Zanidatamab-hrii (ZIIHERA)
National Drug Monograph
March 2026

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services 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.

Abbreviations: AC, active-controlled; BTC, biliary tract cancer; CO, crossover; DB, double-blind; EMA, European Medicines Agency; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Cytolytic bispecific human epidermal growth factor receptor 2 (HER2)-directed antibody. Tumor growth inhibition and cell death occur via complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis activity. Zanidatamab-hrii is the first agent approved for HER2-amplified or HER2-expressed biliary tract cancer (BTC).
Indication Under Review	Treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test. Approved under accelerated approval based on overall response rate and duration of response. Continued approval may be contingent on verification and description of clinical benefit in confirmatory trial(s).
Dosage Regimen	20 mg/kg by IV infusion once every 2 weeks until disease progression or unacceptable toxicity.
Dosage Forms Under Review	300 mg lyophilized powder for injection in a single-dose vial

EFFICACY CONSIDERATIONS	
Trial	**Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study[2]**
Design	Multinational, single-arm, phase 2b, observational study comprised of two cohorts: • Cohort 1 included patients with IHC 2+ or 3+ (HER2-positive) • Cohort 2 included patients with IHC 0 or 1+ (HER2-negative or HER2-low, respectively) *Primary Efficacy Endpoint*: Objective response rate, defined as the proportion of patients who received drug and had a confirmed best overall response of complete response or partial response.
Inclusions/ Population	• Age ≥ 18 years; • Confirmed *HER2*-amplified, unresectable, locally advanced, or metastatic biliary tract cancer (gallbladder cancer [GBC], intrahepatic cholangiocarcinoma [ICC], or extrahepatic cholangiocarcinoma [ECC]); • Disease progression on ≥ 1 gemcitabine-based systemic therapy for unresectable, locally advanced or metastatic disease (or in the neoadjuvant or adjuvant setting with progression or recurrence within 6 months of completion); • ≥ 1 measurable target lesion; • left ventricular ejection fraction ≥ 50%; • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ***Major Exclusions**:* Previous treatment with HER2-targeting agents; untreated or symptomatic central nervous system metastases or leptomeningeal disease. ***Population Baseline Characteristics, Cohort 1 (n = 80) | Cohort 2 (n = 7)*:** • Median age 64 | 62; male 44% | 71%; • Asian 65% | 71%; White 29% | 29%; North America 23% | 0%; • GBC 51% | 57%; ICC 29% | 43%; ECC 20% | 0%; • HER2 3+ 78% | 0%; HER2 2+ 23% | 0%; HER2 1+ 0% | 43%; HER2 0 0% | 57%; • tumor stage III 11% | 14%; stage IV 89% | 86%; • median number of previous lines of therapy for metastatic or locally advanced disease 1 | 2; • previous systemic therapy – gemcitabine-based 100% | 100%; gemcitabine + cisplatin 76% | 57%; • fluoropyrimidine-based 34% | 57%; PD-1 or PD-L1 inhibitor 26% | 14%; fluoropyrimidine 6% | 0%.
Intervention	Zanidatamab 20 mg/kg on Days 1 and 15 of each 28-day cycle (or once every 2 weeks, per prescribing information)
Comparator	None
Results	**Tumor Response in Cohort 1 (n=80; patients with IHC 2+ or 3+ (HER2-positive)**

Outcome	Zanidatamab
Objective Response Rate, n/N (%)	33/80 (41.3)
Complete response	1/80 (1)
Partial response	32/80 (40)
Stable disease	22/80 (28)
Median time to first response, mo (range)	1.8 (1.6, 5.5)
Median duration of response, mo (range)	12.9 (1.5, 16.9+)
Duration of response ≥ 16 weeks, n/N (%)	55/80 (68.8)
Progression-free survival, n/N (%)	54/80 (68)
Median progression-free survival, mo (range)	5.5 (0.3, 18.5+)
Overall survival at 9 months	69.9 (57-79.1)

Independent central review assessment
[α] Downgraded for risk of bias (no blinding)
[β] Downgraded for indirectness (OS was estimated since data were immature at cutoff date; PFS is an image-based surrogate for OS)
[γ] Downgraded for imprecision (uncertain width of CI)

Most Common Anticancer Therapies After Discontinuation of Zanidatamab: Folinic acid, fluorouracil + oxaliplatin (FOLFOX) or other fluorouracil-based therapies; levantinib, pyrotinib (a HER2-targeted TKI approved/marketed only in China), nivolumab, and platinum (cisplatin or oxaliplatin).

Authors' Conclusions	Zanidatamab showed meaningful activity, including rapid and durable responses, and a favorable safety profile in the treatment of patients with HER2-positive BTC. It has potential as a new targeted therapy following failure of first-line gemcitabine-based chemotherapy.

SAFETY CONSIDERATIONS	
Boxed Warnings	Embryofetal toxicity
Contraindications	None
Other Warnings	Left ventricular dysfunction Infusion-related reactions Diarrhea
Top 5 AEs (≥ 20%)	Diarrhea, infusion-related reaction, abdominal pain, fatigue
Drug Interactions	No information
Trial Safety Results	*Deaths: 32/80 (40.0%) in Cohort 1 and 5/7 (71.4%) in Cohort 2* *Serious Treatment-related Adverse Events (STRAEs)*: 7/87 (8%) overall *Discontinuations Due to Adverse Events (DAEs)*: 2/80 (2.5%) in Cohort 1; none in Cohort 2

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY FOR HER2-POSITIVE, IHC3+ BTC

DRUG	VANF	CFU	Outcomes	NCCN GUIDELINES[3] ESMO GUIDELINES[4]
Zanidatamab	TBD	TBD	P2 trial (HERIZON-BTC-01[2]) N=80, prev-treated ORR 41%; mOS 16 mos N=7 No HER2-low response Grade 3 AEs 18%	**NCCN v2.2025** Subsequent-line for BTC if disease progression; Useful in Certain Circumstances; Category 2A for HER2+ by IHC3+
Fam-trastuzumab deruxtecan	PA-F	Yes	P2 trial (HERB[4]) N=24 subgroup ORR 36% (90% CI, 19.6-56.1) mPFS 4 mos; mOS 7 mos N=8 HER2-low ORR 13% Any grade ILD 25% (N=8) ≥ Gr 3 anemia 53%, neutropenia 31%	**NCCN v2.2025** Subsequent-line for BTC if disease progression; Useful in Certain Circumstances; Category 2A for HER2+ by IHC3+ **VA Biliary Tract Cancer v3.2025** Fam-trastuzumab deruxtecan for BTC – unresectable or metastatic, 2L, HER2+, IHC3+
Trastuzumab + pertuzumab	PA-F PA-F	Yes Yes	P2 basket study (MyPathway[5]) N=39 prev-treated HER2 overexpressed ORR 23% (n=9) mPFS 4 mos; mOS 11 mos Gr 3 TRAE 8% P2 basket study (TAPUR[6]) N=29 prev-treated ORR 32% (95% CI, 16-52) Gr 3 TRAEs 14% (one each: anemia, diarrhea, fatigue, IRR)	**NCCN v2.2025** Subsequent-line for BTC if disease progression; Useful in Certain Circumstances; Category 2A for HER2+ by IHC3+/ISH+/NGS amplification
Trastuzumab + tucatinib	PA-F PA-F	Yes Yes	P2 basket study (SGNTUC-019[7]) N=30 prev-treated ORR 47% (n=14) mPFS 6 mos; mOS 16 mos Gr 3 TEAE 60% (incl. cholangitis, decr appetite, nausea)	**NCCN v2.2025** Subsequent-line for BTC if disease progression; Useful in Certain Circumstances; Category 2A for HER2+ by IHC3+/ISH+/NGS amplification

POTENTIAL PLACE IN THERAPY OF ZANIDATAMAB

- Zanidatamab has not been directly compared to other therapies for HER2+ advanced BTC
- Through indirect comparisons, it does not appear to provide additional benefit to existing, available therapies and has a more inconvenient dosing schedule (i.e. q 2 weeks vs. q 3 weeks)
- It may be an option for patients who are unable to receive fam-trastuzumab deruxtecan due to concern for ILD, but would also consider trastuzumab + tucatinib, for improved ORR and convenient dosing schedule. Trastuzumab + pertuzumab is another consideration due to its favorable Grade 3 toxicity profile and convenient dosing schedule (i.e. Q 3 weeks); modest PFS benefit in the refractory setting may be reflective of advanced line setting in the trial design. It's important to consider study enrollment criteria, as the differences may account for the variance in outcome comparisons.

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References

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8 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Biliary Tract Cancers, version 6.2024 — January 10, 2025. Available at: btc.pdf. Accessed: 1/9/2026