# Tislelizumab-jsgr (TEVIMBRA)
# National Drug Monograph
# January 2026

**VA Pharmacy Benefits Management Services and National Formulary Committee**

*The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

| FDA APPROVAL INFORMATION | | |
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| | **Description / MOA** | Programmed death receptor-1 (PD-1) blocking antibody |
| | **Indications Under Review**[1] | • First-line treatment, in combo with a platinum-containing regimen in unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥ 1)<br>• Subsequent therapy as a single agent in unresectable or metastatic ESCC if no prior immune checkpoint inhibitor<br>• First-line treatment, in combination with platinum- and fluoropyrimidine-based chemotherapy, for unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (≥ 1) |
| | **Dosage Regimens** | 150mg IV every 2 weeks, 200mg IV every 3 weeks, 300mg IV every 4 weeks or 400mg IV every 6 weeks |
| | **Dosage Forms Under Review** | Injection: 100 mg/10 mL (10 mg/mL) solution in a single dose vial |

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| | **Trial** | **RATIONALE-306; first-line treatment of unresectable or metastatic ESCC** |
| | **Design** | Global, randomized, placebo controlled, double blind |
| | **Population** | Unresectable, recurrent or metastatic ESCC;<br>enrolled regardless of PD-L1 expression level; no prior systemic therapy for advanced disease;<br>≥ 6 month treatment-free interval needed post-neo/adjuvant therapy<br>Exclusions: Active or uncontrolled CNS disease, active autoimmune disease, medical condition requiring systemic corticosteroids or immune suppressants, fistula or esophageal obstruction |
| | **Intervention** | Tislelizumab 200mg IV every 3 weeks + platinum-based chemo* until progression or toxicity |
| | **Comparator** | Placebo every 3 weeks + platinum-based chemo* until progression or toxicity |
| | **Demographics** | Stratified by region, prior definitive therapy and choice of chemotherapy;<br>Median Age 64 years (26-84), 48% ≥ 65 yrs; 87% male; 75% Asian; 24% White<br>86% metastatic disease; ECOG 1 – 67%;<br>34% PD-L1 TAP ≥ 10%; 74% TAP ≥ 1%; 74% CPS ≥ 1% |
| | **Results** | **Tislelizumab + chemo* (n=326) vs. placebo + chemo* (n=323); n=649**<br>**ITT:** median follow-up 16.3 vs. 9.8 mos: **median OS** 17.2 vs. 10.6 mos [HR 0.66 (95% CI 0.54-0.80); p< 0.0001]<br>**Median treatment exposure** 6.4 vs. 4.9 mos<br>**Subsequent therapy received** 48 vs. 55%; subsequent ICI 14 vs. 22%<br><br>Retrospective analysis of RATIONALE-306 population with PD-L1 TAP score ≥ 1%[4]<br>**CPS ≥ 1 (n=480):** follow-up@43 mos, mOS 17 vs. 10 mos [HR 0.66, 95% CI 0.54-0.81]<br>Follow-up@23 mos, PFS 7 vs. 6 mos [HR 0.58, 95% CI 0.46-0.72], ORR 58 vs. 32%<br>**TAP ≥ 1% (n=481):** follow-up@43 mos, mOS 17 vs. 10 mos [HR 0.66, 95% CI 0.54-0.81]<br>Follow-up@23 mos, PFS 7 vs. 6 mos [HR 0.58, 95% CI 0.46-0.72], ORR 58 vs. 32%<br><br>• Due to unbalanced risk/benefit ratio, FDA's ODAC voted against use of ICI in 1L advanced ESCC and PD-L1 TAP < 1% or CPS < 1%<br>• This retrospective analysis confirms results supporting use of tislelizumab + chemo in 1L setting with PD-L1 CPS or TAP ≥ 1% |

* Investigator choice of doublet: cisplatin 60-80 mg/m$^2$ IV on day 1 or oxaliplatin 130 mg/m$^2$ IV on day 1 AND fluorouracil 750-800 mg/m$^2$ IV on days 1 to 5 or capecitabine 1000mg/m$^2$ PO twice daily on days 1 to 14
OR cisplatin 60-80 mg/m$^2$ IV on day 1 or oxaliplatin 130 mg/m$^2$ IV on day 1 AND paclitaxel 175 mg/m$^2$ IV on day 1

**EFFICACY CONSIDERATIONS**

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| **Trial** | **RATIONALE-302 (NCT03430843); second-line treatment of ESCC** |
| **Design** | Multicenter, randomized, open label |
| **Population** | Unresectable advanced or metastatic ESCC who progressed on or after first-line systemic chemotherapy, regardless of PD-L1 expression;<br>Exclusions: prior immune checkpoint inhibitor (ICI) therapy, active CNS mets (symptomatic or requiring treatment), active autoimmune disease, systemic corticosteroids or immune suppressants |
| **Intervention** | Tislelizumab 200mg every 3 weeks until progressive disease, unacceptable toxicity to max 2 years |
| **Comparator** | Investigator's choice of chemotherapy (ICC): paclitaxel 135-175 mg/m$^2$ every 3 weeks or 80-100 mg/m$^2$ weekly, docetaxel 75 mg/m$^2$ every 3 weeks, or irinotecan 125 mg/m$^2$ on days 1 and 8 of every 3-week cycle |
| **Demographics** | Median Age 62 years; 80% Asian; 84% male; 95% metastatic disease;<br>Patients were included regardless of PD-L1 expression levels;<br>PD-L1 TAP $\geq$ 10% in 30% tumors; PD-L1 expression level was unknown in ~ 20% of the ITT population; |
| **Results** | **Tislelizumab vs. chemotherapy (paclitaxel, docetaxel, or irinotecan);** N=512<br>**Primary endpoint:** median OS 8.6 vs. 6.3 months; [HR 0.70 (95% CI, 0.57-0.85); p=0.0001<br>12-month OS: 37.4 vs. 23.7%<br>**Secondary endpoint:** median OS in TAP $\geq$ 10%: 10.3 vs. 6.8 months; [HR 0.54 (95% CI, 0.36-0.790) p=0.0006;<br>Subgroup analysis suggests baseline PD-L1 status of TAP < 10% and unknown (~20%) favor tislelizumab; both confidence intervals cross the value of 1; distribution of patients with TAP $\geq$ 10% was not balanced with 35% vs. 27% in tislelizumab vs. chemotherapy arm<br>• Patient population did not depend on PD-L1 expression level<br>• PD-L1 expression level was unknown in 20% of ITT population<br>• Imbalance of PD-L1 TAP $\geq$ 10% between groups makes it difficult to conclude, with confidence, that patients receiving tislelizumab had improved mOS compared to the chemotherapy arm<br>• Assumption that PD-L1 TAP < 10% and unknown expression level favors tislelizumab therapy cannot be made with confidence due to imbalance among treatment arms and broad Cis. |

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| **Trial** | **RATIONALE-305 (NCT03777657) in 1L gastric or gastroesophageal junction (GEJ) adenocarcinoma** |
| **Design** | Randomized, multicenter, placebo-controlled, double-blind trial |
| **Population** | Untreated, unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in PD-L1 $\geq$ 1 tumors;<br>Enrolled regardless of PD-L1 expression level. Exclusions: active/uncontrolled CNS disease, autoimmune disease, condition requiring systemic corticosteroids/immunosuppressants |
| **Intervention** | Tislelizumab 200mg IV every 3 weeks with ICC* (CAPOX or FP) |
| **Comparator** | Placebo IV every 3 weeks with ICC* (CAPOX or FP) |
| **Demographics** | Stratified by geography, PD-L1 expression, peritoneal metastasis, ICC option<br>Median age 60-61 yrs; male 70%; Asian 75%, White 22%, peritoneal mets 44%, oxaliplatin/capecitabine 94% |
| **Results** | **Tislelizumab + ICC* vs. Placebo + ICC*; n=997 (n=546 TAP $\geq$ 5%)**<br>**Primary endpoint: OS in PD-L1 TAP $\geq$ 5% and all randomized patients**<br>**PD-L1 TAP $\geq$ 5%:** median OS 17.2 vs. 12.6 months [HR 0.74 (95% CI 0.59-0.94); p=0.0006]<br>**All patients:** median OS 15 vs. 12.9 months [HR 0.80 (95% CI 0.70-0.92) p=0.001]<br>Subgroup analysis: Asia, US/Europe, presence of peritoneal mets, oxali/cape favored treatment arm |
| **Results** | Retrospective analysis of RATIONALE-305 in patients with PD-L1 TAP $\geq$ 1%<br>**Tislelizumab + ICC vs. Placebo + ICC; n=997 (n=885 TAP $\geq$ 1%)**<br>**PD-L1 TAP $\geq$ 1%:** median OS 15 vs. 12.8 months [HR 0.77 (95% CI 0.67-0.90)<br>Median duration of exposure to tislelizumab was 5.9 vs. 5.7 months<br>After study discontinuation, more patients in the placebo arm went on to subsequent therapy 53 vs. 59% |
| **Misc** | • Patients were enrolled in RATIONALE-305 regardless of PD-L1 expression<br>• Of 997 enrolled, 546 (55%) had PD-L1 expression score $\geq$ 5%<br>• All patients and those with PD-L1 $\geq$ 5% experienced improved OS in the treatment vs. placebo arms.<br>• A retrospective analysis of patients with PD-L1 $\geq$ 1 showed a modest improvement in OS<br>• Duration of exposure was similar and more patients in the placebo arm received subsequent therapy<br>• Higher PD-L1 expression appears to coincide with higher response; patients, at minimum, should have PD-L1 $\geq$ 1% to be considered for tislelizumab |

***Esophageal and esophagogastric junction cancer***

**Histology: adenocarcinoma**
**NCCN Preferred 1L regimens, HER2-negative:**
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 1 (cat 2A)
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 5 (cat 1)
**UpToDate:**
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 10
Fluoropyrimidine + platinum agent + ICI (nivolumab, tislelizumab) for PD-L1 CPS > 5 and < 10

**Histology: squamous cell carcinoma**
**NCCN Preferred 1L regimens:**
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 1 (cat 1)
Platinum agent + paclitaxel + tislelizumab for PD-L1 CPS > 1 (cat 2A)
**UpToDate:**
Fluoropyrimidine + platinum agent for PD-L1 CPS > 1
Fluoropyrimidine + platinum agent + ICI (nivolumab, tislelizumab) for PD-L1 CPS > 1 and < 10
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab tislelizumab) for PD-L1 CPS > 10
Or Nivolumab + ipilimumab for PD-L1 CPS > 10

**Histology: squamous cell carcinoma**
**NCCN Preferred 2L or subsequent therapy:**
ICI (nivolumab, pembrolizumab, tislelizumab if PD-L1 CPS > 10) (cat 1)
Single agent chemo: docetaxel, paclitaxel, irinotecan (cat 1)
**UpToDate:**
Single agent 2L ICI (nivolumab, tislelizumab) or pembrolizumab for CPS > 10, if no ICI in 1L setting
Chemotherapy if not eligible for ICI

**VA Oncology Clinical Pathways Esophageal Cancer** v7.2025 does not include tislelizumab
**1L Adenocarcinoma, MSS, HER2-negative CPS 1-4 and > 5** directs to nivolumab-containing regimen
**1L Squamous cell carcinoma, CPS > 1** directs to nivolumab + mFOLFOX6 or nivolumab + ipilimumab
**2L Squamous cell carcinoma, CPS > 10** directs to pembrolizumab; CPS < 10 directs to nivolumab

***Gastric and gastroesophageal cancer***

**NCCN: Preferred 1L regimens, HER2-negative:**
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 1 (cat 2A)
Fluoropyrimidine + platinum agent + ICI (nivolumab, pembrolizumab, tislelizumab) for PD-L1 CPS > 5 (cat 1)

**VA Oncology Clinical Pathways Gastric Cancer** v4.2025 does not include tislelizumab
**1L Adenocarcinoma, MSS, HER2+ CPS ≥ 1** directs to pembrolizumab or nivolumab
**1L Adenocarcinoma, MSS, HER2-negative CPS 1-4 and ≥ 5** directs to nivolumab-containing regimen

* ICC Investigator's Choice of Chemotherapy included CAPOX. Oxaliplatin 130mg/m$^2$ IV on day 1 for up to 6 cycles and capecitabine 1000mg/m$^2$ PO twice daily for 14 days (can continue beyond 6 cycles) or FP. Cisplatin 80mg/m$^2$ IV on day 1 and fluorouracil 800mg/m$^2$/day CIVI over 24 hours days 1-5 for up to 6 cycles.

**SAFETY CONSIDERATIONS**

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| **Boxed Warnings** | None |
| **Contraindications** | None |
| **Other Warnings** | Severe and fatal immune-mediated adverse reactions,<br>Infusion-related reactions (all 5%; ≥ gr 3 0.2%) - monitor patients; manage by slowing and/or interrupting infusion rate,<br>Complications of allogeneic hematopoietic stem cell transplantation – complications include GVHD, hepatic veno-occlusive disease,<br>Embryo-fetal toxicity – can cause fetal harm when administered to a pregnant woman |
| **Top 5 AEs** | **Second-line ESCC:** anemia, fatigue, musculoskeletal pain, decreased weight, cough<br>**First-line ESCC:** neutropenia, hyponatremia, hyperglycemia, anemia, fatigue<br>**First-line gastric or GEJ adenocarcinoma:** nausea, fatigue, decreased appetite, anemia, neuropathy |
| **Drug Interactions** | None noted |

| | DRUG | VANF | CFU | FDA | Key Endpoints |
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| PLACE IN THERAPY | **Tislelizumab** | TBD | No | • 1L PD-L1 ≥ 1, mESCC | **RATIONALE-306.** 1L mESCC<br>Median OS (mOS) ITT: 17 vs. 10 mos [HR 0.66] |
| | | | | • 2L+ mESCC | **RATIONALE-302.** 2L mESCC<br>mOS ITT: 8.6 vs. 6.3 mos [HR 0.70]<br>mOS TAP ≥ 10% 10.3 vs. 6.8 mos [HR 0.54] |
| | | | | • 1L PD-L1 ≥ 1, HER2- gastric or GEJ adeno w/platinum + fluoropyrimidine | **RATIONALE-305**. 1L mGastric or GEJ adeno<br>mOS TAP ≥ 5%: 17.2 vs. 12.6 mos [HR 0.74]<br>mOS TAP ≥ 1%: 15 vs. 12.8 mos [HR 0.77] |
| | **Nivolumab** | PA-F | Yes | • 1L PD-L1 ≥ 1, mESCC w/platinum + fluoropyrimidine<br>• 1L PD-L1 ≥ 1, mESCC w/ipilimumab | **CheckMate 648**. 1L ESCC<br>Nivo + chemo vs. chemo alone<br>ITT mOS 13.2 vs. 10.7 mos [HR 0.74];<br>TPS ≥ 1: mOS 15.4 vs. 9.1 mos [HR 0.54]<br>CPS ≥ 1: mOS 13.8 vs. 9.8 mos [HR 0.69] |
| | | | | • 2L+ mESCC | **ATTRACTION-3.** Prev-treated mESCC, no prior ICI<br>Nivo vs. taxane<br>mOS 10.9 vs. 8.5 mos [HR 0.77] |
| | | | | • 1L PD-L1 ≥ 1, gastric, GEJ or eso adeno w/platinum + fluoropyrimidine | **CheckMate 649.** 1L mGastric or GEJ adeno<br>ITT: mOS 13.7 vs. 11.6 mos [HR 0.79]<br>CPS ≥ 5: mOS 14.4 vs. 11.1 [HR 0.70]<br>CPS ≥ 1: mOS 14 vs. 11.3 [HR 0.77] |
| | **Pembrolizumab** | PA-F | Yes | • 1L PD-L1 (CPS ≥ 1) ESCC w/ platinum + fluoropyrimidine | **KEYNOTE 590.** 1L ESCC/adeno (73/27%)<br>Pembro + chemo vs. chemo alone<br>ITT mOS 12.4 vs. 9.8 mos [HR 0.73] SCC<br>CPS ≥ 10 mOS 13.5 vs. 9.4 mos; [HR 0.62] SCC<br>CPS < 10 mOS 10.5 vs. 11.1 mos [HR 0.99] SCC<br>CPS < 10 mOS 12.7 vs. 8.4 mos [HR 0.66] adeno |
| | | | | • 2L+ PD-L1 (CPS ≥ 10) ESCC | **KEYNOTE 181.** 2L+ pembro vs. chemo in SCC<br>CPS ≥ 10 mOS 9.3 vs. 6.7 mos [HR 0.64] |
| | | | | • 1L PD-L1 (CPS ≥ 1) HER2- gastric or GEJ adeno w/platinum + fluoropyrimidine | **KEYNOTE 859.** 1L mGastric or GEJ adeno<br>ITT: mOS 12.9 vs. 11.5 mos [HR 0.78]<br>CPS ≥ 1: mOS 13 vs. 11.4 mos [HR 0.74]<br>CPS ≥ 10. mOS 15.7 vs. 11.8 [HR 0.65] |

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| VHA PLACE IN THERAPY | **Potential Use in VHA** | • There are varying opinions on data interpretation among expert groups regarding PD-L1 expression scores and which ICI is most appropriate<br>• The FDA Oncology Drug Advisory Committee conducted a meta-analysis of data in advanced ESCC to evaluate the addition of ICI (nivolumab, pembrolizumab, tislelizumab) to chemotherapy. A survival benefit was noted among patients with CPS ≥ 1, but not CPS < 1<br>• Data from the RATIONALE program suggests an improvement in response with higher CPS scores<br>• Tislelizumab does not appear to provide additional benefit to the current ICI landscape in ESCC or gastric/GEJ adenocarcinoma |

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