Targeted Therapies Extend Survival in Advanced Cholangiocarcinoma

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Cholangiocarcinoma (CCA) is an aggressive cancer with limited treatment options, particularly in advanced stages. Recent research has focused on identifying and targeting specific genomic alterations to improve patient outcomes. Two key studies, FIGHT-202 and ClarIDHy, provide further evidence for the clinical utility of targeted therapies in this challenging disease.

KEY TAKEAWAYS

- The Pivot: Targeted therapies, pemigatinib and ivosidenib, demonstrate significant clinical benefit in advanced cholangiocarcinoma patients with specific genomic alterations (FGFR2 fusions/rearrangements or IDH1 mutations).
- The Data: Pemigatinib achieved a 37.0% objective response rate and a median overall survival of 17.5 months in FGFR2-altered CCA. Ivosidenib showed a >95% probability of a favorable benefit-risk profile compared to placebo in IDH1-mutated CCA.
- The Action: Routine molecular profiling for FGFR2 fusions/rearrangements and IDH1 mutations is crucial for patients with advanced cholangiocarcinoma to identify those eligible for targeted treatment.

Understanding Cholangiocarcinoma and Targeted Approaches

Cholangiocarcinoma (CCA) is a rare but highly aggressive cancer originating in the bile ducts. Historically, treatment options for advanced or metastatic CCA have been limited, leading to poor prognoses. However, advancements in molecular profiling have identified specific genomic alterations that can be targeted with precision therapies. Two such alterations, fibroblast growth factor receptor 2 (FGFR2) fusions and rearrangements, and isocitrate dehydrogenase-1 (IDH1) mutations, are now recognized as clinically actionable targets 1, 2.

FGFR2 alterations are found in approximately 10-16% of intrahepatic CCA cases, while IDH1 mutations occur in about 15-20% of cases. The development of selective inhibitors for these targets represents a significant step forward in personalizing treatment for patients with advanced CCA 1, 2.

FIGHT-202: Pemigatinib for FGFR2-Altered CCA

The FIGHT-202 study (NCT02924376) was a multicenter, open-label, single-arm, phase II trial designed to evaluate the efficacy and safety of pemigatinib in patients with previously treated, advanced or metastatic CCA. Pemigatinib is an oral inhibitor specifically targeting FGFR1-3 1.

The study enrolled patients aged 18 years or older and categorized them into cohorts based on their FGF/FGFR alteration status: cohort A included patients with FGFR2 fusions or rearrangements, cohort B had other FGF/FGFR alterations,

and cohort C comprised patients with no FGF/FGFR alterations. Patients received 13.5 mg of oral pemigatinib once daily in 21-day cycles (2 weeks on, 1 week off) until disease progression or unacceptable toxicity 1.

Key Findings from FIGHT-202 Extended Follow-up

The final analysis of FIGHT-202, with a median follow-up of 45.4 months, included 147 enrolled patients (108 in cohort A, 20 in cohort B, 17 in cohort C, and 2 with unconfirmed alterations). The primary endpoint, objective response rate (ORR) in cohort A, was 37.0% (95% confidence interval [CI] 27.9% to 46.9%), as assessed by an independent review committee using RECIST v1.1. This included 3 complete responses and 37 partial responses 1.

Secondary endpoints demonstrated durable clinical benefit. The median duration of response (DOR) was 9.1 months (95% CI 6.0-14.5 months). Median progression-free survival (PFS) was 7.0 months (95% CI 6.1-10.5 months), and median overall survival (OS) was 17.5 months (95% CI 14.4-22.9 months) in cohort A 1.

Regarding safety, the most common treatment-emergent adverse events (TEAEs) were hyperphosphatemia (58.5%), alopecia (49.7%), and diarrhea (47.6%). Discontinuation due to TEAEs occurred in 10.2% of patients, with intestinal obstruction and acute kidney injury being the most frequent reasons (n=2 each) 1.

ClarIDHy: Ivosidenib for IDH1-Mutated CCA

The ClarIDHy study (NCT02989857) was a pivotal phase III study investigating ivosidenib versus placebo in patients with previously treated, locally advanced or metastatic mutant IDH1 (mIDH1) cholangiocarcinoma. Ivosidenib is a selective inhibitor of mutant IDH1 2.

A quantitative benefit-risk assessment (BRA) was conducted using data from ClarIDHy to summarize the evidence for ivosidenib. Cholangiocarcinoma experts identified key benefit and risk criteria, which were then used in Multi-Criteria Decision Analysis (MCDA) modeling approaches 2.

Benefit-Risk Profile of Ivosidenib

The ClarIDHy study randomized 187 patients to either ivosidenib 500 mg (n=126) or placebo (n=61). The primary analysis using the Scale Loss Score (SLoS) model indicated a 95.24% probability that the benefit-risk profile of ivosidenib was superior to that of placebo. Sensitivity analyses, employing alternative sets of criteria and different MCDA models (linear and product models), consistently showed a high probability favoring ivosidenib (SLoS model: >95%; linear model: >99%; product model: >94%) 2.

These findings provide comprehensive evidence that ivosidenib offers an effective treatment with a tolerable safety profile for patients with mIDH1 cholangiocarcinoma, reinforcing previous data 2.

Clinical Implications and Editorial Commentary

The final results from FIGHT-202 and the benefit-risk assessment of ClarIDHy underscore the importance of molecular profiling in advanced cholangiocarcinoma. Pemigatinib demonstrated durable responses and extended overall survival with manageable adverse events in patients with FGFR2 fusions or rearrangements. Similarly, ivosidenib showed a highly favorable benefit-risk profile for those with IDH1 mutations. These data solidify the role of these targeted therapies as valuable options in the second-line setting for specific patient populations 1, 2.

Why this matters for clinical practice today: These studies highlight a critical shift in the management of advanced cholangiocarcinoma, moving from a one-size-fits-all approach to precision medicine. For clinicians, this means that comprehensive molecular testing for FGFR2 fusions/rearrangements and IDH1 mutations should be considered standard

practice at diagnosis or progression for all patients with advanced CCA. Identifying these alterations early can guide treatment decisions, allowing for the timely initiation of targeted therapies like pemigatinib or ivosidenib, which have demonstrated significant clinical benefits over conventional treatments. Delaying such testing could mean missing an opportunity to offer patients a more effective and personalized treatment strategy.

Limitations and Next Steps

While both studies provide compelling evidence, some limitations exist. FIGHT-202 was a single-arm, phase II study, which inherently limits direct comparisons to other treatments. The safety profile of pemigatinib, while manageable, includes common adverse events like hyperphosphatemia that require monitoring 1. For ClarIDHy, the benefit-risk assessment relied on expert-determined criteria and modeling, which, while robust, are still based on specific assumptions 2.

Future research should focus on further refining patient selection, exploring combination therapies, and investigating potential resistance mechanisms to these targeted agents. Continued real-world data collection will also be crucial to confirm these findings in broader clinical populations and to assess long-term outcomes and safety profiles 1, 2.

REFERENCES

1. 1. Vogel A, Sahai V, Hollebecque A, et al. An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202. ESMO Open. 2024;9(6):103488. doi:10.1016/j.esmoop.2024.103488

2. 2. Valle JW, Abou-Alfa GK, Kelley RK, et al. Quantitative benefit-risk assessment of data from the phase III ClarIDHy study of ivosidenib versus placebo in patients with mIDH1 cholangiocarcinoma. ESMO Gastrointest Oncol. 2025;8:100159. doi:10.1016/j.esmogo.2025.100159