Zolbetuximab-clzb (VYLOY) in Gastric or Gastroesophageal Junction Adenocarcinoma
National Drug Mini-monograph
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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. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION	
Description / MOA	Zolbetuximab is a claudin 18.2 (CLDN18.2)-directed monoclonal antibody.[1] CLDN18.2 is a protein responsible for the tight junctions of the gastric mucosa maintaining its barrier function. CLDN 18.2 becomes overexpressed on abnormal cancer cells allowing zolbetuximab to bind and activate immune-mediated lysis.[2]
Indication Under Review[1]	In combination with fluoropyrimidine and platinum-containing chemotherapy for first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric or gastroesophageal junction adenocarcinoma with CLDN18.2 positive tumors, as determined by an FDA-approved test.
Dosage Regimen	Initial dose: 800 mg/m2 IV Subsequent doses: 600 mg/m2 IV every 3 weeks or 400 mg/m2 IV every 2 weeks Until disease progression or unacceptable toxicity *(in combination with mFOLFOX6 or CAPOX)*
Dosage Forms Under Review	100 mg lyophilized powder in a single-dose vial

EFFICACY CONSIDERATIONS		
Trial	**SPOTLIGHT (NCT03504397)[3]**	**GLOW (NCT03653507)[5]**
Design	Multicenter, randomized, placebo-controlled, double-blind, phase 3 trial	Global, randomized, double-blind, phase 3 trial
Population	N=565; ages 18 years or older, CLDN18.2-positive tumors (at least 75% of tumor cells showing moderate-to-strong staining), HER2-negative, untreated, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, radiologically evaluable disease, ECOG PS 0-1, with adequate organ function. • Stratification: region, number of organs with metastases, previous gastrectomy	N=507; adults ages 18 years and older, CLDN18.2-positive tumors (at least 75% of tumors cells showing moderate-to-strong staining as determined by VENTANA CLDN18 RxDx Assay), HER2-negative, untreated, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, radiologically evaluable disease, ECOG PS 0-1, adequate organ function
Demographics (zolbetuximab vs. placebo)	Median age: 62.0 vs. 60.0 years; 62% vs. 62% male; 38% vs. 38% female; 30% vs. 29% prior gastrectomy; 77% vs. 74% stomach primary site	Median age: 61.0 vs. 59.0 years; 62.6% vs. 61.7% male; 29.5% vs. 29.6% prior gastrectomy; 86.2% vs. 82.6% stomach primary site
Intervention	Zolbetuximab and mFOLFOX6 (N=283): • Zolbetuximab (Z) 800 mg/m2 IV loading dose, then 600 mg/m2 IV every 3 weeks • Oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, fluorouracil 400 mg/m2 (bolus), fluorouracil 2400 mg/m2 (continuous infusion) IV, Days 1, 15, 29 every 42 days x4 cycles • Then zolbetuximab, 5-fluorouracil, and leucovorin until disease progression or unacceptable toxicity	Zolbetuximab and CAPOX (N=254): • Zolbetuximab 800 mg/m2 IV loading dose, then 600 mg/m2 IV, Day 1 • Capecitabine 1000 mg/m2 PO BID, Days 1-14 • Oxaliplatin 130 mg/m2 IV, Day 1 • Every 3 weeks until disease progression, unacceptable toxicity, start of another anti-cancer treatment or other discontinuation criteria
Comparator	Placebo (P) and mFOLFOX6 (N=282)	Placebo and CAPOX (N=253)
Results	Primary Endpoint: progression-free survival (PFS) Secondary Endpoints: overall survival (OS), objective response rate (ORR), duration of response (DOR)	Primary Endpoint: progression-free survival (PFS) Secondary Endpoints: overall survival (OS), objective response rate (ORR), duration of response (DOR) Median follow-up for PFS:

Median follow-up for PFS:
12.94 months Z vs. 12.65 months P

	Z	P
mPFS (months)	10.61	8.67
HR (95% CI); P-value	0.75 (0.60-0.94); P=0.0066	
24-months PFS (%)	24	15
mOS (months)	18.23	15.54
HR (95% CI); P-value	0.75 (0.60-0.94); P=0.0053	
24-months OS (%)	39	28
ORR (%)	48	48
mDOR (months)	9	8.05

Subgroup analyses for PFS according to certain stratifications:

- Region
  - Asia: HR 0.56 (95% CI 0.37-0.85)
  - Non-Asia: HR 0.85 (95% CI 0.65-1.11)
- Number of organs with metastases
  - 0-2: HR 0.73 (95% CI 0.56-0.94)
  - ≥3: HR 0.84 (95% CI 0.55-1.30)
- Previous gastrectomy
  - Yes: HR 0.62 (95% CI 0.41-0.94)
  - No: HR 0.81 (95% CI 0.62-1.05)
- Primary Site
  - Stomach: HR 0.69 (95% CI 0.53-0.89)
  - GEJ: HR 1.02 (0.65-1.59)

Final overall survival results[4]
Median follow-up for PFS:
18.04 months Z vs. 17.91 months P

	Z	P
mPFS (months)	11.04	8.94
HR (95% CI); P-value	0.734 (0.591-0.910); P=0.0024	
mOS (months)	18.23	15.57
HR (95% CI); P-value	0.784 (0.644-0.954); P=0.0075	
ORR (%)	48.1	47.5

Zolbetuximab and mFOLFOX demonstrated a significant 2-month PFS and OS benefit compared to placebo in the SPOTLIGHT trial in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with CLDN18.2-positive tumors. Patients had the same ORR and similar DOR. While benefit was greater in patients with a primary gastric cancer than GEJ, this should be interpreted with caution given the small population in the GEJ subgroup.

12.62 months Z vs. 12.09 months P

	Z	P
mPFS (months)	8.21	6.80
HR (95% CI); P-value	0.687 (0.544-0.866); P=0.0007	
24-month PFS (%)	14	7
mOS (months)	14.39	12.16
HR (95% CI); P-value	0.771 (0.615-0.965); P=0.0118	
24-month OS (%)	29	17
ORR (%)	42.5	40.3
DOR (months)	6.14	6.08

A forest plot of prespecified subgroups indicates that patients with a primary GEJ tumor site or currently smoking trended towards having a higher risk of death when treated with zolbetuximab though the confidence intervals crossed the value of 1, which may indicate no difference.

Subgroup analyses for PFS:

- Region
  - Asia: HR 0.583 (95% CI 0.436-0.781)
  - Non-Asia: HR 0.928 (95% CI 0.645-1.336)
- Number of sites with metastases
  - 0-2: HR 0.691 (95% CI 0.529-0.904)
  - ≥3: HR 0.682 (95% CI 0.445-1.045)
- Previous gastrectomy
  - Yes: HR 0.726 (95% CI 0.472-1.114)
  - No: HR 0.696 (95% CI 0.533-0.909)
- Primary Site
  - Stomach: HR 0.619 (95% CI 0.484-0.791)
  - GEJ: HR 1.351 (0.731-2.496)

Zolbetuximab and CAPOX demonstrated a significant 2-month PFS and OS benefit compared to placebo in the GLOW trial in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with CLDN18.2-positive tumors. Patients had a similar ORR and DOR. Similar to the SPOTLIGHT trial, the benefit was greater in patients with a primary gastric cancer. However, the GEJ group was a very small population.

Notes

NCCN guidelines Gastric Cancer and Esophageal and Esophagogastric Junction Cancers V5.2024[6,7]:
First-line therapy for unresectable locally advanced, recurrent, or metastatic disease
Preferred regimens (category 1):

- **HER2-negative**
  - Fluoropyrimidine, oxaliplatin, nivolumab (PD-L1 CPS ≥5)
  - Fluoropyrimidine, oxaliplatin, pembrolizumab (PD-L1 CPS ≥10)
  - Fluoropyrimidine, oxaliplatin, **zolbetuximab-clzb (CLDN18.2 positive)**

[redacted]

- Fluoropyrimidine, cisplatin, pembrolizumab (PD-L1 CPS ≥10)

VA Oncology Clinical Pathway:

- Gastric Cancer (V4.2024): not included
- Esophageal Cancer (V1.2025): zolbetuximab is recommended first-line in patients with stage IVB adenocarcinoma (HER2 negative, MSS) who are candidates for cytotoxic chemotherapy and test positive for CLDN18.2 without being candidates for immunotherapy or having PD-L1 CPS ≥5%.

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings Any (gr 3-4)	Hypersensitivity reactions (including anaphylaxis reactions): 18% (2%) Infusion-related reactions: 3.2% (0.4%) • Patients should be monitored during the infusion and for 2 hours afterwards or longer as needed for hypersensitivity and infusion-related reactions. Severe nausea: mFOLFOX6 82% (16%), CAPOX 69% (9%) Severe vomiting: mFOLFOX6 67% (16%), CAPOX 66% (12%) • Pretreat patients with antiemetics for highly emetogenic regimen prior to each infusion and manage with antiemetics or fluid replacement for nausea and vomiting during and after infusions. • Nausea and vomiting occurred most frequently within the first two infusions and is managed with antiemetics, infusion interruptions, and infusion rate adjustments.
Top 5 AEs	• Nausea (69%-82%) • Vomiting (66%-67%) • Decreased albumin (66%-78%) • Leukopenia (66%) • Decreased appetite (41%-47%)
Drug Interactions	Monitor therapy with efgartigimod alfa or rozanolixizumab.

	DRUG	VANF	CFU	FDA	GUIDELINES
PLACE IN THERAPY	Nivolumab + FOLFOX or CAPOX	PA-F	Yes	Approved	Phase 3 (Checkmate 649)[8] • Nivolumab and chemotherapy (CAPOX/FOLFOX) vs. chemotherapy alone • N=1581; untreated, unresectable, HER2-negative gastric/GEF/esophageal adenocarcinoma regardless of PD-L1 expression • PD-L1 CPS ≥5: mOS 14.1 vs. 11.1 months (HR 0.71; 98.4% CI 0.59-0.86; P<0.0001) • 12-month OS rate: 57% vs. 46% • PD-L1 CPS ≥5: mPFS 7.7 vs. 6.05 months (HR 0.68; 98% CI 0.56-0.81; P<0.0001) • 12-month PFS estimate: 36% vs. 22% NCCN: preferred first-line category 1 regimen for HER2-negative tumors in combination with a fluoropyrimidine and oxaliplatin if PD-L1 CPS ≥5 VA Clinical Pathways: preferred agent for first-line therapy in stage IVB MSS HER2-negative disease if PD-L1 CPS ≥5% or if CLDN18.2 negative
	Pembrolizumab + FOLFOX or CAPOX	PA-F	Yes	Approved	Phase 3 (Keynote 859)[9] • Pembrolizumab and chemotherapy (FOLFOX/CAPOX) vs. placebo and chemotherapy • N=1579; untreated locally advanced or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma • ITT: mOS 12.9 vs. 11.5 months (HR 0.78; 95% CI 0.70-0.87; P<0.0001) • PD-L1 CPS ≥1: mOS 13 vs. 11.4 months (HR 0.74; 95% CI 0.65-0.84; P<0.0001) • PD-L1 CPS ≥10: mOS 15.7 vs. 11.8 months (HR 0.65; 95% CI 0.53-0.79; P<0.0001) NCCN: preferred first-line category 1 regimen for HER2-negative tumors in combination with a fluoropyrimidine and oxaliplatin if PD-L1 CPS ≥10 VA Clinical Pathways: not incorporated into the pathway for stage IVB MSS HER2-negative disease but present for patients with HER2-positive disease and MSI-H disease

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. Gastric cancer is a relatively rare cancer in the United States encompassing 1.3% of all new cancer cases in the country. However, it is a leading cause of cancer-related death in the world.[10,11] 2. Symptoms are nonspecific or may not occur in the earlier stages of disease making diagnosis difficult so patients are often diagnosed when the cancer is advanced resulting in a poor prognosis.[12] Between 2013 and 2019, the 5-year relative survival rate for distant disease was 7%.[13] 3. Gastroesophageal junction (GEJ) cancer is also a rare cancer in the United States with incidences rising between 1973-2013. GEJ cancer is associated with a poor prognosis.[14,15,16] 4. Although GEJ cancer is classified with esophageal cancers, treatment for advanced, unresectable, or metastatic GEJ adenocarcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma is interchangeable.[7,17] 5. Standard treatment for locally advanced, unresectable, or metastatic gastric/GEJ cancer is systemic chemotherapy but more recently have included immunotherapy and novel targeted therapies to better attack the tumors' characteristics.[18] 6. Studies report that the CLDN18.2 protein is present in approximately 44% of gastric cancer cases, with a slightly higher prevalence in gastric adenocarcinoma compared to gastroesophageal junction adenocarcinoma, making it a potential target of treatment for many patients.[19,20] 7. Zolbetuximab is the only FDA-approved targeted therapy for CLDN18.2 positive tumors and was shown in both the SPOTLIGHT and GLOW trials to have PFS and OS benefit over placebo when used in combination with a fluoropyrimidine-based chemotherapy. 8. Patients receiving zolbetuximab had significantly higher incidences of treatment-related nausea and vomiting; however, these incidences were most common during the first treatment cycle and decreased in subsequent cycles. Compared to placebo, rates of zolbetuximab discontinuation and treatment-related deaths were similar. 9. Zolbetuximab is a novel targeted therapy for any patient who may have a CDLN18.2 positive tumor with HER2-negative disease and does not require any PD-L1 CPS expression like nivolumab and pembrolizumab do for the same setting. 10. Current NCCN guidelines list zolbetuximab in combination with chemotherapy as a first-line preferred regimen for HER2-negative, CLDN18.2-positive locally advanced, unresectable, or metastatic gastric or GEJ cancer.[6,7] 11. NCCN guidelines also list nivolumab in combination with chemotherapy as a first-line preferred regimen for HER2-negative locally advanced, unresectable, or metastatic disease but in patients with PD-L1 CPS≥5%. The SPOTLIGHT trial reported 13% of its patients having a PD-L1 CPS of 5 or more making them eligible for either nivolumab (per CHECKMATE 649) or zolbetuximab. However, the study did not stratify outcomes based on PD-L1 expression to note whether those with a PD-L1 CPS score did better or worse with zolbetuximab making it difficult to know which agent to use in the first-line setting given that both agents are limited to the first-line setting. 12. There are conflicting data as to whether CLDN18.2 expression correlates to PD-L1 expression, if it indicates a poorer prognosis than those with negative CLDN18.2 expression, or if it influences the efficacy of PD-L1 checkpoint inhibitors. There is also the possibility that CLDN18.2 may be an oncogene that promotes proliferation, differentiation, and migration of tumor cells once overexpressed.[21,22] 13. Considering the limited data regarding the CLDN18.2 protein and the longer 3-year follow-up provided by the CHECKMATE-649 trial compared to the SPOTLIGHT trial, it may be reasonable to administer zolbetuximab first in patients positive for CLDN18.2 and PD-L1 expression unless the CPS score is ≥5% at which nivolumab would be given. However, providers should approach each individual case with clinical judgement.

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References

1. Vyloy (zolbetuximab-clzb) for injection [package insert]. Northbrook, IL: Astellas Pharma US, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761365s000lbl.pdf. Published October 2024. Accessed January 14, 2025.

2. Kubota Y, Shitara K. Zolbetuximab for Claudin18.2-positive gastric or gastroesophageal junction cancer. *Ther Adv Med Oncol*. 2024;16:17588359231217967. Published 2024 Jan 3. doi:10.1177/17588359231217967.
3. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial [published correction appears in Lancet. 2023 Jul 22;402(10398):290. doi: 10.1016/S0140-6736(23)01481-2] [published correction appears in Lancet. 2024 Jan 6;403(10421):30. doi: 10.1016/S0140-6736(23)02762-9]. Lancet. 2023;401(10389):1655-1668. doi:10.1016/S0140-6736(23)00620-7.
4. Shitara K, Cutsem EV, Lordick F, et al. Final overall survival results from phase 3 SPOTLIGHT study evaluating zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients (pts) with claudin 18 isoform 2 (CLDN18.2)+, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. JCO. 2024;42:4036-4036. doi:10.1200/JCO.2024.42.16_suppl.4036.
5. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133-2141. doi:10.1038/s41591-023-02465-7. FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma. Food and Drug Administration. Updated October 18, 2024. Accessed January 14, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zolbetuximab-clzb-chemotherapy-gastric-or-gastroesophageal-junction-adenocarcinoma#:~:text=On%20October%2018%2C%202024%2C%20the,by%20an%20independent%20review%20committee.
6. National Comprehensive Cancer Network. Gastric Cancer (Version 5.2024). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
7. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers (Version 5.2024). https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2.
9. Rha SY, Oh DY, Yañez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial [published correction appears in Lancet Oncol. 2024 Dec;25(12):e626. doi: 10.1016/S1470-2045(24)00650-8]. Lancet Oncol. 2023;24(11):1181-1195. doi:10.1016/S1470-2045(23)00515-6.
10. Cancer Stat Facts: Stomach Cancer. National Cancer Institute. Accessed January 14, 2025. https://seer.cancer.gov/statfacts/html/stomach.html
11. Key Statistics About Stomach Cancer. American Cancer Society. Accessed January 14, 2025. https://www.cancer.org/cancer/types/stomach-cancer/about/key-statistics.html
12. Stomach Cancer. Mayo Clinic. Updated June 19, 2024. Accessed January 14, 2025. https://www.mayoclinic.org/diseases-conditions/stomach-cancer/symptoms-causes/syc-20352438#:~:text=Trouble%20swallowing,with%20your%20health%20care%20provider.
13. Stomach Cancer Survival Rates. American Cancer Society. Accessed January 14, 2025. https://www.cancer.org/cancer/types/stomach-cancer/detection-diagnosis-staging/survival-rates.html.
14. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. *Semin Radiat Oncol*. 2013;23(1):3-9. doi:10.1016/j.semradonc.2012.09.008.
15. Bartel M, Brahmbhatt B, Bhurwal A. Incidence of gastroesophageal junction cancer continues to rise: Analysis of Surveillance, Epidemiology, and End Results (SEER) database. *JCO*. 2019;37(4_suppl):40-40. doi.org/10.1200/JCO.2019.37.4_suppl.40.
16. Greally M, Agarwal R, Ilson DH. Optimal management of gastroesophageal junction cancer. *Cancer*. 2019;125(12):1990-2001. doi:10.1002/cncr.32066.
17. Rüschoff J. Adenocarcinoma of the GEJ: gastric or oesophageal cancer?. *Recent Results Cancer Res*. 2012;196:107-113. doi:10.1007/978-3-642-31629-6_7.
18. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. *J Hematol Oncol.* 2023;16(1):57. Published 2023 May 27. doi:10.1186/s13045-023-01451-3.
19. Shitara K, Xu RH, Ajani JA, et al. Global prevalence of claudin 18 isoform 2 in tumors of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. *Gastric Cancer.* 2024;27(5):1058-1068. doi:10.1007/s10120-024-01518-1.
20. Waters R, Sewastjanow-Silva M, Yamashita K, et al. Retrospective Study of Claudin 18 Isoform 2 Prevalence and Prognostic Association in Gastric and Gastroesophageal Junction Adenocarcinoma. *JCO Precis Oncol.* 2024;8:e2300543. doi:10.1200/PO.23.00543.
21. Waters R, Sewastjanow-Silva M, Yamashita K, et al. Retrospective Study of Claudin 18 Isoform 2 Prevalence and Prognostic Association in Gastric and Gastroesophageal Junction Adenocarcinoma. *JCO Precis Oncol.* 2024;8:e2300543. doi:10.1200/PO.23.00543.
22. Cao W, Xing H, Li Y, et al. Claudin18.2 is a novel molecular biomarker for tumor-targeted immunotherapy. *Biomark Res*. 2022;10(1):38. Published 2022 May 31. doi:10.1186/s40364-022-00385-1.