

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline				
Clinical Question	Recommendation	Type	Evidence Quality	Strength
<p>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:</p> <p>(a) HER2-negative and express PD-L1 as defined by TPS or CPS at cut-off levels of <math>\geq 1</math>, <math>\geq 5</math>, or <math>\geq 10</math>, or</p> <p>(b) those with HER2-positive gastric or GEJ adenocarcinoma?</p>	<p><b>1.1.</b> For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS <math>\geq 5</math>, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended.</p>	EB	M	S
	<p><i>Qualifying statements:</i></p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>			
	<p><b>1.2.</b> For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS <math>\geq 5</math>, or pembrolizumab for PD-L1 CPS <math>\geq 10</math>, in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended.</p>	EB	L	S
	<p><i>Qualifying statements:</i></p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>			
	<p><b>1.3.</b> For patients with ESCC and PD-L1 CPS <math>\geq 10</math>, pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy is recommended.</p>	EB	H	S
<p><b>1.4.</b> For patients with ESCC, and PD-L1 TPS <math>\geq 1\%</math>, nivolumab plus fluoropyrimidine- and platinum-based chemotherapy, or nivolumab plus ipilimumab are recommended.</p>	EB	M	S	
<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> <li>Data from the primary analysis of CheckMate 648 supports Recommendation 1.4 in patients with ESCC and PD-L1 TPS <math>\geq 1\%</math>. Additional exploratory analyses from CheckMate 648 found that 91% of patients across three study arms had PD-L1 CPS <math>\geq 1</math>, therefore, CPS <math>\geq 1</math> may be used as a threshold for treatment decision-making if TPS is not available.</li> </ul>				

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	<p><i>Qualifying statements for Recommendations 1.1 to 1.4:</i></p> <ul style="list-style-type: none"> <li>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.</li> <li>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.<sup>1-4</sup></li> </ul>			
	<p><b>1.5.</b> 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.</p>	EB	L	S
	<p><i>Qualifying statements:</i></p> <ul style="list-style-type: none"> <li>Recommendation 1.5 is applicable irrespective of CPS or TPS levels, however, the Expert Panel notes that PD-L1 CPS was <math>\geq 1</math> in 87% of patients included in the KEYNOTE-811 RCT.</li> <li>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).</li> <li>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.<sup>5</sup> We await the analysis of primary outcomes overall survival and progression-free survival.</li> </ul>			
Is immunotherapy or targeted therapy recommended as second-line or third-line treatment for advanced gastroesophageal adenocarcinoma?	<p><b>2.1.</b> For patients with advanced gastroesophageal or GEJ adenocarcinoma whose disease has progressed following first-line therapy, ramucirumab plus paclitaxel is recommended.</p>	EB	M	S
	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> <li>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.</li> </ul>			
	<p><b>2.2.</b> For HER2-positive patients with gastric or GEJ adenocarcinoma who have progressed following first-line therapy, trastuzumab deruxtecan is recommended.</p>	EB	M	S
	<p><i>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.</i></p>			

**Abbreviations.** CPS, combined positive score; EB, evidence based; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; H, high; IHC, immunohistochemistry; L, low; M, moderate; PD-1 programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial; S, strong; TPS, tumor proportion score

**References.**

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- Janjigian YY, Kawazoe A, Yanez P, et al: The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature* 600:727-730, 2021