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Precision Medicine COMMENTARY

The Innovation Medicine

Paradigm shift in high-risk intrahepatic cholangiocarcinoma: Neoadjuvant GOLP and the dawn of precision perioperative oncology

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Received: March 13, 2026; Accepted: June 23, 2026; Published Online: June 24, 2026; https://doi.org/10.59717/j.xinn-med.2026.100249

Citation: Piao M. and Zhao H. (2026). Paradigm shift in high-risk intrahepatic cholangiocarcinoma: Neoadjuvant GOLP and the dawn of precision perioperative oncology. *The Innovation Medicine* **4**:100249.

Intrahepatic cholangiocarcinoma (iCCA) is an aggressive biliary malignancy characterized by an insidious onset and an exceptionally high rate of postoperative recurrence. For patients with resectable tumors harboring high-risk features—such as tumors larger than 5 cm, vascular invasion, or hepatic portal lymph-node metastasis—the 5-year overall survival (OS) rate following upfront surgery remains dismal, historically hovering around 30%. This clinical reality underscores the probability that micrometastatic dissemination occurs long before surgical intervention, necessitating a paradigm shift toward intensive perioperative systemic therapy.

The publication of the ZSAB-neoGOLP phase 2-3 randomized controlled trial represents a definitive milestone in this evolutionary journey. By prospectively evaluating a triplet neoadjuvant regimen—gemcitabine-oxaliplatin (GEMOX), lenvatinib, and the anti-PD-1 antibody toripalimab—against standard upfront surgery, this trial redefines the boundaries of surgical oncology for high-risk iCCA.[1]

UNPRECEDENTED EFFICACY AND DEPTH OF RESPONSE

The clinical outcomes of the ZSAB-neoGOLP trial provide the most compelling randomized evidence to date supporting the neoadjuvant paradigm. At the interim analysis (median follow-up of 16.9 months), the neoGOLP regimen more than doubled the median event-free survival (EFS) to 18.0 months, compared to 8.7 months in the upfront surgery control cohort. Crucially, the regimen demonstrated a profound capacity for tumor downstaging, achieving an objective response rate (ORR) of 55%. This robust tumor shrinkage facilitated an exceptional 95% R0 resection rate in the neoadjuvant group. Furthermore, the triplet regimen successfully penetrated the dense desmoplastic stroma characteristic of iCCA, inducing a major pathological response (MPR) in 19% of patients, which included a 5% pathological complete response (pCR) rate. Post hoc analyses unequivocally linked these deep pathological responses to prolonged survival, establishing tissue necrosis as the ultimate confirmation of micrometastatic eradication.

THE EVOLUTION OF PERIOPERATIVE PARADIGMS: A HISTORICAL PERSPECTIVE

To truly appreciate the paradigm-shifting nature of the ZSAB-neoGOLP trial, its results must be contextualized within the broader, often frustrating, historical evolution of perioperative therapies for biliary tract cancers (Table 1). Historically, post-surgical adjuvant chemotherapy was the sole recognized standard. The BILCAP trial established capecitabine as a standard approach, offering a modest OS benefit over observation.[2] Concurrently, the rigorous ASCOT (JCOG1202) trial cemented S-1 as a standard in East Asia.[3] However, attempts to intensify the adjuvant approach have consistently failed; the PRODIGE 12 trial proved that administering the stronger GEMOX doublet postoperatively yielded no recurrence-free survival (RFS) or OS benefit—in fact, the chemotherapy arm was numerically inferior to observation alone (median RFS, 18.5 vs. 30.4 months)—highlighting the biological limitations of treating micrometastases in a surgically traumatized, immunosuppressed microenvironment.

The realization that upfront surgery followed by adjuvant therapy was insufficient led to early neoadjuvant explorations. The single-group NEO-GAP phase 2 trial tested neoadjuvant gemcitabine, cisplatin, and nab-paclitaxel in high-risk iCCA. While it proved safety and feasibility, the ORR was limited, and the median recurrence-free survival was a mere 7.1 months, revealing the efficacy ceiling of purely cytotoxic approaches. The subsequent phase 3 AIO/CALGP/ACO-GAIN trial, which explored neoadjuvant gemcitabine plus cisplatin, generated powerful efficacy signals but was prematurely closed due to limited enrollment.[4]

The ZSAB-neoGOLP trial shatters the limitations of its predecessors by moving beyond purely cytotoxic mechanisms. By combining chemotherapy to induce immunogenic cell death and neoantigen exposure, lenvatinib to promote immune-cell infiltration and normalize tumor vasculature, and toripalimab to augment the antitumor immune response, the neoGOLP regimen leverages profound biologic synergy. This allows it to achieve a 55% ORR relying solely on standardized systemic administration. It is also vital to contrast this with other contemporary approaches, such as the NEO-ERA-01 phase 2 study, which utilized continuous Hepatic Arterial Infusion Chemotherapy (HAIC-GEMOX) combined with adebrelimab and lenvatinib. While such trials highlight the extreme local control achievable via interventional radiology, the purely systemic neoGOLP approach is far less invasive, bypasses the risks of arterial catheterization, and is vastly more scalable across global oncology centers.

OPTIMIZING THE THERAPEUTIC INDEX: THE PROMISE OF DOSE DE-ESCALATION

While the ZSAB-neoGOLP trial established a new efficacy benchmark, the triplet regimen inevitably introduces toxicity, with 28% of patients experiencing grade≥3 adverse events during the neoadjuvant phase. In the perioperative setting, preserving the patient's performance status to ensure they remain fit for major hepatic resection is just as critical as achieving tumor shrinkage. This highlights an urgent need to optimize the therapeutic index. A compelling path forward is illustrated by the recent phase 2 study by Piao et al. (2026), which evaluated a mechanistically identical backbone—pembrolizumab, lenvatinib, and a reduced-dose GEMOX regimen—as an initial treatment for advanced biliary tract cancer.[5] This study demonstrated that attenuating the cytotoxic chemotherapy dose can preserve potent systemic and immunomodulatory antitumor efficacy while significantly mitigating cumulative toxicity. Applying this reduced-dose chemotherapy concept to the neoadjuvant iCCA setting could be the key to maximizing surgical compliance, ensuring patients safely reach the operating room without compromising the profound downstaging effects observed in the neoGOLP cohort.

CONCLUSION AND FUTURE DIRECTIONS

While the ZSAB-neoGOLP trial provides compelling evidence that routine, immediate upfront surgery for high-risk iCCA should be critically reconsidered, these findings must be interpreted with cautious optimism. Although the neoGOLP triplet provides a robust systemic option that addresses the chemoresistance and immunosuppression inherent to biliary tumors, this trial was conducted exclusively within Chinese centers. Consequently, the reproducibility of these profound downstaging effects across diverse global populations—particularly in Western cohorts with varying etiological backgrounds of iCCA—remains an essential question for future multi-regional phase 3 trials to address. Furthermore, while the interim event-free survival is unprecedented, definitive conclusions regarding survival benefits must await the maturation of long-term overall survival data.

Looking forward, the focus must shift toward precision biomarker integration. While 55% of patients responded robustly to GOLP, avoiding toxicity in primary non-responders requires dynamic monitoring tools, such as circulat-

Table 1. Evolution of perioperative treatment paradigms in resectable biliary tract cancers.

Trial	Phase / Setting	Regimen Strategy	Target Population	ORR	R0 Resection Rate	Key Survival Outcomes & Notes
BILCAP	Phase 3 / Adjuvant	Capecitabine	Resected BTC (n=447)	N/A	N/A (Post-op)	mOS (ITT): 51.1 vs. 36.4 mo (HR 0.81, p=0.097) mOS (Per-Protocol): 53.0 vs. 36.1 mo (HR 0.75, p=0.028)
ASCOT (JCOG1202)	Phase 3 / Adjuvant	S-1	Resected BTC (n=440)	N/A	N/A (Post-op)	3-yr OS: 77.1% vs. 67.6% (Primary Endpoint) 3-yr RFS: 62.4% vs. 50.9%
PRODIGE 12	Phase 3 / Adjuvant	GEMOX	Resected BTC (n=196)	N/A	N/A (Post-op)	mRFS: 30.4 vs. 18.5 mo (Not statistically significant; Negative trial)
NEO-GAP	Phase 2 / Neoadjuvant	GAP (Gemcitabine, Cisplatin, nab-Paclitaxel)	High-risk iCCA (n=30)	23%	73%*	mRFS: 7.1 mo mOS: 24.0 mo
GAIN	Phase 3 / Neoadjuvant	GemCis	Resectable BTC (n=68)	N/A	83.3% vs. 40.0%	mOS: 27.8 vs. 14.6 mo (Note: Trial faced premature closure due to limited enrollment)
NEO-ERA-01	Phase 2 / Neoadjuvant	HAIC-GEMOX + Adebrelimab (IO) + Lenvatinib (TKI)	High-risk iCCA (n=16)	57.10%	90.9%*	MPR: 100% (in the resected subset)
ZSAB-neoGOLP	Phase 2-3 / Neoadjuvant	Systemic GEMOX + Toripalimab (IO) + Lenvatinib (TKI)	High-risk iCCA (n=178)	55%	95% vs. 93%	mEFS: 18.0 vs. 8.7 mo (p<0.001) MPR: 19% (includes 5% pCR)

* Indicates the proportion of total enrolled patients who successfully underwent surgical resection, not the comparative rate between trial arms.

Abbreviations: BTC, Biliary tract cancer; EFS, Event-free survival; GAP, Gemcitabine, cisplatin, and nab-paclitaxel; GemCis, Gemcitabine and cisplatin; GEMOX, Gemcitabine and oxaliplatin; HAIC, Hepatic arterial infusion chemotherapy; HR, Hazard ratio; iCCA, Intrahepatic cholangiocarcinoma; IO, Immuno-oncology; ITT, Intention-to-treat; mEFS, Median event-free survival; mo, Months; mOS, Median overall survival; MPR, Major pathological response; mRFS, Median recurrence-free survival; ORR, Objective response rate; OS, Overall survival; pCR, Pathological complete response; Post-op, Post-operative; pts, Patients; R0, Microscopically margin-negative resection; TKI, Tyrosine kinase inhibitor; yr, Year.

ing tumor DNA (ctDNA) clearance kinetics. Furthermore, the uniform application of adjuvant capecitabine for eight cycles in all patients in the ZSAB-neoGOLP trial, regardless of their neoadjuvant pathological response, indicates an urgent need for adaptive trial designs. Tailoring postoperative regimens—such as exploring adjuvant capecitabine plus immunotherapy or maintaining targeted agents for patients achieving an MPR—will be a critical step toward optimizing this evolving perioperative paradigm.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by Beijing Natural Science Foundation(L248022), National High Level Hospital Clinical Research Funding[2025-PUMCH-C-015][2025-PUMCH-D-001)], CAMS Innovation Fund for Medical Sciences（CIFMS）[2022-I2M-C&T-A-003],CAMS Innovation Fund for Medical Sciences (CIFMS) [2021-I2M-1-061] [2021-I2M-1-003], Hangzhou East Clinical Oncology Research Center Program[ECCO-KY-25004], Beijing Bethune Charitable Foundation [GDZL024]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.