https://doi.org/10.70844/jmhrp.2025.2.2.44

Journal of Medical Health Research and Psychiatry

Review Article

JMHRP-25-050

Zanidatamab in HER2-Positive Biliary Tract Cancer: A First Narrative Literature Review

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Received date: 21 October, 2025, **Accepted date:** 28 October, 2025, **Published date:** 04 November, 2025

Citation: Poudel P, Khanal A, Ahmed F (2025) Zanidatamab in HER2-Positive Biliary Tract Cancer: A First Narrative Literature Review. J Med Health Psychiatry 2: 2.

Abstract

Biliary Tract Cancers (BTCs) are uncommon but aggressive tumors with limited therapeutic options and generally poor survival outcomes. Advances in molecular profiling have identified HER2 amplification and overexpression as potential therapeutic targets in a subset of these patients. Zanidatamab, a new monoclonal antibody that targets HER2, received Food and Drug Administration (FDA) approval in 2024 for patients with previously treated HER2-positive BTC, representing a significant development in targeted cancer therapy. The drug, marketed as ZIIHERA® (zanidatamab-hrii), is indicated for adults with unresectable or metastatic HER2-positive (IHC 3+) Biliary Tree Cancers (BTCs), confirmed *via* an FDA-approved diagnostic test. Zanidatamab is being developed by Jazz Pharmaceuticals and BeiGene Ltd under license from Zymeworks Inc., the original creator of the molecule, for treating HER2-expressing solid tumors. This review summarizes the pharmacodynamic and pharmacokinetic properties of Zanidatamab, evaluates its clinical efficacy and safety based on emerging clinical trial data and discusses its potential role in the evolving treatment landscape of BTC.

Keywords: Biliary tree cancers, FDA, Zanidatamad, HER2, Targeted cancer therapy

Introduction

Biliary tract cancers, comprising intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer, represent approximately 3% of gastrointestinal malignancies but are associated with disproportionately high mortality [1,2]. The majority of patients present with advanced-stage disease and systemic therapy remain the cornerstone of management. Standard first-line chemotherapy with gemcitabine and cisplatin has shown modest benefit, with median overall survival rarely exceeding one year [3]. The urgent need for more effective therapeutic options has encouraged research into molecularly targeted therapies.

HER2 (human epidermal growth factor receptor 2) amplification and overexpression are most commonly associated with breast and gastric cancers but are also present in around 10% of biliary tract cancers. [2]. In HER2-positive tumors, the HER2 gene is either amplified or overexpressed, which promotes aggressive tumor growth in various cancers, including breast, ovarian, pancreatic and gastric cancers. To detect these alterations, several diagnostic techniques are employed, including immunohistochemistry, next-generation sequencing and fluorescence in situ hybridization. Additionally, emerging technologies such as biosensors and circulating tumor DNA (ctDNA) are enhancing diagnostic accuracy. In terms of treatment, therapies targeting HER2, such as trastuzumab, as well as newer options like zanidatamab, are showing promise for treating HER2-positive cancers [4]. These HER2 alterations offer a clear target for treatment. Zanidatamab is a humanized IgG1 antibody that targets two separate regions on the HER2 protein, which helps bring the receptors together, promotes their internalization and boosts the body's immune response to attack cancer cells. Zanidatamab stands superior as its unique approach compared to traditional HER2-targeting monoclonal antibodies, offering a potentially more powerful way to treat HER2-positive cancers (Figure 1).

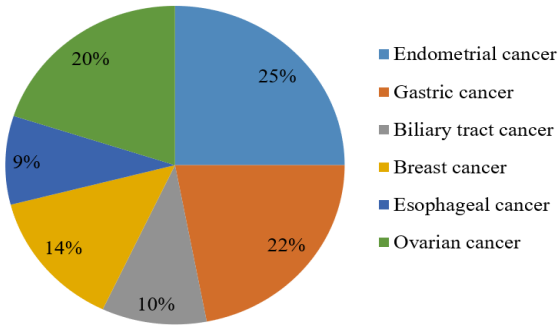

Figure 1: Incidence of HER2-positive tumors.

https://doi.org/10.70844/jmhrp.2025.2.2.44

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The recent FDA approval of Zanidatamab for HER2-positive, previously treated BTC represents the first HER2-directed therapy approved in this malignancy. This review provides an overview of Zanidatamab's pharmacologic characteristics, summarizes clinical trial outcomes and discusses its emerging role in precision oncology for BTC.

Pharmacodynamic properties of zanidatamab

Zanidatamab is a humanized bispecific IgG1 antibody designed to bind to two distinct epitopes on the extracellular domain of HER2, specifically subdomains II and IV. This dual-binding approach improves the clustering of HER2 receptors, facilitates their internalization and disrupts downstream HER2 signaling more efficiently than traditional, monospecific HER2 antibodies. Moreover, the bispecific nature of zanidatamab enhances immune responses by promoting Fc-mediated activities, such as Antibody-Dependent Cellular Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC) [5].

Preclinical research has shown that zanidatamab effectively downregulates HER2 receptors, inhibits the growth of tumor cells and initiates immune-driven tumor destruction in HER2-positive cancer cell lines. In xenograft models of HER2-positive Biliary Tract Cancer (BTC), zanidatamab was found to reduce tumor growth and extend survival. When compared to trastuzumab, zanidatamab's mechanism results in a more sustained inhibition of HER2, leading to stronger antitumor effects (Figure 2) [5].

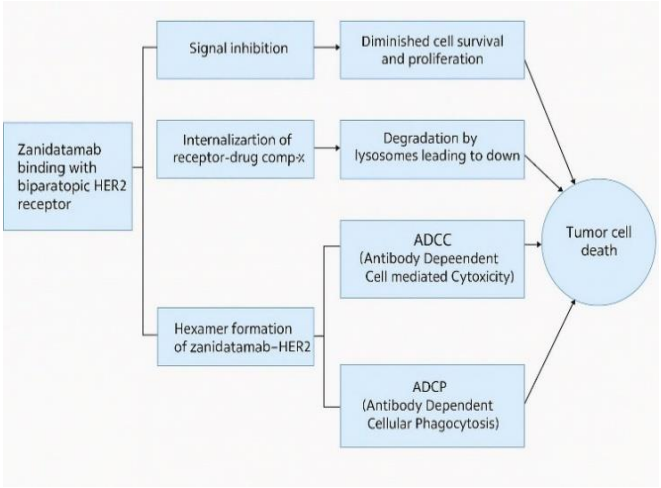

Figure 2: Mechanism of action of zanidatamab.

A first-in-human phase 1 study explored zanidatamab, a bispecific antibody targeting two different HER2 domains, in patients with advanced HER2-expressing or HER2-amplified solid tumors. The results showed that zanidatamab was generally well tolerated, with most side effects being mild to moderate and manageable. No dose-limiting toxicities were observed, allowing for the determination of a recommended dose for further studies. The trial also demonstrated promising anti-tumor effects across several cancer types, reinforcing the potential of HER2 as a therapeutic target not only in breast and gastroesophageal cancers but also in other malignancies. These findings provide strong support for the continued development of zanidatamab as a treatment for a wide range of HER2-positive cancers [6].

Pharmacokinetic properties of zanidatamab

The pharmacokinetic profile of zanidatamab is similar to other monoclonal antibodies. After intravenous administration, it exhibits a biphasic distribution with serum concentrations increasing proportionally to the dose [7].

- **Absorption:** Zanidatamab is administered intravenously, ensuring complete bioavailability.
- **Distribution:** It primarily distributes in the vascular and interstitial spaces, with a central volume of 7.5 L.
- **Metabolism and elimination:** The drug is broken down through proteolytic degradation and its elimination is not reliant on liver metabolism.
- **Half-life:** With a half-life of 21 days, zanidatamab is usually given every 2–3 weeks. Clearance: 0.012 L/hr.
- **Special populations:** Data on its use in patients with hepatic or renal impairments is limited and there are no current recommendations for dose adjustments in these populations.

Zanidatamab exhibits both linear and nonlinear clearance, with linear clearance being the dominant process at therapeutic doses of 20 mg/kg every 2 weeks and 30 mg/kg every 3 weeks. At steady state, zanidatamab's trough levels remain within 10% of baseline even after a 1- or 2-week dose delay with the 30 mg/kg every 3 weeks regimen, demonstrating its ability to tolerate minor dosing interruptions [7].

Several factors were found to influence zanidatamab's pharmacokinetics, including body weight, sex, albumin levels, gastroesophageal adenocarcinoma subtype, baseline tumor size and post-baseline anti-drug antibodies. However, these factors had less than a 30% effect on drug exposure and their clinical significance was considered minimal. Population Pharmacokinetic (PK) modeling predicted that both weight-based dosing (30 mg/kg every 3 weeks) and two-tiered flat dosing (1800/2400 mg every 3 weeks, with a 70 kg threshold) result in similar drug exposure. These findings support flexible dosing options, improving convenience for caregivers and reducing drug wastage, while ensuring consistent pharmacokinetic profiles [7].

While zanidatamab holds significant promise for treating HER2-positive cancers, further research is crucial to fully understand its long-term benefits, tackle potential resistance mechanisms and refine its use in enhancing outcomes for patients with challenging, hard-to-treat cancers [4].

Therapeutic efficacy of zanidatamab

The clinical development of Zanidatamab in BTC has been driven by HER2 amplification/overexpression in a subset of patients. Early-phase studies established proof of concept, while recent trials provided robust efficacy data leading to FDA approval.

The HERIZON-BTC-01 phase IIb multicenter trial evaluated the efficacy of zanidatamab in patients with previously treated Biliary Tract Cancer (BTC). The median age at diagnosis was 61.5 years (IQR: 55-69), with gallbladder cancer being the most common subtype (60%). (8) After a median follow-up of 8.5 months (95% CI: 3.3-11.8), the median Progression-Free Survival (PFS) was 6.7 months (95% CI: 1.3-11.8) and the 1-year Overall Survival (OS) rate was 79.1% (95% CI: 53.2–91.6). (8) The Disease Control Rate (DCR) was 65%, with 40% of patients achieving partial responses and a median duration of response of 7.3 months (95% CI: 2.06–16).(8) Subgroup analysis revealed that patients with high HER2 expression

https://doi.org/10.70844/jmhrp.2025.2.2.44

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(IHC 3+) had a longer median PFS of 8 months (95% CI: 1.5–18.4), compared to those with moderate expression (IHC 2+) or confirmed HER2 amplification, who had a median PFS of 1.4 months (95% CI: 1.1–6.8; P = 0.02). However, there was no significant difference in the 1-year OS between these groups (P = 0.39) [8].

The HERIZON-BTC-01 study demonstrated that zanidatamab could be a promising treatment option for HER2-positive biliary tract cancer (BTC) following the failure of standard chemotherapy. Centered on these encouraging results, zanidatamab entered accelerated approval from the FDA in 2024 for the treatment of HER2-positive BTC (Table 1) [9].

Efficacy parameter	**ZIIHERA (N=62)**
Objective response rate (95% CI)	52% (39, 65)
Complete response, n (%)	2 (3.2%)
Partial response, n (%)	30 (48%)
Duration of Response (DOR)	N=32
Median, months (95% CI)	14.9 (7.4, NE)
DOR ≥ 6 months, n (%)	19 (59%)
DOR ≥ 12 months, n (%)	14 (44%)

Table 1: Efficacy of zanidatamab based on ZIIHERA study.

Safety and Tolerability of Zanidatamab

Zanidatamab demonstrates a manageable safety profile. Common Adverse Effects: Diarrhea, infusion reactions, nausea, fatigue, rash. Serious Adverse Effects: Elevated liver enzymes, severe diarrhea, rare infusion reactions, Left ventricular dysfunction, Embryofetal toxicity (Table 2).

Study/Protocol ID	**Phase**	**Trial No**	**Adverse effects (AE)**
Harding et al. (HERIZON-BTC-01) [10]	Phase IIb	NCT04466891	Diarrhea (37%), infusion-related reactions (33%), decreased ejection fraction (3%)
ZWI-ZW25-202	Phase II	NCT04224272	Diarrhea (80%), neutropenia (59%), nausea (39%), stomatitis (37%), anemia (29%), vomiting (25%), asthenia (24%)
Wang X	Phase II	NCT04276493	Treatment-related adverse events (TRAE) (97%, with 67.5% being ≥ Grade 3), neutropenia, leukopenia
Lee et al.	Phase 1b/2	NCT04276493	Diarrhea, nausea, decreased appetite, peripheral sensory neuropathy, fever, hypokalemia, palmar-plantar erythrodysesthesia syndrome, fatigue, stomatitis, weight loss
Meric-Bernstam et al.	Phase I	NCT02892123	Diarrhea (65%), nausea (45%), infusion reactions (37.1%), peripheral neuropathy (35%), fatigue (30%)

Table 2: Adverse events in different clinical trials.

Zanidatamab has demonstrated a generally manageable safety profile across multiple clinical trials, with diarrhea, infusion-related reactions, nausea, fatigue and rash being the most common adverse events. Grade ≥3 toxicities were infrequent and cardiac dysfunction was rare (≈3%), though careful monitoring remains essential [11].

When compared with trastuzumab-based regimens, important distinctions emerge. In BTC, trastuzumab combined with pertuzumab produced only modest efficacy (objective response rate ~23%) but was associated with a higher frequency of grade 3-4 toxicities, including diarrhea, fatigue, anemia and transaminase elevation, with nearly half of patients experiencing severe adverse events. By contrast, zanidatamab yielded higher response rates (~41%) and more durable responses while maintaining a lower incidence of severe treatment-related toxicity [11].

Trastuzumab deruxtecan (T-DXd), another HER2-directed option estimated in BTC and other solid tumors, demonstrates activity comparable to zanidatamab (ORR ~40%), but at the cost of substantial toxicity, including pneumonitis/interstitial lung disease and hematologic suppression. These adverse effects can be life-threatening and may limit its broader use outside of later-line settings.

Taken together, zanidatamab appears to offer a superior therapeutic index compared with traditional trastuzumab-based regimens in BTC, balancing efficacy with tolerability. While the safety data are encouraging, longer-term follow-up and real-world validation are needed to clarify risks of cumulative toxicities such as cardiac dysfunction, gastrointestinal toxicity and rare infusion reactions (Table 3).

Therapy	**Mechanism**	**ORR (%)**	**Median DOR/OS**	**Common AEs**	**Key limitations**
Zanidatamab	Bispecific HER2 Ab	~41	DOR ~12–15 months; OS ~15 months	Diarrhea, infusion rxns, nausea	Limited long-term data
Trastuzumab + Pertuzumab	Dual HER2 Ab blockade	~23	PFS ~2.6 months; OS ~3.9 months	Diarrhea, fatigue, anemia, LFT ↑	Modest efficacy, higher toxicity
Trastuzumab Deruxtecan (T-DXd)	HER2 ADC	~40	DOR ~6–8 months	Nausea, cytopenias, ILD risk	High-grade toxicities, ILD

Table 3: Comparison of HER2-directed therapies in biliary tract cancer.

Following this comparison, it is evident that zanidatamab currently offers the most favorable balance of efficacy and tolerability among HER2-directed therapies in biliary tract cancer. However, several challenges remain. The available data are derived primarily from single-arm, early-phase and industry-sponsored studies with small patient populations, which limits generalizability. The absence of randomized head-to-head trials means that the true comparative benefit of zanidatamab over trastuzumab-based regimens or trastuzumab deruxtecan remains unproven. Moreover, the optimal sequencing of zanidatamab with chemotherapy, immunotherapy and other HER2-targeted agents is unclear. Mechanisms of primary and acquired resistance also require further investigation and predictive biomarkers beyond HER2 IHC remain to be defined. Future directions should include phase III trials evaluating zanidatamab in combination regimens, prospective real-world studies to validate efficacy and safety and expansion of systematic HER2 testing to identify eligible patients. Until such data matures, zanidatamab should be considered a promising but still evolving option within the broader treatment landscape of BTC [11]. Overall, Zanidatamab is well tolerated, supporting long-term administration

Conclusion and Future Directions

The approval of zanidatamab by FDA represents a meaningful step forward for HER2-positive biliary tract cancer, a subset historically lacking targeted options. Its bispecific design offers theoretical advantages over conventional HER2 monoclonal antibodies and early-phase data demonstrate encouraging response rates and disease control. However, current evidence is based largely on single-arm, industry-sponsored trials with relatively small patient populations, short follow-up durations and limited diversity in BTC subtypes. Long-term efficacy, durability of response and late toxicity remain uncertain.

A critical question moving forward is how zanidatamab should be integrated with existing standards such as gemcitabine–cisplatin and immune checkpoint inhibitors and whether it will maintain efficacy in real-world populations that differ from those enrolled in clinical trials. Comparative studies with other HER2-directed therapies including trastuzumab-deruxtecan and dual HER2 blockade regimens are urgently needed to clarify relative benefit, toxicity and sequencing strategies. Additionally, resistance mechanisms to zanidatamab are poorly understood and require systematic investigation.

The most relevant confirmatory trial is the Phase 3 HERIZON-BTC-302 study (NCT06282575), which is evaluating zanidatamab in combination with Standard-of-Care (SOC) treatment compared to SOC alone as a first-line therapy for patients with HER2-positive advanced or metastatic Biliary Tract Cancer (BTC) [12]. This trial will be pivotal for regulatory and clinical decision-making.

In summary, while zanidatamab represents a promising addition to the BTC treatment protocol, its precise role in clinical practice will depend on forthcoming phase III data, real-world validation and rational integration with other systemic therapies. Until then, it should be regarded as an emerging option with potential but not yet a definitive standard of care.

Author Contributions

All authors assisted in formatting, editing and revising the manuscript; all authors interpreted the data and wrote the first and final draft of the manuscript; all authors revised the article critically for important intellectual content and they gave final approval of the article to be published.

Competing Interests

The authors declare no conflict of interests for this article.

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