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ORIGINAL RESEARCH ARTICLE

Real-World Outcomes of Ivosidenib in *IDH1*-Mutant Biliary Tract Cancer: A Multicenter Retrospective Analysis and Comparison with the TrinetX Database

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Abstract

Background Ivosidenib is established as targeted therapy in patients with isocitrate dehydrogenase 1 (*IDH1*)-mutant advanced biliary tract cancer based on results of the phase III ClarIDHy trial. However, data on the efficacy of ivosidenib in real-world cohorts are limited.

Objective This retrospective analysis aims to provide data on the efficacy and safety of ivosidenib in biliary tract cancer in a real-world cohort.

Methods Patients with *IDH1* mutant biliary tract cancer treated with ivosidenib at four German university medical centers from 2020 to 2024 were retrospectively identified. Clinicopathological parameters and treatment courses were collected. Furthermore, clinical outcomes of patients with biliary tract cancer who received ivosidenib were retrospectively retrieved from the global health network database TriNetX.

Results In total, 14 patients who received ivosidenib were identified. Mean age at diagnosis was 61 years and 50% of patients were female. Nine patients had an *IDH1 R132C*, four an *IHD1 R132L*, and one an *IDH1 R132S* mutation. Ten patients received ivosidenib as second-line therapy and four in later lines. Partial response was observed in two patients, stable disease in three, and progressive disease in nine patients. Median progression-free survival was 5.6 months (95% confidence interval 4.3, not estimated) and median overall survival was 12.7 months (95% confidence interval 8.2, not estimated). No discontinuation of ivosidenib because of toxicity was observed. A total of 228 patients were identified in the TriNetX database. Mean age was 64.4 years and 64% of patients were female. Median overall survival in this cohort was 9.6 months (95% confidence interval 8.07, 11.19).

Conclusions Real-world data from our cohort and the TriNetX database support the oncological outcomes reported in the ClarIDHy trial and other real-world cohorts.

Key Points

Real-world multicenter retrospective study in isocitrate dehydrogenase 1-mutant biliary tract cancer treated with the isocitrate dehydrogenase 1 inhibitor ivosidenib.

Survival outcomes and treatment-related toxicity matched results reported in the ClarIDHy trial.

A subgroup of patients achieved durable tumor control with ivosidenib.

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1 Introduction

Biliary tract cancer (BTC) is a rare disease with an unfavorable prognosis and limited therapeutic options in advanced stages of the disease. Seventy percent of patients present with locally advanced or metastatic disease at the time of diagnosis, without the possibility for curative resection [1]. Even after surgical resection, more than half of patients experience disease recurrence [2, 3]. Five-year survival rates range between 7 and 20%, underlining the need for more effective treatment strategies [4]. In non-resectable disease, chemotherapy combined with immunotherapy has become standard as first-line therapy since 2022, based on the results of the TOPAZ-1 trial [5].

However, in further therapy lines, treatment options are limited. Immunohistochemical staining to detect mismatch repair deficiency and overexpression of the human epidermal growth factor receptor 2 receptor is recommended as well as tumor genome sequencing to detect potentially actionable mutations [6].

The mutational landscape of BTC is heterogeneous and depends on the location of the disease. However, up to 60% of BTC harbor potentially actionable genetic alterations [7]. Recently, new targeted therapeutic strategies have been introduced and in part been integrated in therapeutic management of these patients [8], including pemigatinib or futibatinib for BTC with *FGFR2* fusions or rearrangements [9] or dabrafinib plus trametinib for *BRAF V600E* mutant BTC [10]. Mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in up to 18% of patients with intrahepatic BTC and less frequently in extrahepatic BTC (0.8%) [11, 12]. These mutations, typically located at the R132 residue, lead to abnormal enzymatic activity that results in excessive production of the oncometabolite D-2-hydroxyglutarate. D-2-hydroxyglutarate fuels tumorigenesis via epigenetic dysregulation, alterations in cell differentiation, and immune suppression [13].

Ivosidenib is an oral small-molecule inhibitor of IDH1 that has shown stabilization of tumor growth in preclinical tumor models [14]. Ivosidenib received US Food and Drug Administration approval in 2021 for patients with *IDH1*-mutant BTC based on the results of the phase III ClarIDHy trial. In this randomized controlled trial, ivosidenib was compared to placebo in 185 pre-treated patients with BTC. Median progression-free survival (PFS) was significantly longer in the ivosidenib group (2.7 vs 1.4 months), and median overall survival (OS) was 10.3 months with ivosidenib versus 7.5 months with placebo in the final survival analysis [15, 16]. The safety profile was favorable in this trial with nausea being the most common adverse event. Serious treatment-related adverse events were reported in three patients, including grade 3 hyperbilirubinemia and cholestastic jaundice, grade 2 prolonged QT interval, and grade 3 pleural effusion. No treatment-related deaths were reported. Despite these positive results from the ClarIDHy trial, real-world data on the efficacy and safety of ivosidenib in BTC remain limited. A recent large real-world study by Niger et al. reported on outcomes of 46 patients treated with ivosidenib for *IDH1*-mutant advanced or metastatic BTC. Median PFS was 3.7 months and median OS was 11.5 months in this cohort [17]. The disease control rate was 50%, with 13.6% of patients experiencing a partial response (PR). Grade 3 and 4 adverse effects occurred in 8.7% of patients, with nausea being the most common.

Most real-world data on oncological outcomes of novel therapies are derived from single centers or regional collaborations, and these results may be biased by site-specific differences in accessibility of medical services. To overcome this challenge, global research networks for real-world data such as TriNetX, Medidata, and PCORnet have been established [18, 19]. TriNetX is a web-based research platform aggregating real-world data from electronic health records, cancer registries, and genomic testing laboratories on a global scale, thereby facilitating data-driven clinical research [20–22]. Structured and unstructured clinical data are harmonized in TriNetX and processed by natural language processing and made accessible to network members, providing a valuable resource of data from clinical practice. In our study, we combined retrospective clinical data from four university medical centers in Germany with aggregated outcomes from the TriNetX database to determine real-world efficacy and safety of ivosidenib in patients with BTC.

2 Methods

2.1 Data Acquisition from Medical Records

We retrospectively identified patients with BTC treated with ivosidenib between January 2020 and December 2024 from university hospitals in Heidelberg, Mannheim, Regensburg, and Kiel. Clinical data were extracted from medical records, and included diagnostic and therapeutic procedures, pathological and molecular data, type of genome sequencing platform, treatment courses, therapy-related toxicity, and survival data.

2.2 Data Acquisition from the TrinetX Database

TriNetX is a global web-based research platform that currently aggregates anonymized real-world clinical data, for example, from in-patient and out-patient electronic health records of more than 250 million patients from more than 220 participating healthcare organizations worldwide [21]. Patients were selected from the US Collaborative Network of the TriNetX database. Seventy-one out of 71 participating healthcare organizations were online at data acquisition and relevant data were provided by 40 participating healthcare organizations. Analyses were performed using the following inclusion criteria: patients were (1) diagnosed with BTC between 1 January, 2014 and 31st December, 2024 and (2) received at least one prescription of ivosidenib (RxNorm: 2049873) after diagnosis. To ensure sufficient follow-up quality, (3) patients had at least one documented follow-up visit (1 year or later after initiation of ivosidenib treatment) or had died within the first year after initiation of ivosidenib treatment. (4) The diagnoses of acute myeloid leukemia and mylodysplastic syndrome were used as exclusion criteria to avoid inclusion of

patients receiving ivosidenib for acute myeloid leukemia or mylodysplastic syndrome treatment. The starting date of ivosidenib was set as the index date. Data query on the TriNetX platform was performed on 7 October, 2025. Table 1 of the Electronic Supplementary Material (ESM) contains International Classification of Diseases codes used for the TriNetX query.

2.3 Statistical Analysis

Progression-free survival was defined as time from the beginning of ivosidenib treatment until radiological disease progression or the time of data cut-off (25 November, 2025) or death from any cause, and OS was defined as time from the beginning of ivosidenib treatment to death from any cause. The disease control rate was defined as the sum of complete response, PR, and stable disease (SD). Survival analysis was performed using R (version 4.5.1) within the RStudio environment (Posit Software, Boston, MA, USA). Statistical analyses of the TriNetX cohort were performed using the built-in Analyze Outcomes Tool implemented in the Advanced Analytics Tools of TriNetX software, as TriNetX only provides aggregated data (TRINETX, LLC, Cambridge, MA, USA). Figures were created with the ggplot2 package for data visualization, and additional functions from the dplyr, stringr, and scales packages were used for data handling and formatting.

Table 1 Patient characteristics

Characteristics at baseline	*n*	%
Total	14	100
Age at diagnosis years; mean (range)	61 (43–82)	
Sex		
Male	7	50.0
Female	7	50.0
ECOG PS		
0–1	12	85.7
2–3	2	14.3
Cancer type		
iCCA	13	92.9
Gallbladder cancer	1	7.1
Prior curative-intent resection		
Yes	9	64.3
No	5	35.7
No. of prior lines of chemotherapy		
1	10	71.4
2	1	7.1
3	3	21.4
First-line chemotherapy		
Gemcitabine/cisplatin/durvalumab	6	42.9
Gemcitabine/cisplatin	6	42.9
Gemcitabine/cisplatin/pembrolizumab	1	7.1
FOLFIRI	1	7.1

ECOG PS Eastern Cooperative Oncology Group Performance Status, *iCCA* intrahepatic cholangiocellular carcinoma

2.4 Ethics Board Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Heidelberg University (identifier: 2022-823_1-AF 11) and approved by all participating centers. Because of the retrospective design of the study, no written informed consent from patients was required, as decided by the local ethics board. As TriNetX utilizes aggregated de-identified patient records, an analysis of data provided by the TriNetX database does not require approval by the local ethics committee.

3 Results

3.1 Clinico-Pathological Characteristics

We identified patients with BTC between 2020 and 2024 at four academic medical centers in Germany. Overall, 498 patients with BTC were treated for unresectable or metastatic disease across the participating centers, of whom 298 underwent next-generation sequencing. Among these, 42 patients with an *IDH1* mutation were identified, of whom 14 received ivosidenib. Of those, 13 patients had intrahepatic cholangiocellular carcinoma and one had gall bladder cancer. A flowchart of patient selection is shown in Fig. 1. Mean age was 61 years (range 43–82 years) and 50% of patients were female. All patients had metastatic disease at the time of ivosidenib initiation. Of those, nine patients underwent previous tumor surgery with curative intention. At the time of therapy initiation, performance status was good in most patients (Eastern Cooperative Oncology Group 0–1) [see Table 1]. In ten patients, ivosidenib was given as second-line and in four patients as third-line or fourth-line therapy. Except for one patient receiving FOLFIRI, first-line therapy was gemcitabine/cisplatin without durvalumab in six patients, with durvalumab in six patients and with pembrolizumab in one patient. Further regimens used in second-line treatment before application of ivosidenib were FOLFIRI ($n=2$), FOLFOX ($n=1$), and gemcitabine/cisplatin and immunotherapy ($n=1$). After disease progression on ivosidenib, patients received the following treatment regimens: FOLFOX ($n=2$), FOLFIRI ($n=5$), lenvatinib/pembrolizumab ($n=1$), gemcitabin/nab-paclitaxel ($n=1$), and gemitabin/cisplatin ($n=2$).

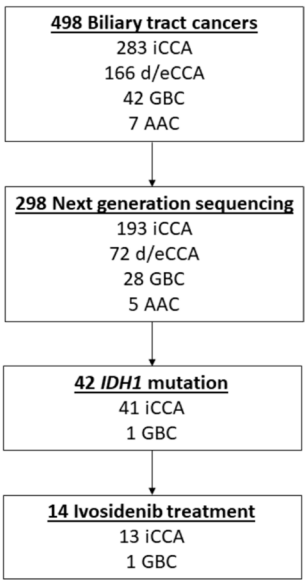


Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) diagram. *AAC* ampullary adenocarcinoma, *dCCA* distal cholangiocarcinoma, *eCCA* extrahepatic cholangiocarcinoma, *GBC* gallbladder cancer, *iCCA* intrahepatic cholangiocellular carcinoma

3.2 Molecular and Immunohistochemistry Profiling

All patients received genomic profiling of their respective cancers. Different DNA sequencing platforms and technologies were applied using DNA from formalin-fixed paraffin embedded tissues. These platforms include Ion Torrent Oncomine Focus or Comprehensive assay, Trusight Oncology 500 assay, Trusight Tumor 170 assay, Archer Pan Solid Tumor panel, or whole genome sequencing. The number of detected alterations varied between the genome sequencing platform used. The following *IDH1* mutations were identified: ten patients had an *IDH1 R132C* mutation, three patients an *IDH1 R132L* mutation, and one patient an *IDH1 R132S* mutation. The most common co-occurring pathological mutations were detected in *ARID1A*, *CDKN2A*, *FGF7*, *FGFR3*, *HRAS*, *NBN*, *PIK3CD*, *SHQ1*, *TET2*, and *TNFRSF14* genes (Table 2). Immunohistochemical staining for mismatch repair deficiency was performed in 12 patients and revealed no evidence of mismatch repair deficiency in all cases. Human epidermal growth factor receptor 2 expression was negative in five patients, and for nine patients no information was provided.

3.3 Oncological Outcomes and Safety

After a median follow-up time of 34.3 months (interquartile range: 20.7 months), median PFS was 5.6 months (95% confidence interval [CI] 4.3, not estimated) and median OS was 12.7 months (95% CI 8.17, not estimated) in our cohort (Figs. 2 and 3). Partial response was observed in two patients (14.3%), and three patients achieved SD (21.4%), while the majority of nine patients had progressive disease (64.3%). Overall, the disease control rate was 35.7%. In patients with PR, the duration of response was 23.2 and 26.7 months, respectively. No difference in survival was observed for different *IDH1* mutation variants. Three patients experienced grade I diarrhea, as classified by Common Terminology Criteria for Adverse Events (CTCAE). Two patients had CTCAE grade 1 nausea and vomiting. Fatigue occurred in three patients (CTCAE grade 1 in two patients, CTCAE grade 2 in one patient). One patient experienced CTCAE grade 3 elevation of gamma-glutamyl transferase. In this patient, ivosidenib was paused for 1 month and then continued. In all other cases, ivosidenib was not discontinued because of adverse events. No toxicity-related death was reported.

3.4 Patient Characteristics and Clinical Outcomes of the TriNetX Cohort

Using the above-mentioned search criteria, we identified a total of 332 patients with BTC who were treated with ivosidenib in the TriNetX cohort. In 103 patients, follow-up quality was insufficient as neither follow-up visits nor deaths were documented. In addition, one patient had a diagnosis of acute myeloid leukemia or mylodysplastic syndrome and was excluded as ivosidenib may have been prescribed based on either diagnosis. In the final cohort comprising 228 patients, median follow-up time was 12.2 months (interquartile range: 19.4 months). Mean age at diagnosis was 64.4 years (range: 29–90 years) and 64% of patients were female. 144 (63.2%) were classified as intrahepatic cholangiocellular carcinoma, 29 as extrahepatic cholangiocarcinoma (13%), 12 as gallbladder cancer (5%), and 10 as ampullary adenocarcinoma (4%). In 33 patients, the information regarding the anatomic subtype was not provided. The TriNetX data did not allow us to assess the number and order of previous therapy lines at the patient level, but the composition of systemic therapies that patients had received prior to ivosidenib could be determined. A high proportion of patients had received treatment with gemcitabine and cisplatin (62–64%), and 18% of patients were also pre-treated with durvalumab. In many cases, patients had also received additional chemotherapeutic agents including 5-fluorouracil/capecitabine, oxaliplatin, irinotecan, or paclitaxel prior to ivosidenib (see Table 3). The TriNetX data did not allow us to determine PFS because of insufficient data resolution regarding the timepoint of radiological or clinical disease progression. In contrast, documentation of patient death in the database was sufficient to calculate the median OS for the

Table 2 Molecular data and clinical courses

Patient ID	Number of previous lines of chemotherapy	Time on ivosidenib (months)	Best response	PFS (months)	OS (months)	Panel	*IDH1* mutation	Concomitant mutations
1	3	2.5	PD	2.5	12.0	Oncomine Comprehensive Assay (Thermo Fisher Scientific)	*R132C*	*TP53*
2	3	3.1	PD	3.1	3.1	Oncomine Focus Assay (Thermo Fisher Scientific)	*R132C*	-
3	3	6.4	PD	6.4	13.3	Oncomine Comprehensive Assay (Thermo Fisher Scientific) and Archer Pan Solid Tumor panel (IDT)	*R132C*	*AKT1, ARID1A, CCND1, FGF19, FGF3, HRAS, TERT*
4	1	4.4	PD	4.4	8.2	TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132C*	*FGF7*
5	1	23.2	PR	23.2	30.3	Oncomine Comprehensive Assay (Thermo Fisher Scientific) and TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132C*	*BAP1, CTCF, MUTYH*
6	1	7.0	PD	7.0	13.9	TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132C*	*ARID1A, BAP1, FLT3, HRAS, KDR, MITF, NBN, SDHB, SDHD, SHQ1, TET2, TGFBR2*
7	1	4.3	PD	4.3	4.3	TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132C*	*NBN*
8	1	2.7	PD	2.7	12.2	TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132L*	*CDKN2A,CDKN2A,CDKN2B, PIK3C2G, RASA1*
9	1	3.4	PD	3.4	6.4	TruSight Oncology 500 (Thermo Fisher Scientific) and TruSight 170 (Illumina)	*R132S*	*BRCA2, FOXO1, RB1, DIS3, PIK3R2, TET2*
10	1	4.7	PD	4.7	4.7	TruSight Oncology 500 (Thermo Fisher Scientific) and Archer Pan Solid Tumor panel (IDT)	*R132L*	*FAT1, FGF7*
11	1	20.3	SD	20.3	34.3	Oncomine Focus Assay (Thermo Fisher Scientific)	*R132C*	*BRAF*
12	1	26.7	PR	26.7	34.9	Single gene sequencing (IDH1, IDH2)	*R132C*	-
13	1	55.8	SD	67.4	67.4	QIAseq TMB Panel (Qiagen)	*R132C*	-
14	1	9.7	SD	19.3	19.3	TruSight Oncology 500 (Thermo Fisher Scientific)	*R132L*	*FGFR2, PPP2R2A*

Only pathogenic or likely pathogenic genetic variants are shown

ID identification, *IDH1* isocitrate dehydrogenase 1, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression-free survival, *SD* stable disease

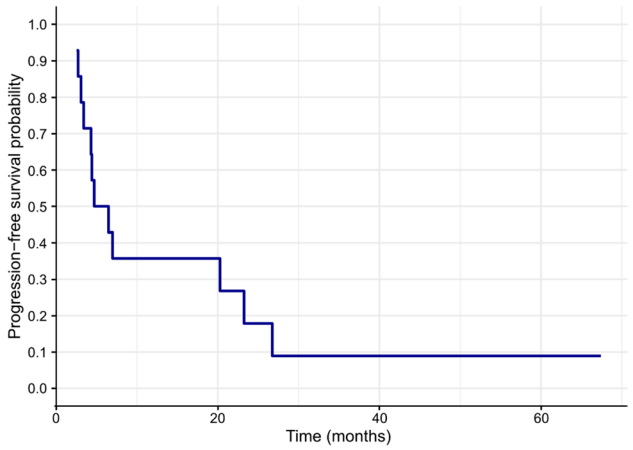


Fig. 2 Kaplan–Meier curve for progression-free survival of the German real-world cohort

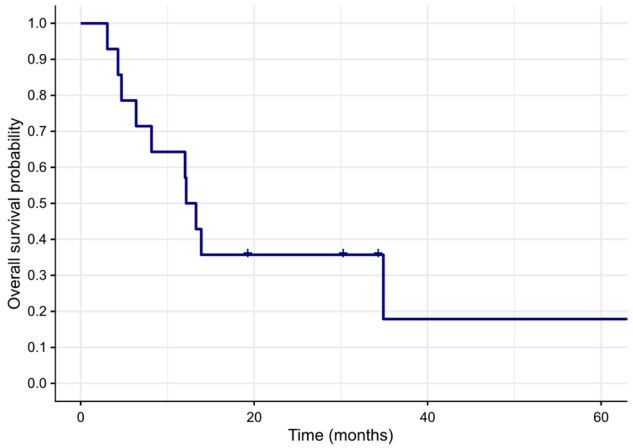


Fig. 3 Kaplan–Meier curve for overall survival of the German real-world cohort

cohort of 228 patients, which was 9.6 months (95% CI 8.07, 11.19) [Fig. 4].

4 Discussion

Biliary tract cancer remains a disease with an unfavorable prognosis and a strong need for more effective treatment options [23, 24]. Ivosidenib is the first approved targeted therapy for *IDH1* mutant BTC, based on results of the ClarIDHy trial [16]. In our real-world cohort of 14 patients from four German university hospitals, median PFS was 5.6 months and median OS was 12.7 months. Furthermore, results from the TriNetX database comprising 228 patients showed a shorter OS of 9.6 months.

Table 3 Clinical characteristics of the TriNetX cohort

Characteristics at baseline	*n*	%
Total	228	
Age at diagnosis years; mean (range)	64.4 (29–90)	
Sex		
Male	76	33
Female	147	64
Unknown	10[a]	4[a]
Prior therapy		
Gemcitabine	147	64
Cisplatin	141	62
Durvalumab	18	8
Oxaliplatin	31	14
Paclitaxel	23	10
Irinotecan	11	5
Capecitabine	37	16
5-Fluorouracil	34	15

[a]To protect patients' anonymity, groups with fewer than 10 patients were rounded to 10

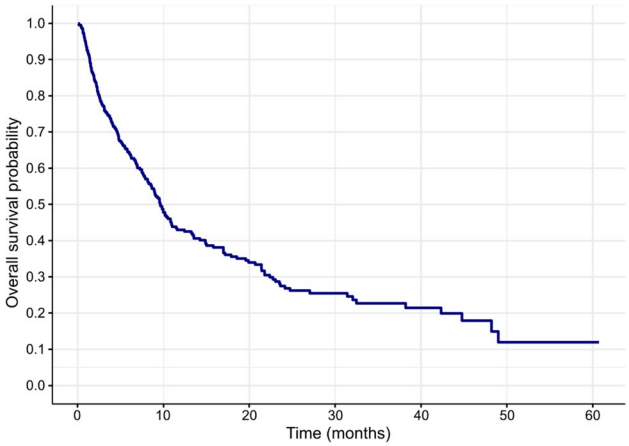


Fig. 4 Kaplan–Meier curve for overall survival of the TriNetX cohort

Real-world data evaluating the efficacy and safety of ivosidenib are emerging, primarily from European centers. The recently published, largest real-world cohort comprised 46 patients from different European institutions and reported a median PFS and OS of 3.7 (95% CI 2.2, 36.5) and 11.5 months (95% CI 9.5, 36.5), respectively [17]. Other real-world studies reported similar PFS and slightly shorter OS. In a Chinese cohort comprising five patients receiving ivosidenib, PFS was 5.1 (range: 2.0–28.5) and OS was 9.5 months (range: 3.2–30.5) [25]. A real-world cohort with 33 patients treated with ivosidenib in the USA reported a median PFS of 4.0 months and median OS of

10.5 months [26]. In contrast, data from a Polish cohort with 13 patients treated with ivosidenib reported the lowest PFS and OS rates, with 2.5 and 6.3 months, respectively [27]. Overall, the published evidence from real-world studies supports a PFS between 2.5 and 5.1 months and an OS between 6.3 and 11.5 months. These results align with the outcomes reported in the ClarIDHy trial, which showed a PFS of 2.7 and an OS of 10.3 months.

Compared with other real-world cohorts and the results of the ClarIDHy trial, we observed a longer PFS and OS in our German cohort. Notably, in the two patients who responded to ivosidenib treatment, duration of response was long lasting with 23.2 months and 26.7 months. Partial response or SD were observed exclusively in patients who received ivosidenib as a second-line treatment, whereas all three patients treated in further lines experienced progressive disease. Compared with the ClarIDHy and other real-world cohorts, our data show a longer PFS and OS in patients receiving ivosidenib, possibly caused by the two cases of exceptional responses. The disease control rate in our cohort is lower (35.7%) compared with 53% in the ClarIDHy trial, even though most patients received ivosidenib as second-line therapy. The limited efficacy seen in later lines of therapy underlines the importance of early use of ivosidenib in metastatic BTC. The application of ivosidenib as neoadjuvant therapy and in combination with other chemotherapy or immunotherapy in earlier lines of treatment is being evaluated by ongoing clinical trials (NCT06501625, NCT05921760) [28, 29].

Regarding safety and tolerability, previous studies have consistently reported a low incidence of severe adverse events and no treatment-related deaths [16]. In the ClarIDHy trial, ascites was the most common grade 3 or higher adverse event (9% in the intervention group) and serious treatment-related adverse events were reported in three patients. In the largest real-world cohort, 8.7% patients experienced grade 3 or higher adverse events, with anemia, thrombocytopenia, pneumonia, and skin toxicity being the most common [17]. In the Polish cohort, three patients experienced grade 3 adverse events (asthenia and ascites) and in the Chinese cohort, adverse events were reported in one patient and were not higher than grade 1 [27]. Our data further support these findings, as ivosidenib was generally well tolerated, even in heavily pretreated patients. Only one patient experienced grade 3 toxicity (elevation of gamma-glutamyl transferase), which did not require permanent discontinuation of therapy. This favorable safety profile is particularly important for patients with advanced disease, who often have limited tolerance towards aggressive treatment regimens.

Real-world databases such as TriNetX can complement results from controlled clinical trials by providing access to routine medical data on a global scale. This approach is particularly valuable for rare therapy regimens such as ivosidenib, enabling the evaluation of a sufficiently large patient number. However, data from TriNetX are not curated, less detailed, and prone to documentation bias. In addition, data quality may be impaired by use of diagnoses codes applied for billing purposes heavily relying on methods of coding and qualification of coding staff and may be influenced by optimization towards revenues. Moreover, participating health care organizations tend to be large, often academic hospitals located in urban areas. Patients included in our analysis were exclusively treated at US healthcare institutions and results may therefore not fully represent the conditions in other regions of the world [20]. Despite these drawbacks, we could show that most patients treated with ivosidenib received prior standard-of-care treatment with gemcitabine/cisplatin and that the OS was 9.6 months, which is shorter than our German cohort but in line with results from other real-world studies.

Our study has several limitations. First, our real-world cohort is relatively small and limited to patients treated at academic medical centers. A critical factor determining survival of patients with BTC is the timely management of complications of advanced disease, such as biliary tract stenosis and infections, and reduced liver function [30]. Hence, multidisciplinary care is essential, which might not be available to all patients treated at non-tertiary centers and in all regions. This might also explain the difference in survival between our German and the TriNetX cohort, which included a broader spectrum of healthcare institutions. Second, our small cohort is heterogenous, as most patients received different pretreatments, including resection in some cases. Moreover, patients received ivosidenib in different lines of therapy, leading to further treatment heterogeneity. To overcome these limitations, which also apply to other published real-world studies on ivosidenib, more high-quality data from global curated registries are needed, which would improve data integration and comparability.

5 Conclusions

Our real-world data from four German academic medical centers and the TriNetX database support the clinical benefit of ivosidenib observed in the ClarIDHy trial and other real-world studies, with a comparable overall PFS and OS. Safety profile was favorable, with grade 3 adverse events observed in one case. Given that all patients with PR exhibited durable tumor control, further investigation is warranted to identify biomarkers that can improve response prediction.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-026-01211-6.

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Declarations

Conflict of Interest Lena Dreikhausen, Alexander Olkus, Michael Dill, Christoph Springfeld, Philipp Heumann, Nadine Schulte, Konstantina Atanasova, Matthias P. Ebert, Anne Letsch, Anna M. Wandmacher, and Tianzuo Zhan have no conflicts of interest that are directly relevant to the content of this article.

Ethical Approval Approval was granted by the Ethics Committee of Heidelberg University (identifier: 2022-823_1-AF 11) and approved by all participating centers. TriNetX utilizes aggregated de-identified patient records, and analysis of the TriNetX database does not require approval by the ethics committee. The study was performed in accordance with the Declaration of Helsinki.

Consent to Participate Because of the retrospective design of the study, no written informed consent from patients was required, as decided by the local ethics board.

Consent for Publication Not applicable.

Availability of Data and Material Genomic data are provided in Table 1. Data used in this article may be made available upon reasonable request from the corresponding author.

Code Availability Not applicable.

Authors' Contributions LD, AMW, and TZ conceived and designed the study. LD, KA, AMW, and TZ analyzed the data. LD, AO, MTD, CS, PH, NS, MPE, AL, AMW, and TZ collected clinical data and provided critical data interpretation. LD, AMW, and TZ. wrote the manuscript. All authors have read and provided comments on the manuscript. All authors approved the manuscript and gave their consent for submission and publication.

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References

1. Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016;13:261–80. https://doi.org/10.1038/NRGASTRO.2016.51.
2. Hasegawa S, Ikai I, Fujii H, Hatano E, Shimahara Y. Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. World J Surg. 2007;31:1256–63. https://doi.org/10.1007/S00268-007-9001-Y.
3. Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer. 2003;98:1689–700. https://doi.org/10.1002/CNCR.11699.
4. Lee JY, Kim JW. Recent 5-year trends in biliary tract cancer survival rates: an analytical big data survey. Med Int. 2025;5:15. https://doi.org/10.3892/MI.2025.214.
5. Oh D-Y, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in advanced biliary tract cancer. NEJM Evid. 2022;1:EVIDoa2200015. https://doi.org/10.1056/EVIDOA2200015.
6. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:127–40. https://doi.org/10.1016/j.annonc.2022.10.506.
7. Kumar-Sinha C, Vats P, Tran N, Robinson DR, Gunchick V, Wu YM, et al. Genomics driven precision oncology in advanced biliary tract cancer improves survival. Neoplasia. 2023;42:100910. https://doi.org/10.1016/j.neo.2023.100910.
8. Zhan T, Betge J, Schulte N, Dreikhausen L, Hirth M, Li M, et al. Digestive cancers: mechanisms, therapeutics and management. Signal Transduct Target Ther. 2025;10:24. https://doi.org/10.1038/S41392-024-02097-4.
9. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21:671–84. https://doi.org/10.1016/S1470-2045(20)30109-1.
10. Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21:1234–43. https://doi.org/10.1016/S1470-2045(20)30321-1.
11. Boscoe AN, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. J Gastrointest Oncol. 2019;10:751–65. https://doi.org/10.21037/JGO.2019.03.10.
12. Frampton JE. Ivosidenib: a review in advanced cholangiocarcinoma. Target Oncol. 2023;18:973–80. https://doi.org/10.1007/S11523-023-01002-3.
13. Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, et al. Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. Nature. 2014;513:110–52. https://doi.org/10.1038/NATURE13441.
14. Salati M, Caputo F, Baldessari C, Galassi B, Grossi F, Dominici M, et al. IDH signalling pathway in cholangiocarcinoma: from biological rationale to therapeutic targeting. Cancers (Basel). 2020;12:1–11. https://doi.org/10.3390/CANCERS12113310.
15. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet

Oncol. 2020;21:796–807. https://doi.org/10.1016/S1470-2045(20)30157-1.
16. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. 2021;7:1669–77. https://doi.org/10.1001/JAMAONCOL.2021.3836.
17. Niger M, Rimini M, Castet F, Melzer A, Rizzato MD, Pressiani T, et al. Ivosidenib for IDH1-mutant intrahepatic cholangiocarcinoma: insights from a multicenter real-world study. Liver Int. 2025;45:e70295. https://doi.org/10.1111/LIV.70295.
18. Najafzadeh M, Fernández Oromendia A, Burcu M, Mcconnochie B, Kim E, Vaccaro T, et al. Linkage of clinical trial data to routinely collected data sources: a scoping review. JAMA Netw Open. 2025;8:e257797. https://doi.org/10.1001/JAMANETWORKOPEN.2025.7797.
19. Kiernan D, Carton T, Toh S, Phua J, Zirkle M, Louzao D, et al. Establishing a framework for privacy-preserving record linkage among electronic health record and administrative claims databases within PCORnet®, the National Patient-Centered Clinical Research Network. BMC Res Notes. 2022;15:337. https://doi.org/10.1186/S13104-022-06243-5.
20. Ludwig RJ, Anson M, Zirpel H, Thaci D, Olbrich H, Bieber K, et al. A comprehensive review of methodologies and application to use the real-world data and analytics platform TriNetX. Front Pharmacol. 2025;16:1516126. https://doi.org/10.3389/FPHAR.2025.1516126.
21. Palchuk MB, London JW, Perez-Rey D, Drebert ZJ, Winer-Jones JP, Thompson CN, et al. A global federated real-world data and analytics platform for research. JAMIA Open. 2023;6:ooad035. https://doi.org/10.1093/JAMIAOPEN/OOAD035.
22. Topaloglu U, Palchuk MB. Using a federated network of real-world data to optimize clinical trials operations. JCO Clin Cancer Inform. 2018;2:1–10. https://doi.org/10.1200/CCI.17.00067.
23. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149:565–74. https://doi.org/10.1001/JAMASURG.2013.5137.
24. Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA. Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. BMC Gastroenterol. 2016;16:117. https://doi.org/10.1186/S12876-016-0527-Z.
25. Chen C, Han N, Chen A, Liu X, Chu X. Real-world survival outcomes with Ivosidenib in Chinese patients with IDH1-mutated intrahepatic cholangiocarcinoma. J Clin Oncol. 2025;43(16_Suppl.):E16227. https://doi.org/10.1200/JCO.2025.43.16_SUPPL.E16227.
26. Zhou KI, Baidya RN, Lin C, Scobie MR, McSkimming D, Kelley MJ, et al. Real world efficacy and safety of Ivosidenib in US veterans with IDH1 mutated cholangiocarcinoma. J Clin Oncol. 2025;43(16_Suppl.):4086. https://doi.org/10.1200/JCO.2025.43.16_SUPPL.4086.
27. Cybulska-Stopa BA, Cybulska-Stopa BJ, Kawecki M, Szymańska P, Duszyński P, Borysiewicz Z, et al. Ivosidenib in treatment of patients with cholangiocarcinoma with IDH1 mutation: real-world data from a multicenter study. Oncol Clin Pract. 2025. https://doi.org/10.5603/OCP.104900.
28. Harding JJ, El-Khoueiry A, Ueno M, Chon HJ, Kim JW, Choi HJ, et al. A phase 1b/2, safety lead-in and dose-expansion trial of Ivosidenib plus Durvalumab and Gemcitabine/Cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation. J Clin Oncol. 2025;43(16_Suppl.):TPS4219. https://doi.org/10.1200/JCO.2025.43.16_SUPPL.TPS4219.
29. Kelley RK, Cleary JM, Sahai V, Baretti M, Bridgewater JA, Hua Z, et al. A phase 1/2, safety lead-in and dose expansion, open-label, multicenter trial investigating the safety, tolerability, and preliminary activity of Ivosidenib in combination with Nivolumab and Ipilimumab in previously treated subjects with IDH1-mutated nonresectable or metastatic cholangiocarcinoma. J Clin Oncol. 2024;42(16_Suppl.):TPS4197. https://doi.org/10.1200/JCO.2024.42.16_SUPPL.TPS4197.
30. Rimassa L, Khan S, Groot Koerkamp B, Roessler S, Andersen JB, Raggi C, et al. Mapping the landscape of biliary tract cancer in Europe: challenges and controversies. Lancet Reg Health Eur. 2025;50:101171. https://doi.org/10.1016/j.lanepe.2024.101171.

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