patients and caregivers include, 'SITC CPG on ICI-related adverse events',[12] 'The European Society for Medical Oncology Patient Guide on Immunotherapy-Related Side Effects and their Management',[197] 'The Oncology Nursing Society Immunotherapy Patient Wallet Card',[198] and 'The Hematology Oncology Pharmacy Association Time to Talk Immuno-Oncology Immune Checkpoint Inhibitors Toolkit'.[199]

Immunotherapy-related toxicities are influenced by the patient's immune system and the ICI(s) used, and by the underlying cancer being treated.[200] For example, IBD is a risk factor for immune-mediated diarrhea and colitis, and patients who develop CRC in the setting of IBD should be educated about their increased risk for developing this irAE. While some risk factors have been identified for the development of irAEs in the short-term, the incidence and pattern of long-term immunotherapy complications are largely unknown as clinical studies rarely report safety data beyond 2 years. It is therefore incumbent upon providers to educate patients receiving immunotherapy on the need for long-term vigilance and reporting for suspected irAEs. Particular attention should be paid to organ systems prone to inflammation secondary to a pre-existing autoimmune disease, radiation exposure, or the location of the primary tumor and any metastatic sites of spread. Box 4 provides call parameters for patients with GI cancers receiving immunotherapy. Prior to initiation of immunotherapy and throughout the duration of treatment, clinicians should discuss how irAEs may look or feel with their patients. Patients should be invited to 'call soon and call often' for any symptoms that are abnormal, even for symptoms that are normally present but may have worsened in severity (eg, increased frequency or volume of diarrhea). The potential for late onset irAEs should also be discussed, especially if immunotherapy is administered in the perioperative setting. Patients should be advised that irAEs may manifest at any time, including years after the last dose of ICI, which is why it is important to communicate a history of immunotherapy treatment to future healthcare providers. In addition to irAE guidance, providers should also educate their patients about the importance of reporting any medication changes (including receipt of vaccinations) while receiving immunotherapy as several medications, most notably steroids, may alter the efficacy of ICIs. Some patients may forget the name of a new medication by the time they arrive for their visit, and for these patients, reporting medication changes may be most feasible through an online patient portal.

Box 4 Patient and caregiver education for call parameters for immune-related adverse events (irAEs)

You should contact your healthcare providers for any of the following symptoms (or call 911 or seek emergency services as indicated)*:

- ⇒ New or worsening cough
- ⇒ New or worsening shortness of breath
- ⇒ Chest pain
- ⇒ Fever
- ⇒ Persistent diarrhea
- ⇒ Abdominal pain
- ⇒ Nausea or vomiting
- ⇒ New (diffuse) rash
- ⇒ New neurological symptoms such as severe headaches, confusion, vision changes (including a droopy eyelid or double vision), weakness, difficulty in speaking/swallowing/chewing, or tingling or numbness
- ⇒ Joint/muscle pain or immobility
- ⇒ Significant fatigue or lethargy
- ⇒ Excessive thirst, hunger, or urination
- ⇒ Unexplained and significant weight loss or gain

*Note to providers—these call parameters for patients are not exhaustive but do highlight the following irAEs (symptoms may overlap): arthritis, colitis, dermatitis, encephalitis, endocrinopathies (including type 1 diabetes mellitus), esophagitis, Guillain-Barré syndrome, myasthenia gravis, myocarditis, myositis, and pneumonitis.

In addition to understanding irAEs, it is imperative that patients understand the goals of their specific immunotherapy treatment. Over the past decade, immunotherapy has transformed some cancers (such as stage IV melanoma) from almost universally fatal diseases to potentially curable conditions. At the time of guideline writing, however, this was not necessarily the case for advanced stage GI cancers (with the potential exception of some patients with MSI-H/dMMR tumors). Patients receiving immunotherapy for a GI cancer may experience prolonged disease control, a more limited-term extension of survival and relief from disease symptoms, or no response at all. Without definitive biomarkers to predict whether tumors will respond to immunotherapy and how long these responses will last, it can be challenging for clinicians to communicate expectations for outcomes of treatment. Regardless of these challenges, the goals of treatment with immunotherapy should be presented to patients in a realistic yet hopeful manner, with transparency about disease-specific prognosis and our current limitations on predicting long-term outcomes with immunotherapy.

The nuances of clinical trial outcome measures (eg, DFS vs OS), a lack of predictive tools, and the variable goals of immunotherapy treatment indications can understandably contribute to patient and caregiver confusion. In one study of patients with advanced melanoma and NSCLC, 34% of participants responded in a Prognosis and Treatment Perceptions Questionnaire (PTPQ) that the primary goal of their treatment is to cure their cancer.[201] This underscores the importance of patient education provided by the primary oncology team, as patients who understand their cancer treatment goals are

more likely to enroll in and derive the benefits of hospice at the end of life.[202] Clinicians should endeavor to use plain language whenever possible when discussing the goals of treatment with their patients and be receptive to questions or a need for multiple explanations.

QOL support for patients with gastrointestinal cancer being treated with immunotherapy

QOL should be proactively assessed and all patients receiving immunotherapy should receive aggressive and early symptom management regardless of the stage of their GI cancer. Cancer-related symptoms are likely to change throughout the course of treatment, and an ongoing provider-to-patient conversation should be established to assess the patient's dynamic needs.

Some data suggest that QOL is predictive of survival for patients receiving cancer treatment. For example, a prospective study of 110 patients with ESCC treated with RT with or without chemotherapy demonstrated that EORTC-quality of life questionnaire (QLQ)-core (C)30 pretreatment physical function and 2-month post-treatment dysphagia scores were independently predictive of survival. Although postmarket 'real-world' data on HRQOL measures for patients receiving immunotherapy for GI cancers are not yet widely available, existing QOL data from other disease settings support the use of immunotherapy. A meta-analysis of 13 randomized controlled trials compared patient-reported outcomes (PROs) from studies comparing single-agent anti-PD-(L)1 antibodies versus SOC treatment (mammalian target of rapamycin [mTOR] inhibitor, CTLA-4 inhibitor, or chemotherapy) for patients with a variety of advanced cancers.[203] With a median follow-up of 15 weeks, the pooled difference in mean change of EORTC-QLQ-C30 item score between treatment groups was 5.1 (p<0.001) in favor of the anti-PD-(L)1 treatment group and the time to deterioration (TTD) was significantly longer for the anti-PD-(L)1 group (HR 0.72; p=0.011).

Patients living with cancer have disproportionately high rates of affective disorders such as anxiety and depression.[204] Patients with esophageal cancer are at particularly high risk for these disorders, with an estimated prevalence of depression of 75.81% in one study (compared with 66.72% among all patients with cancer). Through mechanisms not fully understood, depression increases mortality and non-compliance and worsens postoperative outcomes in patients with cancer. While there are no established criteria for the treatment of affective disorders in patients with cancer, a variety of interventions have been studied in this population with some success. Oncology providers should maintain a high index of suspicion for anxiety and depression to promptly identify patients in need of psychological support.

Several registrational trials for the treatment of GI cancers have reported HRQOL as secondary or exploratory end points, and these data have demonstrated equivalent or superior PROs for immunotherapy compared with chemotherapy and/or placebo, as summarized in table 4. Exploratory HRQOL analyses from the CheckMate 577 trial of adjuvant nivolumab vs placebo demonstrated a trend toward improvement in Functional Assessment of Cancer Therapy – Esophageal (FACT-E) and EuroQol (EQ)-5 dimension (D)-3 level (L) PROs measured at baseline and 12 months for both treatment groups.[205] The KEYNOTE-590 study of chemotherapy plus pembrolizumab versus chemotherapy plus placebo for advanced esophageal/GEJ cancer included change in QOL questionnaire scores as prespecified secondary end points.[206] Median TTD in EORTC-QLQ-C30 global health status (GHS)/QOL was not significantly different between the two treatment arms (HR 0.86; 95% CI 0.66 to 1.13; p=0.2864). The least squares mean (LSM) changes for the questionnaires were either not significantly different between the two treatments or favored the pembrolizumab arm. For example, the LSM change from baseline to 18 weeks for the EORTC-QLQ-OES18 pain subscale favored pembrolizumab plus chemotherapy (−2.94; 95% CI −5.86 to −0.02; p=0.0487) whereas there was no significant difference between the treatment groups for change in reflux (−1.19; 95% CI −4.49 to 2.10; p=0.4781) or dysphagia (−2.35; 95% CI −7.78 to 3.07; p=0.3945). In the KEYNOTE-062 study of pembrolizumab monotherapy versus chemotherapy for advanced, PD-L1-positive gastric/GEJ cancer, change in HRQOL questionnaire data from baseline to 18 weeks was also measured as a secondary end point.[207] At week 18, the mean EORTC-QLQ-C30 GHS/QOL scores for pembrolizumab versus chemotherapy were similar (66.4 and 63.6, respectively) with no difference in LSM between arms (−0.16; 95% CI −5.0 to 4.7; nominal p=0.948). While the TTD for the EORTC-QLQ-C30 appetite loss and EORTC-QLQ-STO22 pain subscales was similar between treatment arms, the EORTC-QLQ-C30 nausea/vomiting subscale TTD was significantly longer for pembrolizumab compared with chemotherapy (HR 0.61; 95% CI 0.44 to 0.85; nominal p=0.003). Prespecified HRQOL exploratory end points were reported from the KEYNOTE-177 study of pembrolizumab monotherapy versus chemotherapy for the first-line treatment of patients with metastatic, MSI-H/dMMR CRC.[208] The change in EORTC-QLQ-C30 GHS/QOL LSM from baseline to 18 weeks was significantly better for the pembrolizumab group (LSM difference 8.96; 95% CI 4.24 to 13.69; p=0.0002), with median TTD favoring pembrolizumab as well (HR 0.61; 95% CI 0.38 to 0.98; one-sided nominal p=0.019). Pembrolizumab median TTD subscale scores were also significantly better than chemotherapy in the physical functioning (HR 0.50; 95% CI 0.32 to 0.81; one-sided log-rank p=0.0016), social functioning (HR 0.53; 95% CI 0.32 to 0.87; one-sided log-rank p=0.0050), and fatigue domains (HR 0.48; 95% CI 0.33 to 0.69; one-sided log-rank p<0.0001). The CheckMate 649 study of patients with advanced, untreated gastric, GEJ, and esophageal adenocarcinoma demonstrated a quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) improvement of 2.8 and 1.8 months with the addition of nivolumab to chemotherapy for

Table 4 HRQOL outcomes reported from GI cancer ICI registration trials

Study	Study population	Agents evaluated	PROs measured	Outcomes
CheckMate 577 (NCT02743494)	Patients with stage II/III E/GEJ cancer and residual pathological disease status post-NA chemoradiotherapy and an R0 resection	Adjuvant nivolumab Adjuvant placebo	FACT-E EQ-5D-3L	Trend toward improvement in both treatment groups from BL to week 49 for FACT-E total, ECS, and EQ-5D VAS and Utility Index scores
CheckMate 649 (NCT02872116)	Patients with advanced, untreated gastric, GEJ, and esophageal adenocarcinoma	Chemotherapy plus nivolumab Chemotherapy	Q-TWiST Relative Q-TWiST gains (Q-TWiST difference divided by chemo only OS) defined as clinically important (≥10%) and clearly clinically important (≥15%)	Q-TWiST improvement with addition of nivolumab to chemotherapy: ► PD-L1 CPS ≥5: 2.8 months (95% CI 1.0 to 3.7; relative gain 20.6% [clearly clinically important]) ► All randomized patients: 1.8 months (95% CI 0.9 to 2.7; relative gain 12.7% [clinically important])
KEYNOTE-062 (NCT02494583)	Patients with PD-L1-positive (CPS ≥1) advanced G/GEJ cancer and no prior treatment	Pembrolizumab monotherapy Pembrolizumab plus chemotherapy Chemotherapy	EORTC-QLQ-C30 EORTC-QLQ-STO22	LSM change in EORTC-QLQ-C30 GHS/QOL: no between-arm difference (–0.16; 95% CI –5.01 to 4.69; p=0.948) LSM TTD subscale changes: ► GHS/QOL: similar between arms (HR 0.96; 95% CI 0.67 to 1.38; p=0.826) ► Appetite loss: similar between arms (HR 0.83; 95% CI 0.58 to 1.20; p=0.314) ► Pain: similar between arms (HR 1.22; 95% CI 0.78 to 1.91; p=0.381) TTD for nausea/vomiting subsale: longer for pembrolizumab (HR 0.61; 95% CI 0.44 to 0.85; p=0.003)
KEYNOTE-177 (NCT02563002)	Patients with MSI-H or dMMR metastatic colorectal cancer with no prior treatment	Pembrolizumab Chemotherapy	EORTC-QLQ-C30 GHS/QOL	LSM change (BL to prespecified week 18): EORTC-QLQ-C30 GHS/QOL: clinically meaningful improvement for pembrolizumab versus chemotherapy (8.96 [95% CI 4.24 to 13.69]; two-sided nominal p=0.0002) Median TTD was longer with pembrolizumab versus chemotherapy: ► GHS/QOL (HR 0.61 [95% CI 0.38 to 0.98]; one-sided nominal p=0.019) ► Physical functioning (0.50 [95% CI 0.32 to 0.81]; one-sided nominal p=0.0016) ► Social functioning (0.53 [95% CI 0.32 to 0.87]; one-sided nominal p=0.0050) ► Fatigue (0.48 [95% CI 0.33 to 0.69]; one-sided nominal p<0.0001)

Continued

Table 4 Continued

Study	Study population	Agents evaluated	PROs measured	Outcomes
KEYNOTE-590 (NCT03189719)	Patients with locally advanced/unresectable or metastatic adenocarcinoma or ESCC or Siewert type 1 esophagogastric junction adenocarcinoma with no prior treatment	Chemotherapy plus pembrolizumab Chemotherapy plus placebo	EORTC-QLQ-C30 (GHS/QOL and physical functioning), TTD and change from BL to week 18	LSM change (BL to week 18) in GHS/QOL status: no difference between arms (–0.10 [95% CI –3.40 to 3.20]; p=0.9530)
				Median TTD in EORTC-QLQ-C30 GHS/QOL: no difference between treatment arms (HR 0.86 [95% CI 0.66 to 1.13]; p=0.2864)
			EORTC-QLQ-OES18 (pain, reflux, dysphagia), TTD and change from BL to week 18	LSM changes (BL to 18 weeks) for EORTC-QLQ-OES18 subscales: ► Pain: pembrolizumab plus chemotherapy better (–2.94 [95% CI –5.86 to –0.02]; p=0.0487) ► Reflux: no difference between treatment arms (–1.19 [95% CI –4.49 to 2.10]; p=0.4781) ► Dysphagia: no difference between treatment arms (–2.35 [95% CI –7.78 to 3.07]; p=0.3945)
			EQ-5D-5L, TTD and change from BL to week 18	

BL, baseline; CI, confidence interval; CPS, combined positive score; dMMR, mismatch repair deficient; ECS, esophageal cancer subscale; EQ-5D-VAS, EuroQol 5 dimension visual analogue scale; ESCC, esophageal squamous cell carcinoma; G, gastric; GEJ, gastroesophageal junction; GHS, global health status; GI, gastrointestinal; ICI, immune checkpoint inhibitor; LSM, least squares mean; MSI-H, microsatellite instability-high; NA, neoadjuvant; OS, overall survival; PD-L1, programmed death-ligand 1; PRO, patient-reported outcome; QOL, quality of life; TTD, time to deterioration.

patients with PD-L1 CPS ≥5 and all randomized patients, respectively.[209]

Financial hardship, which is associated with worse QOL and survival outcomes, is common among patients with cancer as they navigate costly medications, procedures, and hospitalizations.[210 211] Immunotherapy agents are also among the most expensive anticancer drugs. In a survey of patients receiving immunotherapy for stage IV NSCLC, 52% of participants reported financial hardship across multiple Medical Expenditure Panel Survey-Experiences with Cancer Survivorship Supplement (MEPS-ECSS) psychological, behavioral, or material domains.[212] Only 7% of patients reported no out-of-pocket expenses and 37% reported worry about losing health insurance due to their cancer diagnosis. A cancer diagnosis can also impact caregivers—42% of patients reported that their caregiver reduced their employment level (ie, took time off or changed working hours). This reduction in caregiver employment was significantly associated with patient financial hardship (p=0.03) and financial distress as measured by Comprehensive Score for Financial Toxicity–Functional Assessment of Chronic Illness Therapy (FACIT-COST; p=0.01). Although longitudinal data to establish a causal relationship between immunotherapy and patient financial hardship are lacking, caregiver employment reduction may be an important sign of financial hardship for the patient.

Providers must be attuned to the likely possibility for financial distress for their patients and proactive in establishing open lines of communication throughout treatment. For example, a provider might initiate a conversation by asking if patients are feeling concerned about money for any reason and emphasizing that resources to help pay for the costs associated with treatment are available. This should not be a one-time conversation but rather an ongoing discussion to identify any difficulties with finances before they become crises. Patients should be encouraged to voice their financial concerns to any of their treating providers, and these concerns should be addressed with immediate referral to a social worker or financial counselor. Early referrals for financial support can help to address multiple potential barriers to care (eg, cost of medications and transportation) and improve overall care and communication.

Resources to support quality of life during and after immunotherapy treatment

Different strategies can be offered to proactively improve QOL for patients with GI cancers including participation in a cancer support group, which has been shown to lower anxiety and depression.[213] National support groups specific for GI cancers include the Anal Cancer Foundation (ACF), Farrah Fawcett Foundation, Colorectal Cancer Alliance, Love Your Buns, Esophageal Cancer Action Network (ECAN), Esophageal Cancer Awareness Association (ECAA), Esophageal Cancer Education Foundation, The Cholangiocarcinoma Foundation, the Hirshberg Foundation for Pancreatic Cancer Research, Pancreatic Cancer Action Network (PanCAN), Debbie's Dream Foundation: Curing Stomach Cancer, Hope for Stomach Cancer, and No Stomach for Cancer, among others.

Early referral for professional dietary support services is another way to improve QOL for some patients with GI cancers, particularly for patients with esophageal cancer.[214] Up to 85% of patients diagnosed with esophageal cancer are malnourished, and their nutritional status often worsens during cancer treatment. Patients' nutritional status should be regularly assessed throughout treatment with a validated oncology nutrition tool with prompt referral of moderate-risk to high-risk patients to a nutrition specialist.

Some patients with GI cancers face the additional challenge of an enteral ostomy, which is associated with adverse impacts on HRQOL.[215 216] Although immunotherapy-specific data are lacking, ostomy complications (eg, pyoderma gangrenosum) have been reported in the context of autoimmune disease.[217 218] It is therefore imperative for oncology providers to proactively assess stoma health for patients receiving ICIs. Providing ostomy education to patients results in improved HRQOL, and an increase in psychosocial adjustment.[219] In addition to referral to a specialized ostomy nurse, patients may be referred to the following online resources: American Cancer Society Colostomy Guide, Memorial Sloan Kettering Cancer Center Caring for your Ileostomy or Colostomy, and the United Ostomy Associations of America New Ostomy Patient Guide.

Palliative care is associated with improved QOL as well as improved survival, decreased need for acute hospital care, and decreased cost of end-of-life care.[220] While hospice care should be offered, when appropriate, providers should clearly communicate that palliative care is distinct from end of life care and is meant to provide symptomatic management throughout a patient's cancer journey regardless of disease stage or treatment intent. Patients should be frequently encouraged to reach out to their primary oncology provider to request palliative care if or when they require symptom management.

Immunotherapy can present unique challenges to delivering palliative care warranting careful consideration of the risks versus benefits of certain palliating treatments. For example, glucocorticoids used to alleviate pain and swelling, improve energy, and stimulate appetite have a known immunosuppressive effect and patients receiving steroids are commonly excluded from clinical trials of immunotherapy.[221] Although steroids used to manage irAEs do not seem to diminish checkpoint blockade efficacy in real-world studies,[222] receipt of ≥10 mg prednisone for palliative indications has been associated with shorter PFS and OS.[223] Lastly, antibiotics may profoundly perturb the immune system due to dysbiosis, which could alter the efficacy of immunotherapy.[224] Patients receiving immunotherapy with concomitant palliative care should be monitored closely, with prompt taper or discontinuation of these potentially counteracting palliative medications when clinically appropriate.

Panel recommendations

- Patient and caregiver education should include a focused discussion of the fundamental differences between immunotherapy, targeted therapy, and chemotherapy tailored to the patient's learning style. Patient education should include an extensive discussion of irAEs.
- Providers should initiate a conversation about the cost associated with ICIs and cancer care early and address financial hardship throughout the course of care.
- Realistic expectations and goals of treatment should be discussed at the time of diagnosis and at times of changes in clinical status for all patients with GI cancer.
- Providers should advise their patients to promptly report all medication changes to their oncology team as several medications, particularly steroids (LE:4), may impact the efficacy of immunotherapy.

CONCLUSION

Cancers of the GI and pancreaticobiliary tract were historically treated with interventions that too often produced only short-term benefit. KEYNOTE-016 opened the door for immunotherapy to treat MSI-H/dMMR cancers, allowing a select group of patients with advanced GI cancers to achieve a durable survival benefit. Subsequent studies have carved out indications for ICIs to treat BTCs and esophagogastric cancers, including in the adjuvant setting. However, GI cancers remain unresponsive to immunotherapy for hundreds of thousands of patients, particularly those with PDAC and MSS/pMMR CRC. Continued clinical and reverse translational studies are needed to inform future drug development strategies for agents and combinations capable of inflaming immunologically cold GI tumors. Biomarker discovery is also needed to identify the patients most likely to gain the long-term survival benefit that immunotherapy may offer. Numerous studies addressing these obstacles are ongoing, and it is incumbent upon the entire oncology community to prioritize clinical trial enrollment in shared decision-making with their patients. This guideline will be updated as highly anticipated new data on immunotherapy for the treatment of GI cancers become available.

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