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Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer

ASCO Guideline

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Overview

1. Background & Methodology

- Introduction
- ASCO Guideline Development Methodology
- Clinical Questions
- Target Population and Audience

2. Summary of Recommendations

3. Discussion

- Patient and Clinician Communication
- Cost Implications
- Additional Resources
- Expert Panel Members

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1

Background & Methodology

Introduction

- Gastroesophageal cancers, inclusive of gastric and esophageal cancer and cancers of the GEJ, are amongst the most prevalent gastrointestinal malignancies globally.
- Targeted cancer therapies inhibit tumor growth by blocking important chemical pathways or mutant proteins, while the goal of immunotherapy is to elicit a host immune response that results in destruction of the tumor.¹
- These therapies are more effective in subgroups of gastroesophageal cancer patients who possess certain biomarkers such as PD-L1 protein expression.
- The TPS, which is the ratio of PD-L1 expressing cells to all viable tumor cells, can be used to quantify PD-L1 expression, however, in gastric and GEJ cancer, the CPS, which also includes the number of PD-L1 positive lymphocytes and macrophages, is considered a more prognostic biomarker for immunotherapy efficacy.²

Introduction

- Various cut-offs for TPS and CPS have been used across studies in an attempt to balance the minimum number of patients needed to obtain meaningful results within subgroups, and an awareness that PD-L1 inhibitors are likely more effective for patients with higher scores on measures of PD-L1 positivity.
- MSI or dMMR proteins also predict response to immunotherapy, as demonstrated in the KEYNOTE-158 multi-disease-site trial.
- Another biomarker of interest for this guideline is HER2, which is predictive of response to HER2-targeted therapy such as trastuzumab or trastuzumab deruxtecan.
- The purpose of this guideline is to provide recommendations for the treatment of advanced gastroesophageal cancer that include targeted therapy and immunotherapy options in the first-line treatment setting and beyond for the overall population of patients with unresectable, incurable, metastatic gastroesophageal adenocarcinoma or squamous cell carcinoma whose tumors express relevant predictive biomarkers.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
 - a systematic literature review by ASCO guidelines staff
 - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
 - final guideline approval by ASCO EBMC
- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses two clinical questions:

1. Is immunotherapy or targeted therapy in combination with chemotherapy recommended as first-line treatment for advanced gastroesophageal adenocarcinoma or squamous cell carcinoma, for subgroups of patients who are
 - a. HER2-negative and express PD-L1 as defined by TPS or CPS at cut-off levels of ≥ 1 , ≥ 5 , or ≥ 10 , or
 - b. those with HER2-positive gastric or GEJ adenocarcinoma?
2. Is immunotherapy or targeted therapy recommended as second-line or third-line treatment for advanced gastroesophageal adenocarcinoma?

Target Population and Audience

Target Population

- Patients with advanced gastroesophageal cancer.

Target Audience

- Medical oncologists and other healthcare professionals who are involved in the care and treatment of advanced gastroesophageal cancer, patients, and caregivers.

2

Summary of Recommendations

Summary of Recommendations

First-Line Therapy

Recommendation 1.1

- For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS ≥ 5 , first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended

Qualifying statements:

- *For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 1-5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy may be considered on a case-by-case basis.*
- *For patients with gastric adenocarcinoma and PD-L1 CPS 0, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy, without the addition of nivolumab, is recommended.*

Evidence-based benefits outweigh harms	
Evidence Quality	Strength of Recommendation
Moderate	Strong

Summary of Recommendations

Recommendation 1.2

- For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS ≥ 5 , or pembrolizumab for PD-L1 CPS ≥ 10 , in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended.

Evidence-based benefits outweigh harms

Evidence Quality
Low

Strength of Recommendation
Strong

Qualifying statements:

- *For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS 1-5, or pembrolizumab for patients with PD-L1 CPS 1-10, in combination with fluoropyrimidine- and platinum-based chemotherapy, may be recommended on a case-by-case basis.*
- *For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 0 or PD-L1 TPS 0%, first-line therapy with fluoropyrimidine- and platinum-based chemotherapy, without the addition of PD-1 inhibitors, is recommended.*

Summary of Recommendations

Recommendation 1.3

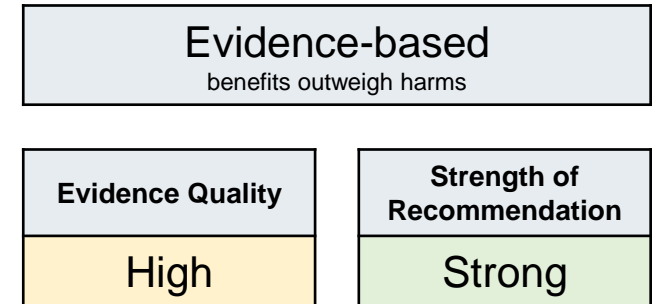
- For patients with ESCC and PD-L1 CPS ≥ 10 , pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy is recommended.

Evidence-based benefits outweigh harms	
Evidence Quality	Strength of Recommendation
High	Strong

Summary of Recommendations

Recommendation 1.4

- For patients with ESCC, and PD-L1 TPS $\geq 1\%$, nivolumab plus fluoropyrimidine- and platinum-based chemotherapy, or nivolumab plus ipilimumab are recommended.



Qualifying statement:

- Data from the primary analysis of CheckMate 648 supports Recommendation 1.4 in patients with ESCC and PD-L1 TPS $\geq 1\%$. Additional exploratory analyses from CheckMate 648 found that 91% of patients across three study arms had PD-L1 CPS ≥ 1 , therefore, CPS ≥ 1 may be used as a threshold for treatment decision-making if TPS is not available.

Summary of Recommendations

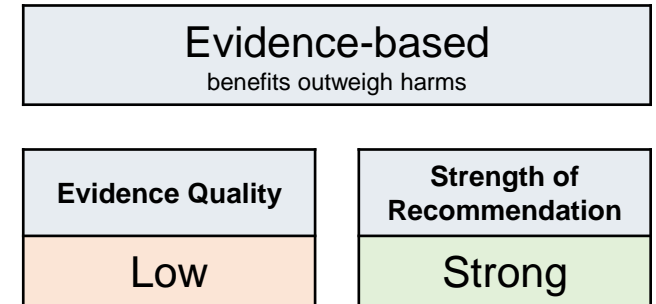
Qualifying statements for Recommendations 1.1 to 1.4:

- *The PD-L1 cut-offs in Recommendations 1.1 to 1.4 are based on subgroup analyses presented in included studies. All possible cut-offs have not been assessed; therefore, optimal PD-L1 cut-offs are unknown.*
- *Several additional studies of immunotherapy with PD-1 inhibitors plus chemotherapy, compared to placebo plus chemotherapy have shown efficacy, however, these therapy options are not currently FDA-approved.³⁻⁶*

Summary of Recommendations

Recommendation 1.5

- For patients with HER2-positive gastric or GEJ previously untreated, unresectable or metastatic adenocarcinoma, trastuzumab plus pembrolizumab is recommended, in combination with fluoropyrimidine- and oxaliplatin-based chemotherapy.



Qualifying statements:

- Recommendation 1.5 is applicable irrespective of CPS or TPS levels, however, the Expert Panel notes that PD-L1 CPS was ≥ 1 in 87% of patients included in the KEYNOTE-811 RCT.*
- HER2 positivity was defined in KEYNOTE-811 as IHC 3+ or IHC 2+ with positive in-situ hybridization (details of testing methodology are contained in Literature review and analysis section).*
- Trastuzumab plus pembrolizumab and chemotherapy is recommended based on an interim analysis showing a response benefit in the first 264 patients enrolled in KEYNOTE-811.⁷ We await the analysis of primary outcomes overall survival and progression-free survival.*

Summary of Recommendations

Second- or Third-Line Therapy

Recommendation 2.1

- For patients with advanced gastroesophageal or GEJ adenocarcinoma whose disease has progressed following first-line therapy, ramucirumab plus paclitaxel is recommended.

Qualifying statement:

- *Although outside the scope of this review, for patients with gastric or GEJ adenocarcinoma, trifluridine and tipiracil may be offered following progression on second-line therapy.*

Evidence-based benefits outweigh harms	
Evidence Quality	Strength of Recommendation
Moderate	Strong

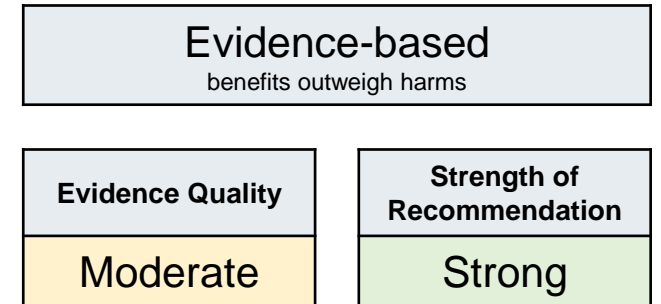
Summary of Recommendations

Recommendation 2.2

- For HER2-positive patients with gastric or GEJ adenocarcinoma who have progressed following first-line therapy, trastuzumab deruxtecan is recommended.

Note:

- *Although the key evidence for this recommendation includes patients who received therapy in the third-line setting, this option is FDA-approved as a second-line and later therapy option.*



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3

Discussion

Patient and Clinician Communication

- A shared decision-making approach is recommended throughout the guideline, 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 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.⁸

Cost Implications

- As part of the development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options.
- One cost-effectiveness analysis on the topic of this guideline found that second-line treatment with targeted therapy or immunotherapy for patients with metastatic gastric cancer improved survival and quality-adjusted life years, however, costs were prohibitively expensive at a QALY threshold of \$100,000 USD, while single-agent paclitaxel was cost-effective at this threshold.⁹
- Medication prices may vary markedly, depending on negotiated discounts and rebates.
- Additionally, patient out-of-pocket costs may vary depending on insurance coverage
- When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape,¹⁰ including compassionate use/expanded care or pharmaceutical patient support resources.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines
- Patient information is available at www.cancer.net

Guideline Panel Members

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Abbreviations

- ASCO, American Society of Clinical Oncology
- CPS, combined positive score
- dMMR, deficiency of mismatch repair
- EBMC, Evidence Based Medicine Committee
- ESCC, esophageal squamous cell carcinoma
- FDA, U.S. Food and Drug Administration
- GEJ, gastroesophageal junction
- HER2, human epidermal growth factor receptor 2
- IHC, immunohistochemistry
- MSI, microsatellite instability
- PD-L1, programmed death-ligand 1
- PGIN, Practice Guidelines Implementation Network
- QALY, quality-adjusted life-year
- RCT, randomized controlled trial
- TPS, tumor proportion score
- USD, U.S. dollar

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