Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline Update

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE To provide updated recommendations for immunotherapy and targeted therapy for patients with advanced gastroesophageal cancer.

METHODS ASCO convened an Expert Panel to conduct a systematic review of relevant studies and develop recommendations for clinical practice.

RESULTS Twelve newly published or updated phase III randomized controlled trials met the inclusion criteria for the systematic review.

RECOMMENDATIONS The target population for these recommendations is patients with unresectable locally advanced, advanced, or metastatic gastroesophageal cancer. Results from testing for actionable biomarkers should be available as soon as possible to inform treatment decision making. Immunotherapy with doublet chemotherapy is recommended for patients with proficient mismatch repair (pMMR)/microsatellite stable (MSS) human epidermal growth factor receptor 2 (HER2)–negative gastroesophageal adenocarcinoma or squamous cell carcinoma and PD-L1 expression ≥1; patients with higher PD-L1 expression are more likely to benefit from immunotherapy. Zolbetuximab is recommended for patients with gastroesophageal adenocarcinoma, PD-L1 <1, and positive CLDN18.2 expression. Patients with dual PD-L1 and CLDN18.2 positivity should engage in shared decision making, considering the factors outlined in the guideline. Doublet chemotherapy alone is recommended for patients who are not positive for actionable biomarkers or are not considered candidates for targeted therapy or immunotherapy. For patients with pMMR/MSS HER2-positive gastric/gastroesophageal junction (GEJ) adenocarcinoma, trastuzumab and doublet chemotherapy is recommended; for patients with PD-L1 expression ≥1, the addition of pembrolizumab is recommended. Immunotherapy alone or with doublet chemotherapy is recommended for patients with mismatch repair deficient/microsatellite instability–high gastroesophageal cancer. Second-line therapy options include ramucirumab with paclitaxel, trastuzumab deruxtecan for HER2-positive gastric/GEJ adenocarcinoma, and immunotherapy for PD-L1 ≥1 esophageal squamous cell carcinoma after first-line combination chemotherapy without immunotherapy.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Gastroesophageal cancers, inclusive of gastric, esophageal, and gastroesophageal junction (GEJ) cancers, are among the most prevalent GI malignancies globally. There were just under one million new cases and approximately 760,000 deaths due to gastric cancer in 2022, which ranks fifth globally in incidence and mortality. In addition, there were over 500,000 new cases and 445,000 deaths worldwide due to esophageal cancer in the same year.[1] Incidence of gastric cancer is higher in East Asia compared with other areas of the world, while cancer of the GEJ is the fastest growing site of cancer in Western populations.[2] Squamous cell carcinoma accounts for more than 85% of esophageal cancers worldwide.[3] Because earlier stages can be asymptomatic, gastric and GEJ cancer is often diagnosed at a more advanced stage,[4] and 5-year survival is approximately 10% for these patients.[5] In the United States, there were an estimated 52,000 new cases and 27,000 deaths due to gastroesophageal cancer in 2025.[6]

Historically, the standard treatment for advanced or metastatic gastric and GEJ adenocarcinoma was doublet chemotherapy with folinic acid, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX).[7] This treatment is associated with a median survival time of approximately 1 year.[4] More recently, immunotherapy and targeted therapy options have been developed that can inhibit tumor growth by blocking important chemical pathways or mutant proteins.[8] Patients with gastric and GEJ adenocarcinoma have a relatively high rate of actionable mutations that may be targeted for therapy and have therapeutics developed and approved to target them. For example, the prevalence for aberrant activation of human epidermal growth factor receptor (HER) tyrosine kinases, including HER2, is approximately 10% to 30% in patients with gastric cancer.[9,10] Anti–PD-1 immune checkpoint inhibitors, which bind to the cancer surface cell protein PD-1, block cancer cells from suppressing the immune system. The real-world rate of PD-L1 positivity at threshold of combined positive score (CPS) of at least 1 is estimated to be approximately 79% in gastroesophageal adenocarcinoma.[11] A pathologic variant of one of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), which can lead to high DNA microsatellite instability (MSI), is present in approximately 5% of patients.[12] Claudin 18.2 (CLDN18.2), which is expressed in differentiated gastric mucosal membrane epithelial cells, is present in almost 40% of patients with gastric cancer, although this rate varies by geographic area.[13] These biomarkers may not be mutually exclusive.[14]

ASCO previously published a guideline in 2023 with recommendations for first-line therapy for patients with specific biomarkers, including PD-L1 and HER2, as well as limited later-line targeted or immunotherapy options. This update includes new data on previously recommended first-line and later-line therapy options, good practice statements on biomarker testing, and advice on shared decision making for patients who express positivity for multiple biomarkers.

TARGET POPULATION AND AUDIENCE

Target Population
Patients with locally advanced unresectable, advanced, or metastatic gastroesophageal cancer.

Target Audience
Medical oncologists and other health care professionals who are involved in the care and treatment of advanced gastroesophageal cancer, patients, caregivers, and health care systems.

BACKGROUND

Predictive Biomarker Testing in Gastric and GEJ Adenocarcinoma and Esophageal Squamous Cell Carcinoma

Consistent with previous ASCO guidance, the Expert Panel recommends that predictive biomarker testing be conducted before development of the treatment plan.[15] Several guideline recommendations in Table 1 are based on a patient's personal biomarker profile; therefore, the Expert Panel endorses recommendations for testing for the following predictive biomarkers in gastroesophageal adenocarcinoma at the time of diagnosis: HER2, MMR and/or MSI, CLDN18.2, and PD-L1.[16] Relevant biomarkers for esophageal squamous cell carcinoma (ESCC) are MMR/MSI and PD-L1. Detailed recommendations on testing methods are outside the scope of this guideline; however, the Expert Panel agrees that clinicians should consider using broad-based next-generation sequencing (NGS) for actionable biomarker testing. In addition, the results of molecular testing should be available at the time of treatment decision making.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions for patients with unresectable locally advanced, advanced, or metastatic cancer:

1. Is immunotherapy or targeted therapy plus chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with proficient mismatch repair (pMMR)/microsatellite stable (MSS) HER2-negative gastroesophageal adenocarcinoma? The following subgroups are of interest:
   a. PD-L1 expression at cutoff levels of <1 versus ≥1, <5 versus ≥5, and <10 versus ≥10;
   b. CLDN18.2-positive, defined as ≥75% of viable tumor cells demonstrating moderate (2+) to strong (3+) membranous CLDN18 staining.[16]

TABLE 1. Summary of Recommendations for Patients With Locally Advanced Unresectable, Advanced, or Metastatic Gastroesophageal Cancer

Patient Population	Recommendation
General Note. The following recommendations (strong or conditional) and terminology [see the Data Supplement] represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible. The treatment algorithms demonstrate a visual representation of the recommendations.	
Note regarding fluoropyrimidine-based chemotherapy. Approximately 4%-8% of the population has partial DPD enzyme deficiency from carrying one of four *DPYD* genetic variants.[49,58] These patients are at higher risk of severe fluoropyrimidine toxicity. For this reason, patients should be tested for *DPYD* genetic variants before initiating treatment. For patients with partial *DPYD* deficiency, dosage should be individualized and modified based on tolerability and intention of treatment. Fluoropyrimidine use should be avoided completely in DPD-deficient patients (ie, carrying two no-function *DPYD* alleles).	
Predictive biomarker testing	1.1. Testing to determine the presence of predictive biomarkers PD-L1, dMMR/MSI-H, CLDN18.2, and HER2 in gastroesophageal adenocarcinoma is recommended, and PD-L1 and dMMR/MSI-H status should be tested for ESCC. Clinicians should consider broad-based NGS testing, which includes pan-tumor biomarkers. The results of predictive biomarker testing should be available as soon as possible to inform treatment decision making. (Good Practice Statement)
First-line therapy	
pMMR/MSS HER2-negative gastric/GEJ and esophageal adenocarcinoma	2.1. For patients with pMMR/MSS HER2-negative gastric/GEJ or esophageal adenocarcinoma with PD-L1 expression ≥1 and absence of CLDN18.2 expression, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy in combination with immunotherapy may be recommended. (Evidence quality: High; Strength of recommendation: Conditional)
	Qualifying statements for Recommendation 2.1 Immunotherapy benefit has shown a positive association with higher PD-L1 expression (eg, greater benefit with PD-L1 expression ≥10). Not all possible PD-L1 cutoff scores have been assessed; therefore, the optimal PD-L1 cutoff score balancing benefits and harms is unknown. Recommended immunotherapy agents include pembrolizumab, nivolumab, or tislelizumab. These agents are considered to have similar efficacy.[50] Selection of a specific agent should be based on dosing schedule, cost considerations, toxicity, and method of administration. Taking into account the clinical situation, clinicians should avoid withholding the start of chemotherapy while awaiting biomarker testing results.
	2.2. For patients with pMMR/MSS HER2-negative gastric/GEJ adenocarcinoma with PD-L1 expression <1 and positive CLDN18.2 expression, fluoropyrimidine- and platinum-based chemotherapy combined with zolbetuximab should be offered. (Evidence quality: Moderate; Strength of recommendation: Strong)
	2.3. For patients with pMMR/MSS HER2-negative gastric/GEJ adenocarcinoma with PD-L1 expression ≥1, and CLDN18.2 expression positivity, fluoropyrimidine- and platinum-based chemotherapy combined with immunotherapy or zolbetuximab may be offered on a case-by-case basis. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statement for Recommendation 2.3: Choice of therapy should take into consideration degree of PD-L1 expression, toxicity profile, burden of symptoms, and anticipated improvement in symptoms associated with response to treatment, patient comorbidities, and prior medical and treatment history.
	2.4. For patients with pMMR/MSS HER2-negative gastroesophageal adenocarcinoma, PD-L1 expression <1, and absence of CLDN18.2 expression, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy should be offered. (Evidence quality: High; Strength of recommendation: Strong)
pMMR/MSS HER2-positive gastric/GEJ adenocarcinoma	3.1. For patients with pMMR/MSS HER2-positive gastric/GEJ adenocarcinoma with PD-L1 expression ≥1, pembrolizumab plus trastuzumab should be offered, in combination with fluoropyrimidine- and oxaliplatin-based chemotherapy. (Evidence quality: Moderate; Strength of recommendation: Strong)
	3.2. For patients with pMMR/MSS HER2-positive gastric/GEJ adenocarcinoma with PD-L1 expression <1, trastuzumab should be offered in combination with fluoropyrimidine- and oxaliplatin-based chemotherapy. (Evidence quality: Moderate; Strength of recommendation: Strong)
dMMR/MSI-H gastric/GEJ or esophageal adenocarcinoma or ESCC	4.1. Immunotherapy in combination with fluoropyrimidine- and oxaliplatin-based chemotherapy may be offered. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	4.2. Immunotherapy alone is an additional treatment option that may be offered on a case-by-case basis. (Evidence quality: Low; Strength of recommendation: Conditional)
ESCC that is locally advanced unresectable and not amenable to definitive chemoradiation, advanced or metastatic	5.1. For patients with pMMR/MSS ESCC and PD-L1 expression ≥1, first-line therapy with immunotherapy in combination with fluoropyrimidine- and platinum-based chemotherapy or nivolumab plus ipilimumab may be offered. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statement for Recommendation 5.1: Immunotherapy benefit has shown a positive association with higher PD-L1 expression (ie, greater benefit with PD-L1 expression ≥10). Not all possible PD-L1 cutoff scores have been assessed; therefore, the optimal PD-L1 cutoff score balancing benefits and harms is unknown.
	5.2. For patients with pMMR/MSS ESCC with PD-L1 expression <1, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy may be offered. (Evidence quality: Low; Strength of recommendation: Conditional)
	Qualifying statement for Recommendations 2.1 to 5.2: Chemotherapy alone may be offered to patients who express predictive biomarkers but are not considered candidates for targeted therapy or immunotherapy.

(continued on following page)

TABLE 1. Summary of Recommendations for Patients With Locally Advanced Unresectable, Advanced, or Metastatic Gastroesophageal Cancer (continued)

Patient Population	Recommendation
Second- or third-line therapy	
pMMR/MSS HER2-negative gastric/GEJ adenocarcinoma	6.1. For patients with pMMR/MSS advanced gastroesophageal adenocarcinoma whose disease has progressed after first-line therapy, ramucirumab plus paclitaxel may be offered. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statements for Recommendation 6.1 Ramucirumab plus FOLFIRI may be an option for patients who have previously been treated with docetaxel or experienced neurotoxicity with first-line treatment. Although outside the scope of this review, for patients with gastric or GEJ adenocarcinoma, trifluridine and tipiracil may be offered after progression on second-line therapy. *Note for Recommendation 6.1:* CLDN18.2 inhibitor zolbetuximab has not been studied as second-line therapy for previously treated patients with gastroesophageal adenocarcinoma and is therefore not recommended for this patient population.
pMMR/MSS HER2-positive gastric/GEJ adenocarcinoma	6.2. For HER2-positive patients with gastric/GEJ adenocarcinoma and progressive disease after first-line therapy, trastuzumab deruxtecan should be offered. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Note for Recommendation 6.2: Repeat tumor testing after progression on trastuzumab is recommended to ensure that the tumor maintains HER2 expression after progression on first-line HER2-directed therapy.
ESCC	6.3. For patients with ESCC whose disease has progressed after first-line combination chemotherapy without immunotherapy and with PD-L1 ≥1, nivolumab or tislelizumab may be offered, and for patients with PD-L1 ≥10, pembrolizumab may be offered. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Note to Recommendation 6.3: This is expected to be a rare circumstance as patients who are candidates for immunotherapy should receive it as first-line therapy.

NOTE. The strength of the recommendation is defined as follows, Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.
Abbreviations: CLDN18.2, claudin 18.2; dMMR, deficient mismatch repair; DPD, dihydropyrimidine dehydrogenase; ESCC, esophageal squamous cell carcinoma; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NGS, next-generation sequencing; pMMR, proficient mismatch repair.

2. Is immunotherapy or targeted therapy plus chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with pMMR/MSS HER2-positive gastroesophageal adenocarcinoma?
3. Is immunotherapy or targeted therapy plus chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with ESCC that is not amenable to definitive chemoradiation?
4. Is immunotherapy or targeted therapy alone or with chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with deficient mismatch repair (dMMR)/microsatellite instability–high (MSI-H) gastroesophageal adenocarcinoma or ESCC?
5. Is immunotherapy or targeted therapy recommended as second-line or third-line treatment for gastroesophageal adenocarcinoma or ESCC?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were developed with a systematic review of evidence identified through online searches of PubMed from April 2022 to June 2025 for phase III randomized controlled trials (RCTs) and systematic reviews of phase III RCTs. Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: patients with unresectable locally advanced, advanced, or metastatic gastric, GEJ, or esophageal adenocarcinoma, or ESCC with biomarkers including HER2, PD-L1, CLDN18.2, and dMMR/MSI-H.
- Interventions: immunotherapy or targeted therapy with or without chemotherapy.
- Comparisons: other immunotherapy or targeted therapy with or without chemotherapy, chemotherapy alone (ie, fluoropyrimidine and platinum), placebo, or best supportive care.
- Outcomes: overall survival (OS), progression-free survival (PFS), grade 3-5 treatment-related adverse events (TRAEs), health-related quality of life (HRQOL).

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals within 2 years; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. Comparisons of one type of chemotherapy versus another for patients without biomarker expression were outside the scope of this guideline.

The Expert Panel met via teleconference, and members were asked to provide ongoing input on the guideline development protocol, assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. Ratings for the strength of the recommendation and evidence quality are provided with each recommendation, defined in Appendix Table A2. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[17,18] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. This rating includes study design, risk of bias, consistency and precision of outcomes, directness of evidence, and publication bias assessed by one reviewer. Heterogeneity was assessed using the I^2 statistic and informally categorized as low: <40%, moderate: 30%-60%, substantial: 50%-90%, or considerable: 75%-100%.[17] GRADE summary of findings tables, and Figure 1 were created using MAGICApp software. All funding for the administration of the project was provided by ASCO.

Data Analysis

Hazard ratios (HRs) were extracted where available for time-to-event data; for other dichotomous outcomes, relative risk (RR) was calculated using reported events and population totals in the treatment and control groups. For meta-analyses of grade 3-5 TRAEs, the inverse variance statistical method with random effects analysis model, DerSimonian and Laird heterogeneity estimate, and Wald-type summary effect CI method were used with Cochrane's Review Manager (RevMan). All other meta-analyses were conducted using a random effects model and DerSimonian and Laird heterogeneity estimate with STATA 17.0 (College Station, TX).

Guideline Review and Approval

The draft recommendations were released to the public for open comment from September 10, 2025, through September 29, 2025. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with written comments received. A total of 73% of the 11 respondents either agreed or agreed with slight modifications to the recommendations and 27% of the respondents disagreed with one or more recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Review comments such as consideration of European Society for Medical Oncology (ESMO) meeting results from FORTITUDE-101, and findings of studies of triplet chemotherapy were reviewed by the Expert Panel and integrated into the manuscript. Additionally, a guideline implementability review was conducted. Based on this review, revisions were made to the draft to clarify recommended actions for clinical practice.

All changes were incorporated into the final manuscript prior to ASCO Evidence Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guidelines. Based on formal reviews of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Studies Identified in the Literature Search

In the first-line setting, three phase III RCTs of immunotherapy plus combination fluoropyrimidine- and platinum-based chemotherapy versus chemotherapy alone,[19-21] and two phase III RCTs of CLDN18.2 inhibitor zolbetuximab plus chemotherapy compared with chemotherapy alone met the inclusion criteria for this guideline update.[7,22] Updated or interim analyses from the phase III RCTs CheckMate-649,[12] CheckMate-648,[23] KEYNOTE-811,[41] KEYNOTE-590,[24] and ATTRACTION-4[25] were added to previously published trials of first-line therapy.[25,26] Across studies, patients had favorable performance status (PS) of 0 (fully active, able to carry on all predisease

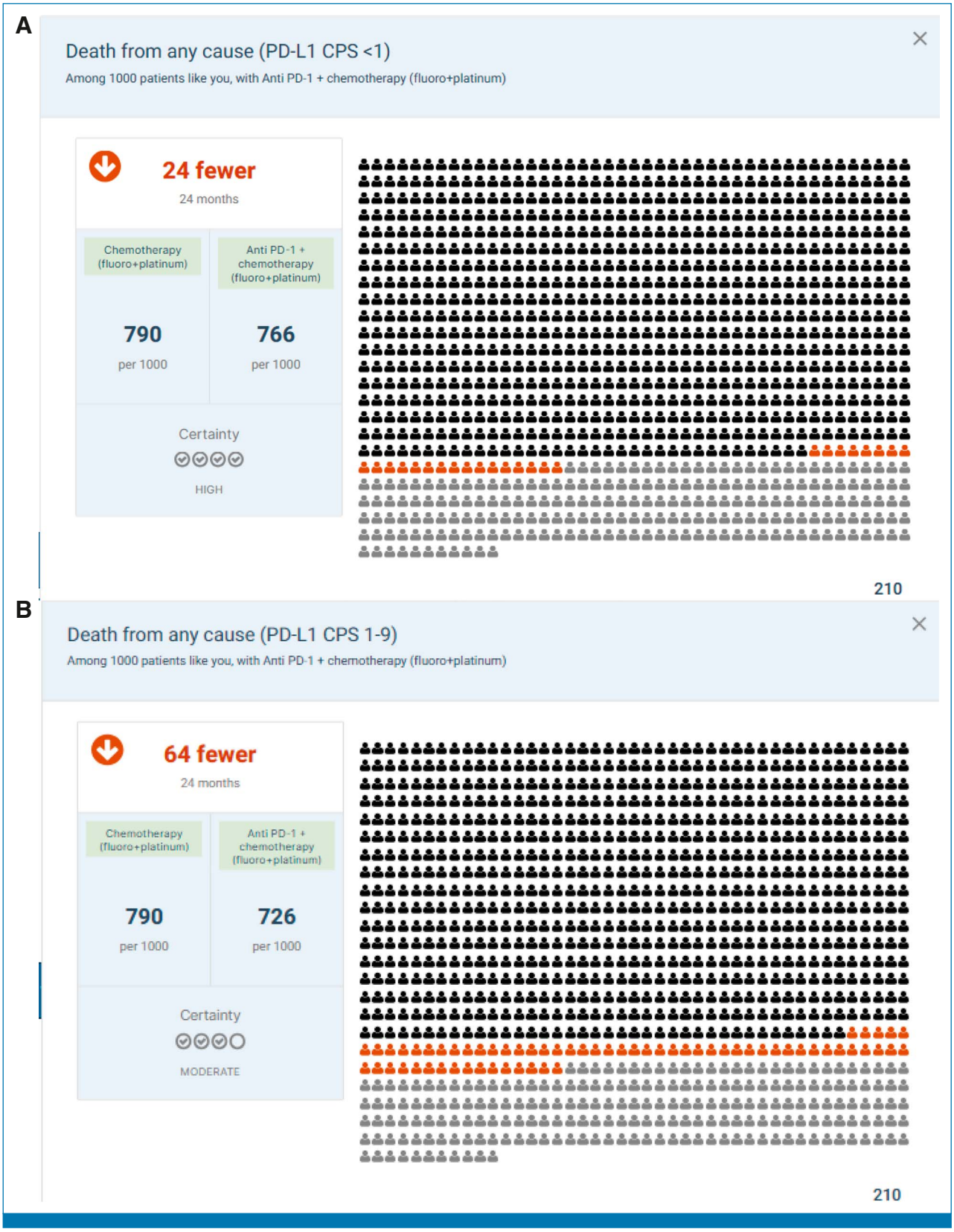

FIG 1. Patients with unresected locally advanced or advanced/metastatic gastric/GEJ adenocarcinoma: estimated rate of death from any cause per 1,000 patients participating in clinical trials of immunotherapy and combined fluoropyrimidine- and platinum-based chemotherapy versus fluoropyrimidine- and platinum-based chemotherapy alone for (A) PD-L1 <1, (B) PD-L1 CPS 1-9 (source: Leone et al[52] with data from Zhao et al.[53] HR for OS was significantly superior with the addition of an immunotherapy agent in this analysis, but the proportional hazards assumption was found to be violated),[52,53] (C) PD-L1 ≥1, and (D) PD-L1 CPS ≥10. Control event rate is derived from KEYNOTE-859 estimated rate of survival at 24 months, with experimental event rate calculated based (continued on following page)

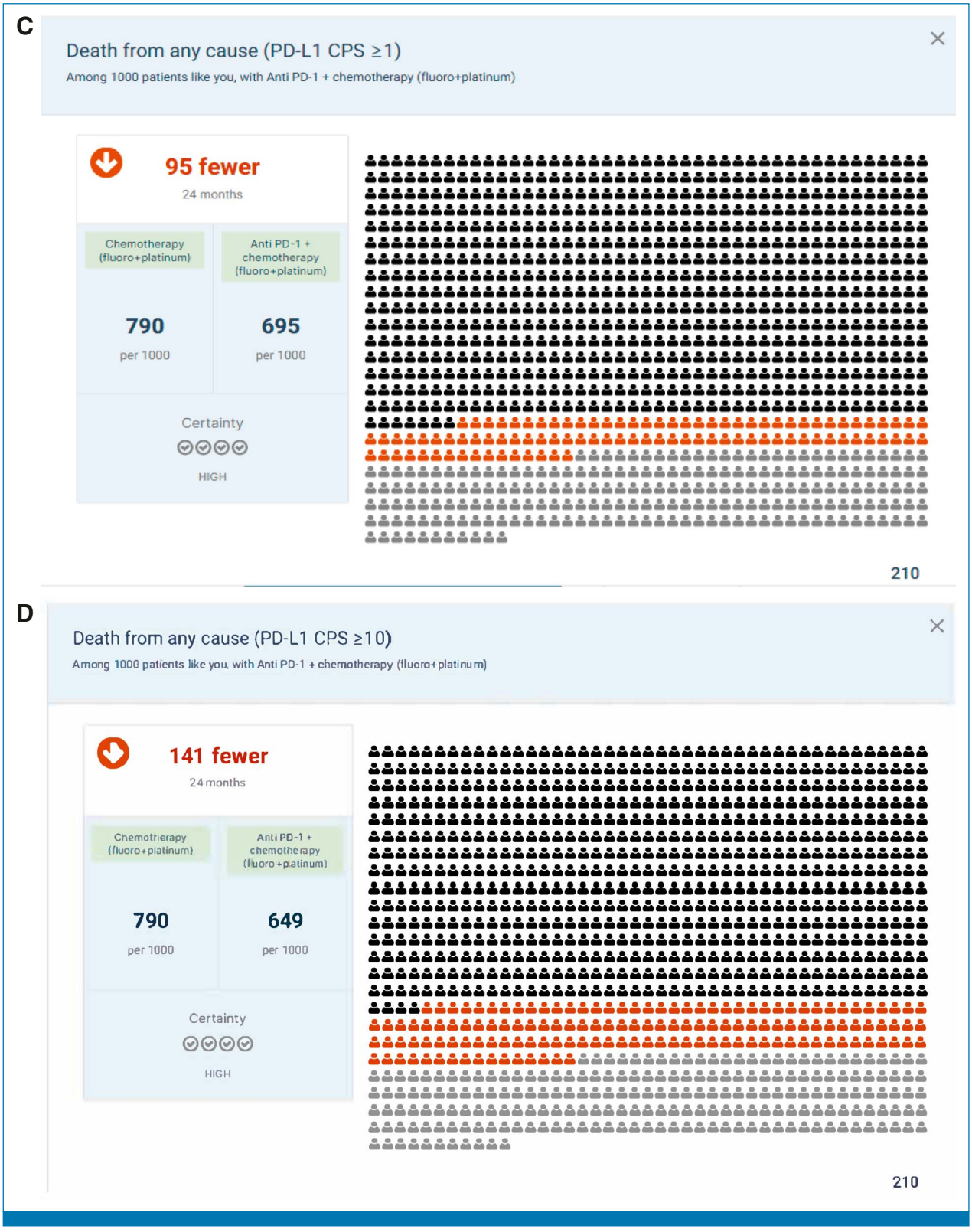

FIG 1. (Continued). on HRs from meta-analyses of all included trials (Table 2). CPS, combined positive score; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival.

performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) according the Eastern Cooperative Oncology Group (ECOG) PS scale.[27] RATIONALE-302,[3] a phase III RCT of tislelizumab versus chemotherapy, and DestinyGastric04,[28] a phase III RCT of

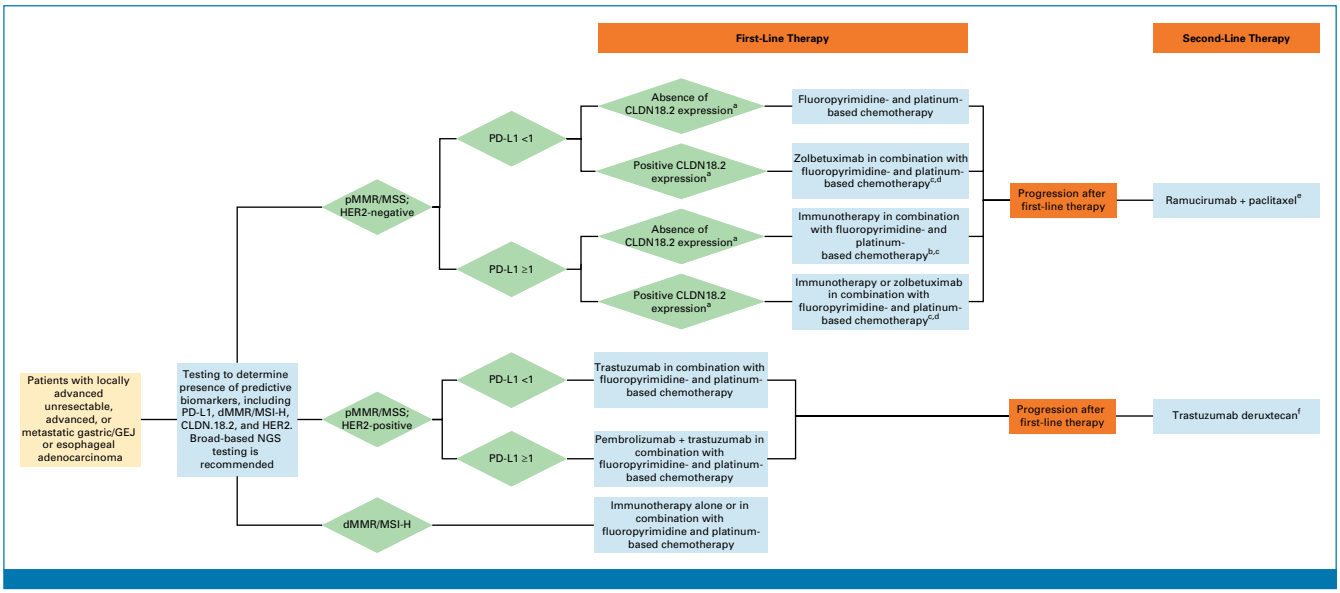

FIG 2. Immunotherapy and targeted therapy for locally advanced unresectable, advanced, or metastatic gastroesophageal adenocarcinoma algorithm. Note regarding fluoropyrimidine-based chemotherapy. Patients should be tested for *DPYD* genetic variants before initiating treatment. For patients with partial *DPYD* deficiency, dosage should be individualized and modified based on tolerability and intent of treatment. Fluoropyrimidine use should be avoided completely in DPD-deficient patients (i.e., carrying two no-function *DPYD* alleles). [a]CLDN18.2 expression positivity is defined as ≥75% of viable tumor cells demonstrating moderate (2+) to strong (3+) membranous CLDN18.2 staining using immunohistochemistry. [b]Immunotherapy benefit has shown a positive association with higher PD-L1 expression. All possible PD-L1 cutoff scores have not been assessed; therefore, the optimal score balancing benefits and harms is unknown. Recommended immunotherapy agents include nivolumab, pembrolizumab, or tislelizumab; these agents are considered to have similar efficacy. Selection of a specific agent should be based on baseline performance status, dosing schedule, cost considerations, toxicity and method of administration. Taking into account the clinical situation, clinicians should avoid delaying the start of chemotherapy treatment while awaiting biomarker testing results. [c]Fluoropyrimidine- and platinum-based chemotherapy alone is an option for patients who are not considered candidates for targeted therapy or immunotherapy. [d]Choice of therapy should take into consideration degree of PD-L1 expression, toxicity profile, burden of symptoms and anticipated improvement in symptoms associated with response to treatment, patient comorbidities, and prior medical and treatment history. [e]FOLFIRI may be an option for patients who have previously been treated with docetaxel or experienced neurotoxicity with first-line treatment. [f]Repeat tumor testing after progression on trastuzumab is recommended to ensure that the tumor maintains HER2 expression after progression on first-line HER2-directed therapy. dMMR, deficient mismatch repair; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability–high; MSS, microsatellite stable; pMMR, proficient mismatch repair.

trastuzumab deruxtecan versus ramucirumab + paclitaxel, were added to previously published trials of later-line therapy.[29-35] Additional publications that focused on HRQOL for participants in these trials are also included in the evidence base.[36-41] Data from RCTs using agents that are not currently US Food and Drug Administration (FDA)–approved are included in the Data Supplement (Tables S9-S14).[42-46] Studies of sintilimab + chemotherapy provided analyses by CPS subgroups and thus were included in the meta-analyses, although this agent is not currently FDA-approved.[47,48] Evidence quality ratings for the outcomes of interest are provided in the footnotes to included data tables. Refer to Appendix Table A2 for definitions for the quality of the evidence, and the Methodology Manual for more information.

RECOMMENDATIONS

All recommendations are available in Table 1, and Figures 2 and 3 show the recommendations as algorithms.

CLINICAL QUESTION 1

Is immunotherapy or targeted therapy plus chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with pMMR/MSS HER2-negative unresectable locally advanced, advanced, or metastatic gastroesophageal adenocarcinoma?

Literature Review and Analysis

First-Line Therapy for Patients With pMMR/MSS HER2-Negative Gastric or GEJ Adenocarcinoma

Immunotherapy + chemotherapy versus chemotherapy. Data from seven phase III RCTs of immunotherapy + combination chemotherapy versus chemotherapy alone in patients with pMMR/MSS HER2-negative gastric or GEJ adenocarcinoma met the inclusion criteria.[12,19,20,25,26,48,51] The control arm across studies was 5-FU and platinum-containing chemotherapy, including 5-FU + cisplatin,

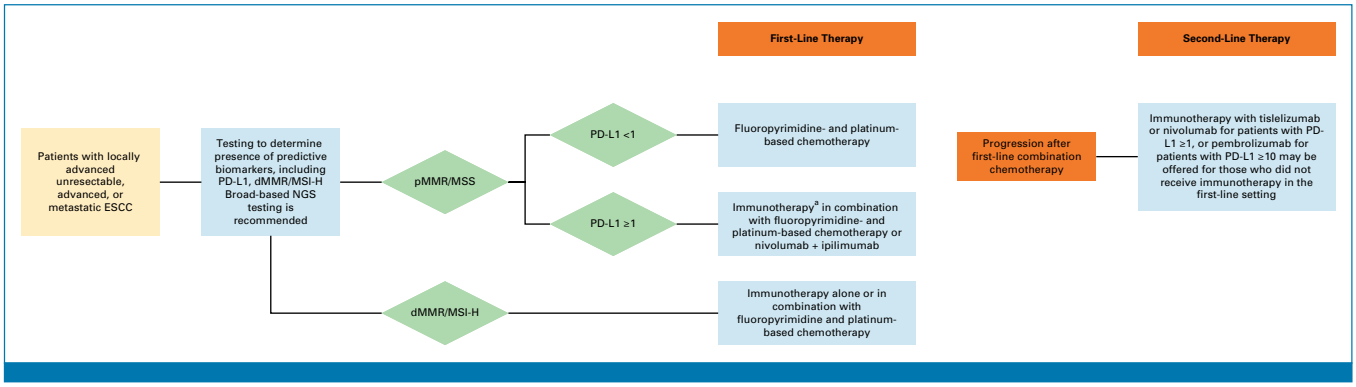

FIG 3. Immunotherapy and targeted therapy for locally advanced unresectable, advanced, or metastatic ESCC algorithm. Note regarding fluoropyrimidine-based chemotherapy. Patients should be tested for *DPYD* genetic variants before initiating treatment. For patients with partial *DPYD* deficiency, dosage should be individualized and modified based on tolerability and intent of treatment. Fluoropyrimidine use should be avoided completely in DPD-deficient patients (ie, carrying two no-function *DPYD* alleles). [a]Immunotherapy benefit has shown a positive association with higher PD-L1 expression. All possible PD-L1 cutoff scores have not been assessed; therefore, the optimal score balancing benefits and harms is unknown. Fluoropyrimidine- and platinum-based chemotherapy alone may be offered to patients who express predictive biomarkers but are not considered candidates for targeted therapy or immunotherapy. Recommended immunotherapy agents include nivolumab, pembrolizumab, or tislelizumab; these agents are considered to have similar efficacy. Taking into account the clinical situation, clinicians should avoid delaying the start of chemotherapy treatment while awaiting biomarker testing results. dMMR, deficient mismatch repair; ESCC, esophageal squamous cell carcinoma; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NGS, next-generation sequencing; pMMR, proficient mismatch repair.

CAPOX, FOLFOX, and S-1 + oxaliplatin (SOX), with or without placebo. Three of these RCTs were multisite international studies, one was conducted in Japan, South Korea, and Taiwan,[25] and another in centers located in China.[48] The number of study participants ranged from 724 to 1,579. The primary outcome in all studies was OS, in the overall population or in specified PD-L1 expression subgroups, with or without a coprimary outcome of PFS. In a meta-analysis of included studies conducted for this guideline, the HR for OS for immunotherapy + chemotherapy versus chemotherapy alone for all HER2-negative patients was 0.80 (95% CI, 0.76 to 0.85; I^2 = 0%; Table 2, Data Supplement, Fig S1). The HR for OS for the PD-L1 CPS <1 group was 0.93 (95% CI, 0.80 to 1.09; Fig 4). HRs for OS for the remainder of the PD-L1 CPS subgroups showed a significant benefit of the addition of immunotherapy to chemotherapy versus chemotherapy alone (Table 2).

In addition, an individual patient data meta-analysis using a KM subtraction methodology found that OS was modestly improved for immunotherapy + combination chemotherapy versus chemotherapy alone in the PD-L1 CPS 1-4, PD-L1 CPS 1-9, and PD-L1 CPS 5-9 subgroups, respectively; however, the proportional hazards assumption was violated for the last two analyses.[52]

Increasing PD-L1 expression is associated with higher rates of response to immunotherapy. Figure 1 includes graphical representations that display the absolute risk reduction at 24 months after treatment initiation in a group of 1,000 clinical trial participants within various PD-L1 subgroups. These representations are available in the Data Supplement for additional subgroups. Forest plots for all meta-analyses can be found in the Data Supplement.

Progression-free survival. In the meta-analysis of six RCTs,[12,19,20,25,48,51] the HR for PFS for immunotherapy + chemotherapy versus chemotherapy for all HER2-negative patients in the target population was 0.74 (95% CI, 0.69 to 0.79; I^2 = 16%). The HR for PFS for immunotherapy + chemotherapy versus chemotherapy for HER2-negative patients with PD-L1 CPS <1 was 0.82 (95% CI, 0.68 to 0.99; three studies; I^2 = 0%); a significant effect was observed for all other PD-L1 CPS subgroups (Data Supplement). There was a significant interaction effect between treatment and control groups and PD-L1 CPS subgroups <1 versus ≥1 (P < .05).

AEs and HRQOL. Gastroesophageal cancer is associated with a high burden of symptoms, including abdominal pain and discomfort, dysphagia, reduced appetite, fatigue, anxiety, and others,[54] which can become worse with disease progression. There was a higher risk of grade 3 to 5 TRAEs with immunotherapy + chemotherapy versus chemotherapy alone for pembrolizumab, nivolumab, and tislelizumab (Table 3). Grade 3 or greater treatment-related diarrhea, anemia, fatigue, and decreased neutrophile count were commonly experienced by patients. All grade 3 or greater AEs experienced by at least 5% of patients are included in the Data Supplement, Table S21.

Grade 3-5 potentially immune-mediated AEs were experienced by 8% versus <2% of patients in the pembrolizumab +

TABLE 2. Immunotherapy + Chemotherapy (fluoropyrimidine + platinum) Versus Chemotherapy Alone in Patients With Unresectable Locally Advanced, Advanced, or Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma, All Patients and PD-L1 Subgroups <1, ≥1, <10, ≥10, 1-9

Outcome Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Summary
		Fluoropyrimidine + Platinum CT	Immunotherapy + Fluoropyrimidine + Platinum CT		
OS (all patients) 24 months	HR, 0.80 (95% CI, 0.76 to 0.85) 6,495 participants in seven studies[12,19,20,25,48,51]	790 deaths per 1,000[20]	713 deaths per 1,000	High (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT improves OS compared with CT alone
		Difference: 77 fewer per 1,000 (95% CI, 95 fewer to 55 fewer)			
OS (PD-L1 CPS <1) 24 months	HR, 0.93 (95% CI, 0.8 to 1.09) 833 participants in four studies[12,19,20,48]	790 deaths per 1,000[20]	766 deaths per 1,000	High (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT has little or no effect on OS compared with chemotherapy alone for patients with PD-L1 CPS <1
		Difference: 24 fewer per 1,000 (95% CI, 77 fewer to 28 more)			
OS (PD-L1 CPS ≥1) 24 months	HR, 0.76 (95% CI, 0.71 to 0.82) 4,439 participants in five studies[12,19,20,26,48]	790 deaths per 1,000[20]	695 deaths per 1,000	High (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT improves OS compared with CT alone for patients with PD-L1 CPS ≥1
		Difference: 95 fewer per 1,000 (95% CI, 120 fewer to 68 fewer)			
OS (PD-L1 CPS <10) 24 months	HR, 0.88 (95% CI, 0.81 to 0.95) 2,967 participants in five studies[12,19,20,48,51]	790 deaths per 1,000[20]	747 deaths per 1,000	High (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT improves OS compared with CT alone for patients with PD-L1 CPS <10
		Difference: 43 fewer per 1,000 (95% CI, 72 fewer to 17 fewer)			
OS (PD-L1 CPS ≥10) 24 months	HR, 0.67 (95% CI, 0.61 to 0.74) 2,182 participants in six studies[12,19,20,26,48,51]	790 deaths per 1,000[20]	649 deaths per 1,000	High (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT improves OS compared with CT alone for patients with PD-L1 CPS ≥10
		Difference: 141 fewer per 1,000 (95% CI, 176 fewer to 105 fewer)			
OS (PD-L1 CPS 1-9) 24 months[52]	HR, 0.83 (95% CI, 0.74 to 0.95) 1,247 participants in two studies[19,20,52]	790 deaths per 1,000[20]	726 deaths per 1,000	Moderate[a] (I^2 = 0%)	Immunotherapy + fluoropyrimidine + platinum CT improves OS compared with chemotherapy alone for patients with PD-L1 CPS 1-9
		Difference: 64 fewer per 1,000 (95% CI, 105 fewer to 17 fewer)			

Abbreviations: CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; OS, overall survival.
[a]Downgrade: The proportional hazards assumption was violated for this subgroup analysis.

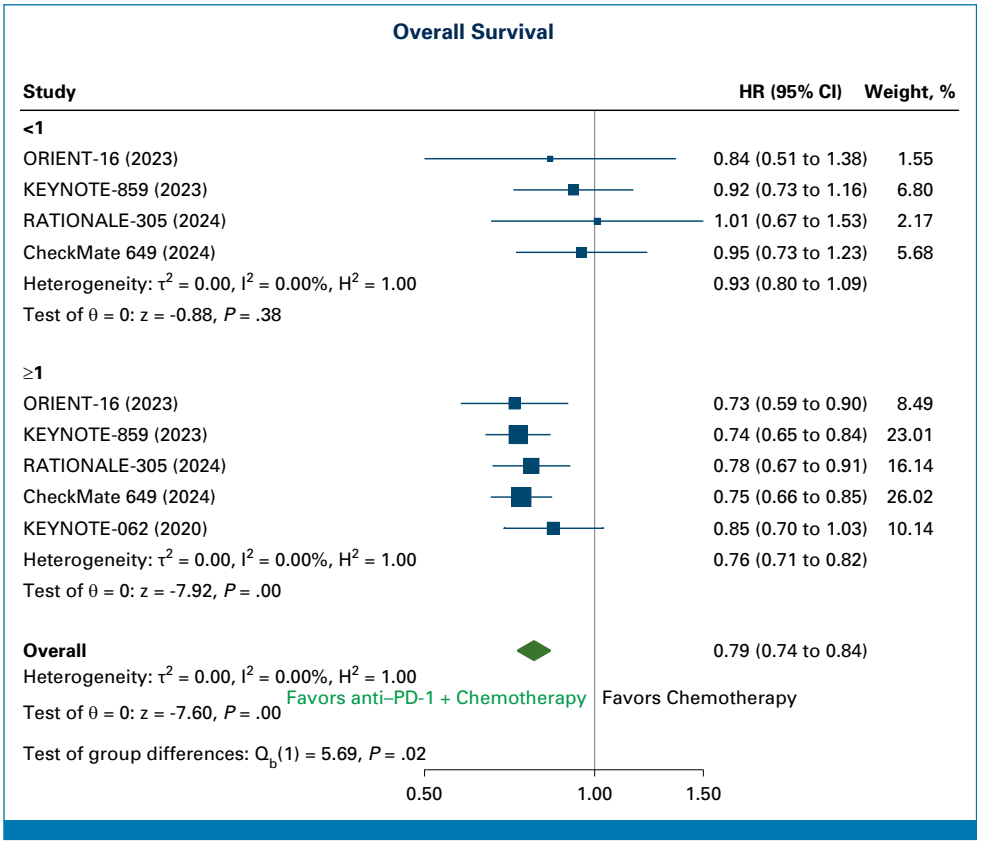

FIG 4. OS for patients with gastric/GEJ adenocarcinoma with PD-L1 CPS score <1 and PD-L1 CPS score ≥1. CPS, combined positive score; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival.

chemotherapy versus chemotherapy arms of KEYNOTE-859. The most common immune-mediated AEs in the immunotherapy treatment group were hypothyroidism (15%), hyperthyroidism (6%), colitis (3%), and pneumonitis (3%); drug discontinuation due to immune-mediated AEs occurred in 3% and 1% of patients in the treatment and control groups, respectively. In KEYNOTE-062, grade 3-5 potentially immune-mediated AEs occurred in 6% versus 6% versus <2% of patients in the pembrolizumab, pembrolizumab + chemotherapy, and chemotherapy arms, respectively. In KEYNOTE-590, the most common immune-mediated AEs were any grade of hypothyroidism (11% *v* 6%), hyperthyroidism (6% *v* 1%), colitis (3% *v* 2%), and pneumonitis (6% *v* 1%). In CheckMate 648, the most common immune-mediated AEs of any grade with nivolumab + ipilimumab versus nivolumab + chemotherapy were rash (17% *v* 8%), pruritus (13% *v* 7%), and hypothyroidism (13% *v* 6%); the majority of these were grade 1-2 AEs.[23] In the RATIONALE-305 study, immune-mediated AEs of any grade for the patients treated with tislelizumab + chemotherapy versus placebo + chemotherapy included hypothyroidism (13% *v* 3%), skin adverse reactions (11% *v* 3%), pneumonitis (4 *v* <1), and hyperthyroidism (3% *v* 1%).[19]

In a meta-analysis of eight RCTs comparing immunotherapy + combination chemotherapy versus chemotherapy alone, the effect estimates favored the immunotherapy arm for the Functional Assessment of Cancer Therapy—Esophageal scores (mean difference [MD]: 2.7 [95% CI, 0.1 to 5.3], $P < .041$) and the European Organisation for Research and Treatment of Cancer esophageal cancer–specific module of the Quality of Life Questionnaire (QLQ-OES18) pain scale (MD −2.2 [95% CI, −4.3 to −0.2], $P < .030$); although this finding is statistically significant, its clinical significance is unclear. There were no other significant differences in quality-of-life ratings between groups.[37] In KEYNOTE-859, scores on the QLQ-C30 pain scale favored pembrolizumab versus placebo in assessments from baseline to week 18, and in time to deterioration.[20]

Zolbetuximab + chemotherapy versus placebo + chemotherapy. Two double-blind global phase III RCTs of patients with HER2-negative tumors and CLDN18.2 biomarker expression met the inclusion criteria.[7,22] Each trial included over 500 patients who were from non-Asia (69%) versus Asia (31%) in the SPOTLIGHT trial, and Asia (62%) versus non-Asia (38%) in the GLOW trial. More patients had gastric versus GEJ adenocarcinoma in the GLOW trial (84% *v* 16%) versus the SPOTLIGHT trial (76% *v* 24%). The SPOTLIGHT trial also enrolled relatively more patients from Japan and South Korea; these patients tend to have a higher OS compared with patients from mainland China.[7] The treatment arms consisted of CLDN18.2 inhibitor zolbetuximab plus mFOLFOX6[22] or CAPOX.[7]

TABLE 3. Grade 3-5 Adverse Events With First-Line Immunotherapy + CT Versus CT for Patients With Unresectable Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer

Outcome	Study Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Summary
		CT	Immunotherapy + CT		
Grade 3-5 TRAEs (pembrolizumab)	RR, 1.08 (95% CI, 1.0 to 1.16) 2,806 participants in three studies[20,26,51]	627 events per 1,000[20,26,51]	677 events per 1,000	Moderate (I^2 = 57%)	First-line therapy with pembrolizumab + CT may worsen grade 3-5 AEs compared with CT alone
		Difference: 50 more per 1,000 (95% CI, 0 fewer to 100 more)			
Grade 3-5 TRAEs (nivolumab)	RR, 1.30 (95% CI, 1.19 to 1.43) 2,880 participants in three studies[12,23,25]	446 events per 1,000[12,23,25]	580 events per 1,000	Moderate (I^2 = 29%)	First-line therapy with nivolumab + CT may worsen grade 3-5 AEs compared with CT alone
		Difference: 134 more per 1,000 (95% CI, 85 more to 192 more)			
Grade 3-5 TRAEs (tislelizumab)	RR, 1.16 (95% CI, 0.97 to 1.15) 1,637 participants in two studies[19,21]	556 events per 1,000[19,21]	589 events per 1,000	Moderate (I^2 = 0%)	First-line therapy with tislelizumab + CT may worsen grade 3-5 AEs compared with CT alone
		Difference: 33 more per 1,000 (95% CI, 17 fewer to 83 more)			

Abbreviations: AE, adverse event; CT, chemotherapy; RR, relative risk; TRAE, treatment-related adverse event.

TABLE 4. Zolbetuximab + Combination Chemotherapy Versus Placebo + Combination Chemotherapy in Patients With CLDN18.2-Positive, Human Epidermal Growth Factor Receptor 2–Negative Locally Advanced Unresectable or Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma

Outcome Timeframe	Study Results	Absolute Effect Estimates		Quality of Evidence	Summary
		Placebo + Chemotherapy[a]	Zolbetuximab + Chemotherapy		
PFS (primary outcome) 12 months	HR, 0.71 (95% CI, 0.61 to 0.84) 1,072 participants in two studies[7,55]	650[55] per 1,000	525 per 1,000	High (I^2 = 0%)	Zolbetuximab + chemotherapy improves PFS, compared with chemotherapy alone
		Difference: 125 fewer per 1,000 (95% CI, 177 fewer to 64 fewer)			
OS 12 months	HR, 0.78 (95% CI, 0.67 to 0.9) 1,072 participants in two studies[7,55]	400[55] per 1,000	329 per 1,000	Moderate[b] (I^2 = 0%)	Zolbetuximab + chemotherapy improves OS compared with chemotherapy alone
		Difference: 71 fewer per 1,000 (95% CI, 110 fewer to 31 fewer)			
Grade ≥3 TEAEs	RR, 1.09 (95% CI, 1.02 to 1.16) 1,060 participants in two studies[7,22]	740 per 1,000	807 per 1,000	High (I^2 = 0%)	Zolbetuximab worsens grade ≥3 TEAEs
		Difference: 67 more per 1,000 (95% CI, 15 more to 118 more)			
Nausea (any grade)	RR, 1.36 (95% CI, 1.24 to 1.48) 1,060 participants in two studies[7,22]	558 per 1,000	759 per 1,000	High (I^2 = 0%)	Zolbetuximab worsens any grade of nausea
		Difference: 201 more per 1,000 (95% CI, 134 more to 268 more)			
Vomiting (any grade)	RR, 1.99 (95% CI, 1.74 to 2.28) 1,060 participants in two studies[7,22]	334 per 1,000	665 per 1,000	High (I^2 = 0%)	Zolbetuximab worsens any grade of vomiting
		Difference: 331 more per 1,000 (95% CI, 247 more to 428 more)			

Abbreviations: HR, hazard ratio; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; OS, overall survival; PFS, progression-free survival; RR, relative risk; TEAEs, treatment-emergent adverse events.
[a]Chemotherapy consisted of capecitabine and oxaliplatin (GLOW) or mFOLFOX6 (SPOTLIGHT).
[b]Approximately half of the patients received subsequent treatments in both studies.

Across both studies combined, the HR for OS (0.78; 95% CI, 0.67 to 0.90), and the HR for primary outcome independently reviewed PFS (0.71; 95% CI, 0.61 to 0.84) significantly favored the zolbetuximab group compared with chemotherapy alone (Table 4), with 0% heterogeneity in both analyses. While the OS and PFS risk reductions were similar across both trials, the median OS was 14.4 months versus 12.2 months in the intervention and control groups of the GLOW trial, compared with 18.2 months versus 15.5 months in the SPOTLIGHT trial. In the zolbetuximab and placebo groups, OS was 58% versus 51% at 12 months and 29% versus 17% at 24 months in the GLOW trial, and 68% versus 60% at 12 months and 39% versus 28% at 24 months in the SPOTLIGHT trial. All grades of nausea (RR: 1.36 [95% CI, 1.24 to 1.48]), vomiting (RR: 1.99 [95% CI, 1.74 to 2.28]), and grade ≥3 treatment emergent AEs (RR: 1.09 [95% CI, 1.02 to 1.16]) were more common in the zolbetuximab group (Table 4). Grade 3 or greater treatment emergent AEs were more common with modified FOLFOX in the SPOTLIGHT trial (87% *v* 78%), compared with the GLOW trial with CAPOX (73% *v* 70%). The findings varied by disease site, as the small number of patients in both trials who had GEJ adenocarcinoma did not derive a significant benefit from treatment with zolbetuximab (HR for OS, 1.12 [95% CI, 0.78 to 1.61]; two trials; $I^2 = 0\%$). Patients with GEJ adenocarcinoma had poor compliance (early discontinuation), so optimal management in these patients should be emphasized.

AEs and HRQOL. Despite clear increase in GI toxicity, notably nausea and vomiting (Table 4), global HRQOL changes were not significantly different from baseline to 49 weeks. Notably, 50% were off trial by week 31 and therefore did not contribute to longer-term HRQOL responses.

Clinical Interpretation

For this update, with more studies and longer-term data, the Expert Panel has included meta-analyses combining several trials at the most commonly reported PD-L1 cutoffs of 1, 5, and 10. Updated meta-analyses indicate that there is significant interaction effect between CPS subgroups at the cutoffs of PD-L1 CPS <1 versus ≥1, <5 versus. ≥5, and <10 versus ≥10 for OS. There is no statistically significant benefit observed across trials for the group of patients with PD-L1 CPS <1 (Table 2). Given the greater magnitude of absolute potential for benefit at or above the PD-L1 threshold of 10, a qualifying statement noting this is included in the recommendations. Authors of a meta-analysis of three studies in the PD-L1 CPS 1-9 subgroup and the PD-L1 CPS 1-4 subgroups concluded that while there was a significant benefit for OS with immunotherapy + chemotherapy, the clinical benefit was modest and apparent in long-term outcomes only for these patients. The combined proportion of patients with PD-L1 CPS ≥1, ≥5, and ≥10 was 84%, 59%, and 42%, respectively, across all RCTs included in the meta-analyses, underscoring the need for biomarker testing to properly identify PD-L1–positive patients. Immunotherapy agents that are approved by the FDA for gastroesophageal cancer in the United States at the time of this guideline publication include tislelizumab, pembrolizumab, and nivolumab. The profile for immune-mediated AEs was similar across recommended immunotherapy agents, and efficacy is similar.[50] ASCO has previously published a guideline for management of immune-related AEs associated with immunotherapy.[56] Zolbetuximab is recommended as an option for patients who are HER2-negative and CLDN18.2-positive with lower PD-L1 expression. A higher rate of nausea and vomiting was observed with zolbetuximab during early cycles of therapy. Consensus guidelines for dealing with these symptoms include recommendations for prophylactic antiemetics, adjusting the zolbetuximab infusion rate, pausing infusion temporarily, using nonprophylactic antiemetics, and/or providing hydration intravenously, as well as considering escalation of antiemetics and support before permanently discontinuing the medication.[57]

CLINICAL QUESTION 2

Is immunotherapy or targeted therapy + chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with pMMR/MSS HER2-positive gastroesophageal adenocarcinoma?

Literature Review and Analysis

First-Line Therapy for Patients With HER2-Positive Gastric or GEJ Adenocarcinoma

This guideline update includes further results from the second and third interim analyses of the KEYNOTE-811 698-patient multicenter, international, double-blind phase III RCT of pembrolizumab with anti-HER2 antibody trastuzumab plus chemotherapy with 5-FU and cisplatin or CAPOX versus combination chemotherapy alone in patients with HER2-positive gastric or GEJ adenocarcinoma.[41] The dual primary end points in this study are PFS by blinded central review and OS in the intention-to-treat (ITT) population. The HR for OS in the overall population was 0.84 (95% CI, 0.78 to 1.01), while the OS in the PD-L1 CPS ≥1 population at the third interim analysis after a median follow-up of approximately 38.5 months was 0.81 (95% CI, 0.67 to 0.98). A final analysis with further OS results is expected. HR for PFS in the overall and PD-L1 CPS ≥1 populations were 0.73 (95% CI, 0.61 to 0.87) and 0.70 (95% CI, 0.58 to 0.85), respectively. There were no significant differences in PFS or OS for the populations with PD-L1 CPS <1. There was no significant difference in rate of grade 3 to 5 TRAEs between groups.

Clinical Interpretation

For the previous version of this guideline, pembrolizumab with trastuzumab and chemotherapy were recommended based on KEYNOTE-811 interim data showing an overall response benefit. New interim analyses for this update

indicate that there is a significant benefit with the addition of pembrolizumab in terms of OS for patients in the PD-L1 CPS ≥1 population, and no significant benefit for patients with PD-L1 CPS <1. The recommendation for HER2-positive patients has been modified to reflect these newer data for this update.

CLINICAL QUESTION 3

Is immunotherapy or targeted therapy plus chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with ESCC that is not amenable to definitive chemoradiation?

Literature Review and Analysis

First-Line Therapy for Patients With ESCC

Immunotherapy + combination chemotherapy versus chemotherapy alone. Four phase III RCTs were included in the evidence base for immunotherapy for patients with ESCC, including the RATIONALE-306 RCT of tislelizumab + chemotherapy with platinum and fluoropyrimidine or paclitaxel versus placebo with chemotherapy (N = 869), updated KEYNOTE-590 data comparing pembrolizumab + 5-FU and cisplatin versus placebo + 5-FU and cisplatin (N = 749 patients, 73% with ESCC), updated data from CheckMate 648, which included comparisons of nivolumab + 5-FU and cisplatin versus nivolumab plus ipilimumab or 5-FU and cisplatin (N = 970), and the ORIENT-15 trial of sintilimab versus chemotherapy (N = 659). Primary end points for these studies included OS in the ITT population (RATIONALE-306) and in subgroups with PD-L1 tumor proportion score (TPS) ≥1 (CheckMate 648), and PD-L1 CPS ≥10 (KEYNOTE-590, ORIENT-15). Patients who were candidates for potentially curable radiation therapy were excluded from these studies, most patients had ECOG PS 0-1, more than 80% were male, and approximately three quarters were current or former smokers. Across studies, the majority of patients were from Asia. The overall HR for OS across all patients with ESCC in these four studies was 0.71 (95% CI, 0.63 to 0.79; Fig 5). In CheckMate 648, there were significant differences in the primary outcomes OS (HR, 0.59 [95% CI, 0.46 to 0.76]) and PFS (HR, 0.67 [95% CI, 0.51 to 0.89]) in patients with PD-L1 score ≥1. The results for OS and PFS for the 9% of patients with PD-L1 <1 were not significantly different between treatment and control groups. Data for patients with PD-L1 <10 versus patients with PD-L1 ≥10 were available from four studies and showed a significant benefit with the addition of immunotherapy to chemotherapy in both groups, with a significant test for interaction between groups (Fig 5). The safety profile for these agents has been reviewed previously.

PD-1 inhibitor nivolumab + cytotoxic T-cell lymphocyte-4 inhibitor ipilimumab versus chemotherapy for patients with ESCC. CheckMate 648 included a comparison of first-line therapy with PD-1 inhibitor nivolumab + cytotoxic T-cell lymphocyte-4 inhibitor ipilimumab versus chemotherapy alone in ESCC patients with PD-L1 TPS ≥1%.[23] Although there was an increase in early death, and no significant difference in PFS (HR, 1.04 [95% CI, 0.79 to 1.36]), OS was significantly improved with the combination therapy, compared with chemotherapy alone (HR, 0.62 [95% CI, 0.48 to 0.80]), while there was little or no effect on grade 3 to 4 AEs in the overall study population. The objective response rate (ORR) was 35% in the nivolumab plus ipilimumab group, compared with 53% (P = .002) in the nivolumab plus chemotherapy group, and 20% (P = .002) in the chemotherapy alone group. In addition, there were no significant differences between the nivolumab plus ipilimumab, and the chemotherapy alone groups for OS and PFS in the PD-L1 TPS <1% subgroup.

Clinical Interpretation

Based on the limited effectiveness of immunotherapy for patients with ESCC and PD-L1 expression <1, the Expert Panel recommends immunotherapy for the population with PD-L1 expression ≥1, although the panel notes that in the KEYNOTE 590 trial of pembrolizumab + chemotherapy versus chemotherapy alone, PD-L1 subgroups were defined at cutoff of 10, and data for a cutoff of 1 were not reported. As with the adenocarcinoma recommendations, a qualifying statement is provided that immunotherapy is more effective in subgroups with higher rates of PD-L1 expression. As mentioned earlier, the efficacy of the immunotherapy agents included in the meta-analysis is similar.[50] Based on data from CheckMate 648, nivolumab with ipilimumab is also recommended as a treatment option for patients with ESCC and PD-L1 CPS ≥1, based on a demonstrated improvement in OS compared with CT alone.

CLINICAL QUESTION 4

Is immunotherapy or targeted therapy alone or with chemotherapy recommended versus chemotherapy alone as first-line treatment for patients with dMMR/MSI-H gastroesophageal adenocarcinoma or ESCC?

Literature Review and Clinical Interpretation

The rate of MSI-H ranged from 3% to 7% across studies included in this guideline. The KEYNOTE-158 study demonstrated a benefit of pembrolizumab in patients with previously treated, advanced noncolorectal cancer and dMMR/MSI-H tumors, including 24 of 233 patients with gastric cancer who had an ORR of 45.8% (95% CI, 25.6 to 67.2).[59] For the 44 patients (3%) with MSI-H tumors in CheckMate 649, there was a significant OS benefit with nivolumab + CAPOX or FOLFOX versus chemotherapy alone (HR, 0.38 [95% CI, 0.17 to 0.84]). In KEYNOTE-062, 6.6% of patients had MSI-H tumors, and for the 33 of these patients in the PD-L1 CPS ≥1 subgroup, there was a significant OS benefit with pembrolizumab alone or with chemotherapy,

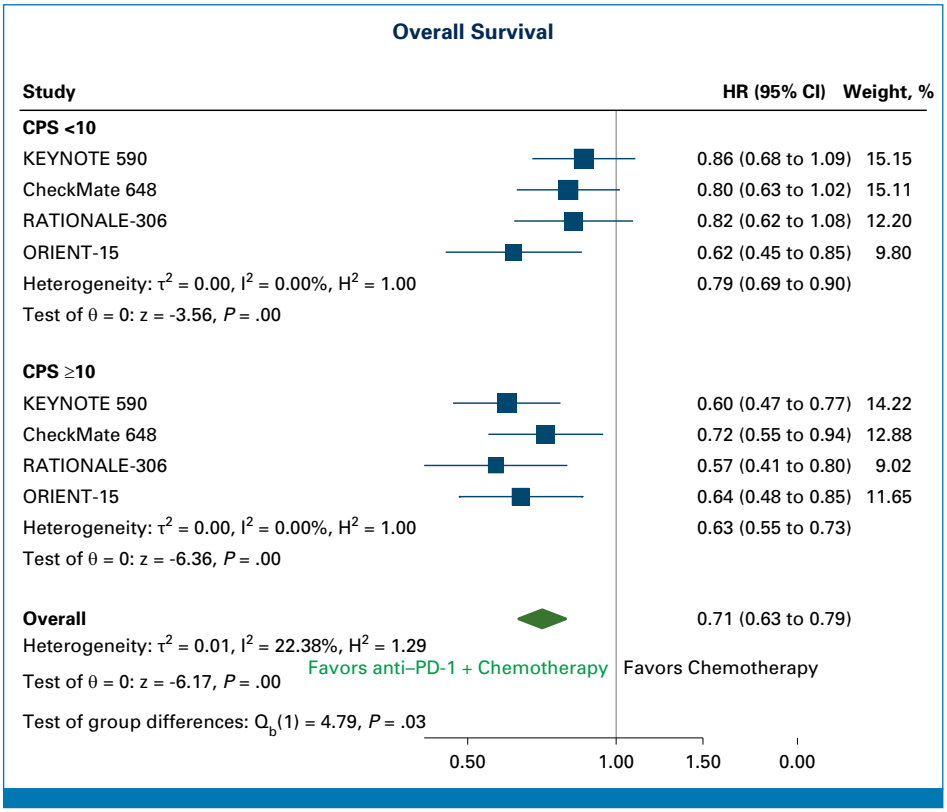

FIG 5. OS for patients with ESCC with PD-L1 CPS score <10 and PD-L1 CPS score ≥10. CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; OS, overall survival.

compared with chemotherapy alone. In RATIONALE-305, there were 40 patients (4%) with MSI-H tumors, and the HR for OS in these patients was 0.66 (95% CI, 0.30 to 1.44), trending toward a benefit for the immunotherapy + chemotherapy group. Data for the dMMR/MSI-H population were also available for CheckMate 649 for the comparison of nivolumab + ipilimumab versus chemotherapy alone; the unstratified HR for OS was 0.28 (95% CI, 0.08 to 0.92). Thus, although there were limited patient numbers in the evidence base for this clinical question, given the potential for benefit, including a relatively high response rate, the Expert Panel recommends immunotherapy alone or with doublet chemotherapy for patients with dMMR/MSI-H gastroesophageal adenocarcinoma or ESCC.

CLINICAL QUESTION 5

Is immunotherapy or targeted therapy recommended as second-line or third-line treatment for gastroesophageal adenocarcinoma or ESCC?

Literature Review and Analysis

Ramucirumab is an established treatment option in the second-line setting for patients with advanced gastroesophageal adenocarcinoma. In the double-blind REGARD phase III RCT,[29] there was a significant benefit in PFS (HR, 0.48 [95% CI, 0.38 to 0.62]) and OS (HR, 0.776 [95% CI, 0.603 to 0.998]) with ramucirumab compared with placebo, and there was little or no effect on grade 3-5 AEs (RR, 0.97 [95% CI, 0.81 to 1.18]). In the RAINBOW double-blind RCT, which was published before studies of immunotherapy in first-line, ramucirumab plus paclitaxel was compared with placebo plus paclitaxel. OS (HR, 0.81 [95% CI, 0.68 to 0.96]) and PFS (HR, 0.64 [95% CI, 0.54 to 0.75]) were significantly improved with the VEGFR2 inhibitor plus chemotherapy; however, grade 3-5 AEs were also significantly more likely in that group (RR, 2.66 [95% CI, 1.86 to 3.80]). Results from 111 patients in the phase II portion of the RAMIRIS trial (AIO-STO-0415) found that ramucirumab + folinic acid, 5-FU, and irinotecan (FOLFIRI) showed a trend toward risk reduction in taxane-pretreated patients, with both regimens associated with significant grade 3-5 AEs (75% *v* 68%). The phase III portion of this study is exploring whether ramucirumab + FOLFIRI is superior to ramucirumab + paclitaxel in terms of OS and response.[60]

For this guideline update, the DESTINYGastric04 phase III RCT of patients who retained HER2-positive disease after progressing on first-line treatment was added; OS was significantly prolonged with trastuzumab deruxtecan versus ramucirumab + paclitaxel (HR, 0.70 [95% CI, 0.55 to 0.90]), with survival rates at 24 months of 29.0% and 13.9%, respectively. PFS was also significantly longer with trastuzumab deruxtecan versus ramucirumab + paclitaxel (HR, 0.74 [95% CI, 0.59 to 0.92]), and the RR of grade 3 or

higher AEs was 50% and 54.1%, respectively (RR, 0.95 [95% CI, 0.78 to 1.16]).[28]

Three phase III RCTs of patients with advanced ESCC that had progressed on first-line therapy were included in the evidence base, including studies of immunotherapy agents nivolumab (ATTRACTION-3),[33] pembrolizumab (KEYNOTE-181),[32] and tislelizumab (RATIONALE-302),[61] compared with single-agent chemotherapy (Data Supplement, Tables S17-S19). An OS advantage was found with nivolumab and tislelizumab, but not pembrolizumab, in the overall study population. There was a statistically significant survival advantage for pembrolizumab in patients with PD-L1 ≥10.

Clinical Interpretation

Ramucirumab plus paclitaxel is a recommended combination for patients with advanced gastroesophageal or GEJ adenocarcinoma who have disease progression after first-line treatment. The panel members recognize that this therapy option was established after the 2014 publication of results from the RAINBOW phase III RCT, and before the publication of RCTs of immunotherapy in the first-line setting. The Expert Panel also notes that the combination of paclitaxel and ramucirumab is currently under investigation for the second-line treatment of advanced ESCC.[62] Based on the RAMIRIS trial, ramucirumab + FOLFIRI could be offered and may be preferred for patients who have previously been treated with docetaxel or experienced neurotoxicity with first-line treatment. The results from DESTINYGastric04 support the recommendation for trastuzumab deruxtecan for patients with HER2-positive metastatic gastric or GEJ adenocarcinoma. Patients with a history of pulmonary problems were excluded from this trial because of the risk of interstitial lung disease with trastuzumab deruxtecan, and the study authors recommended proactive monitoring of signs and symptoms of this complication, the use of imaging to identify potential cases, prompt dose interruption, and early initiation of glucocorticoid treatment.[63]

DISCUSSION

This guideline incorporates the most recent evidence from RCTs of immunotherapy and targeted therapy for patients with advanced gastroesophageal cancer. The previous version of this guideline recommended different PD-L1 thresholds depending on the immunotherapy agent, which was largely reflective of the cutoffs that were used in the respective clinical trials in the evidence base at that time. In addition, immunohistochemistry assessments have been conducted with different assays, and scoring methods include CPS, TPS, or tumor area positivity (TAP).[64] Calculating CPS involves counting the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100; at least 100 viable tumor cells must be present in the sample. The TAP score, which is determined by visually estimating the area covered by PD-L1–positive tumor and immune cells relative to the total tumor area, can be determined more quickly than the CPS. The TPS, which is the ratio of PD-L1–expressing cells to all viable tumor cells, also can be used to quantify PD-L1 expression; however, TPS was developed for use in lung cancer, and in gastric and GEJ cancer, the CPS is considered a more reliable prognostic biomarker for immunotherapy efficacy.[65] The intraclass correlation coefficients ranged from 0.92 to 0.99 for three pathologists using three different assays for determining TAP and CPS scores using surgical samples.[66] These testing methods are not 100% concordant; however, the Expert Panel considers assessment of PD-L1 using any of the three assays is sufficient for determining eligibility for immunotherapy.

In addition to upfront testing, rebiopsy at the time of progression should be considered in patients for whom biomarker-driven therapy is being considered in subsequent lines of therapy, especially after HER2- or CLDN18.2-targeted treatment. However, rebiopsy can be difficult due to tumor location; functional imaging (fluorodeoxyglucose positron emission tomography-computed tomography) can be useful to identify high-yield sites for rebiopsy. If tissue rebiopsy is not feasible, an option is liquid NGS through Clinical Laboratory Improvement Amendments (CLIA)–certified laboratories, for example, HER2 and MSI are validated using liquid technologies, although there is no standard biopsy threshold for choosing HER2-directed therapies. Of note, when PD-L1 is low in the primary tumor, it tends to be low in metastases, but higher PD-L1 in the primary does not necessarily correspond to higher PD-L1 in the metastatic location.[67] In the first-line setting, for patients who do not have recommended biomarker testing or do not have an adequate sample to test for all recommended biomarkers, the panel recommends beginning chemotherapy before receiving biomarker testing results.

According to current definitions, 15%-20% of patients are positive for more than one actionable biomarker. In the SPOTLIGHT trial, 13% of 311 assessed patients also had a PD-L1 CPS of ≥5. In the GLOW trial, this rate was 21.9%. In a retrospective study, the rate of HER2 positivity was 15% in CLDN-positive and CLDN-negative patients, and similar percentages had PD-L1 CPS of ≥5. Other pan-tumor biomarkers were considered rare and thus outside the scope of recommendations for this guideline. For example, tropomyosin receptor kinase (TRK) inhibitors are tissue-agnostic agents that target fusions of the neurotrophic tyrosine receptor kinase 1/2/3 genes. Fusions of the TRK family occur in <1% of patients.[68] There are few estimates of the prevalence in gastroesophageal cancer, but a rate of 0.05% (1 of 1,970 patients) was found in a retrospective cohort study.[69]

Within the main guideline recommendations, the Expert Panel has recommended doublet fluoropyrimidine- and

oxaliplatin-based chemotherapy for patients who do not expression actionable biomarkers or are not candidates for targeted therapy or immunotherapy. The focus of this guideline is the population of patients with actionable biomarkers; therefore, the literature on chemotherapy options for patients who do not express these biomarkers was not systematically reviewed. However, the Expert Panel acknowledges results from the PRODIGE 51-FFDC-GASTFOX phase III RCT of triplet therapy with TFOX (modified docetaxel, 5-FU, and oxaliplatin [FLOT]) compared with FOLFOX, which indicate that TFOX improves PFS, OS, and response, and could be offered as first-line therapy to appropriate patients with HER2-negative advanced gastric or GEJ adenocarcinoma and an absence of actionable biomarkers.[70]

There is still an unmet need for treatment options in the population of patients with advanced and metastatic gastroesophageal cancer. At the time of this publication, results from the FORTITUDE-101 trial of mFOLFOX6 plus bemarituzumab compared to mFOLFOX6 plus placebo were available from ESMO conference proceedings. The HR for OS in 324 patients with FGFR2b expression ≥10% of tumor cells was 0.61 (95% CI, 0.43 to 0.86) after a median follow-up of 11.8 months, with a rate of grade ≥3 AEs of 60% of patients in the bemarituzumab arm (most commonly ocular toxicity), compared with 18% in the placebo arm.[71] The panel awaits full publication of the results from this trial. The Expert Panel also awaits results in 2026 from trials such as ILLUSTRO (ClinicalTrials.gov identifier: NCT03505320), which is evaluating zolbetuximab and pembrolizumab or nivolumab for CLDN18.2-positive tumors and others.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

PATIENT AND CLINICIAN COMMUNICATION

As in the previous version of this guideline, a shared decision-making approach has been recommended, weighing the potential for benefit with the risks of harm associated with targeted therapy and immunotherapy for patients with advanced gastroesophageal cancer. Clinicians are urged to communicate the absolute and relative benefit associated with each of the treatment options. The community practitioner on this guideline panel indicated that a more standard recommendation for anti–PD-1 therapy across agents will make it easier to implement this guideline into clinical practice. In addition, clinicians should communicate to patients that advocacy groups are a valuable resource for patients; they can assist in finding another opinion or guiding the patient to appropriate medical care, providing information regarding their diagnosis, and raising awareness about enrollment in clinical trials. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[72]

PATIENT ACCESS CONSIDERATIONS

Not all patients have consistent access to the resources needed to benefit from ASCO's expert recommendations on best practices for prevention, screening, palliative and supportive care, and disease management of cancer. In the United States, many patients remain unable to reap the benefits of innovative prevention and early detection programs, biomarker testing, and new cancer therapies due to challenges including lack of transportation, stable housing, adequate insurance coverage, food insecurity, health literacy, proximity to a dedicated cancer center, and cost of treatment and other services.[73] In advanced gastroesophageal cancer, where many of the treatment recommendations are based on patients' specific actionable biomarkers, access to timely and comprehensive biomarker testing is a prerequisite for appropriate use of immunotherapy and targeted therapy. Acknowledging that this testing does not always occur in a timely manner, the Expert Panel has added a qualifying statement to indicate that chemotherapy treatment alone can be started before biomarker testing results are received. Further, geographic disparities can also impact the quality of care patients receive. Rural patients are more likely to have worse survivorship outcomes and experience higher mortality rates compared to nonrural patients. This can be attributed, in part, to a lower density of specialists and dedicated cancer centers, as only 21% of nonmetropolitan counties in the United States have one or more practicing oncologists.[74]

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[75,76] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[77,78]

Discussion of cost can be an important part of shared decision making.[79] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[79]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effectiveness analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; or are industry-sponsored. For this guideline, testing for actionable biomarkers is recommended, which involves upfront allocation of resources; however, the cost of comprehensive biomarker testing for all

patients is less than the cost of suboptimal treatment.[80] Biomarker testing to identify patients who are more likely to benefit from immunotherapy is increasingly important as there is considerable literature demonstrating the high cost to benefit ratio for immunotherapy when patients are treated on a large scale.[81] A recent systematic review of cost-effectiveness analyses in second- or later-line advanced or metastatic gastric cancer found that most interventions were more effective and more costly than comparators, and overall, not cost-effective; however, the quality-adjusted life-years estimates varied considerably across studies.[82] The authors conclude that this is a challenge for sustainable and affordable coverage of cancer therapy in gastric cancer. The proportion of these costs that must be covered by the patient out of pocket may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[79]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/gastrointestinal-cancer-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are published in the *Journal of Clinical Oncology*.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit www.asco.org/gastrointestinal-cancer-guidelines. The Data Supplement for this guideline includes additional evidence tables and forest plots. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well being of all patients. ASCO guidelines are intended to apply to and be discussed clearly and compassionately with all patients. For this reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

RELATED ASCO GUIDELINES

- Palliative Care for Patients with Cancer[83] (http://ascopubs.org/doi/10.1200/JCO.24.00542)
- Patient-Clinician Communication[72] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy[84] (https://ascopubs.org/doi/10.1200/JCO.23.00933)
- Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy[56] (https://doi.org/10.1200/JCO.21.01440)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/gastrointestinal-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline Update

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer Guideline Update Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Manish A. Shah, MD, co-chair	Weill Cornell Medicine, New York, NY	Medical Oncology
Lakshmi Rajdev, MD, MS, co-chair	Icahn School of Medicine at Mount Sinai, New York, NY	Medical Oncology
Dana Deighton, BA	The Melanoma Research Alliance, Washington, DC	Patient Representative
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Sarbajit Mukherjee, MD	Miami Cancer Institute, Miami, FL	Medical Oncology
Christopher Nevala-Plagemann, MD, MSCI	University of Utah Huntsman Cancer Center, Salt Lake City, UT	Medical Oncology
Anwaar Saeed, MD	University of Pittsburgh, Pittsburgh, PA	Medical Oncology
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Thomas Semrad, MD, MAS	Gene Upshaw Memorial Tahoe Forest Cancer Center, Truckee, CA	Medical Oncology/Community Oncology
Kohei Shitara, MD	National Cancer Center East, Kashiwa, Japan	Medical Oncology
Laura Tenner, MD	University of Nebraska, Omaha, NE	Medical Oncology
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Melani Vincelli	Debbie's Dream Foundation, Plantation, FL	Patient Representative
Davit Zohrabyan, MD	Yerevan State Medical University, Yerevan, Armenia	Medical Oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Evidence Quality and Recommendation Rating Definitions

Term	Definition
Evidence quality	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of Recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Conditional	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook, Schünemann et al.[85]