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Systematic review

Systematic review of randomized clinical trials of patients with IDH1 R132-mutant cholangiocarcinoma treated with ivosidenib.

Revisão sistemática de ensaios clínicos randomizados de pacientes com colangiocarcinoma mutante IDH1 R132 tratados com ivosidenibe

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ABSTRACT

Objective: To evaluate the efficacy and safety of ivosidenib as a monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma harboring the IDH1 R132 mutation, previously treated with at least one line of systemic therapy. **Method**: The evidence search was conducted in electronic databases Medline via PubMed, Embase, Cochrane and Lilacs, with a cutoff date of December 2024, to identify randomized clinical trials. Analyzed outcomes included progression-free survival (PFS), overall survival (OS), quality of life, and adverse events. Two investigators performed the search, study selection, data extraction, and assessed quality and risk of bias using the Cochrane RoB2 tool. The certainty of evidence was analyzed with the support of the GRADE tool. **Results**: Two publications derived from the same pivotal randomized clinical trial, identified as ClarIDHy, were included. The median PFS was 2.7 months in patients treated with ivosidenib, compared to 1.4 months in those who received a placebo (HR = 0.37; 95%CI: 0.25 to 0.54). The six- and 12-month PFS rates were 32% and 22%, respectively. The final OS analysis indicated a benefit of ivosidenib compared to placebo. Overall, the safety profile of ivosidenib was favorable, with nausea, diarrhea, and fatigue being the most commonly reported adverse events in both groups. **Conclusion**: In patients with locally advanced or metastatic cholangiocarcinoma harboring the IDH1 mutation, ivosidenib emerges as a viable therapeutic option; however, this conclusion should be interpreted with caution, as it is primarily based on two publications derived from a single pivotal clinical trial, which limits the robustness of the available evidence.

Keywords: Cholangiocarcinoma; Bile Duct Neoplasm; Intrahepatic Cholangiocarcinoma; Extrahepatic Cholangiocarcinoma; Ivosidenib.

RESUMO

Objetivo: Avaliar a eficácia e a segurança do ivosidenibe como monoterapia no tratamento de pacientes adultos com colangiocarcinoma localmente avançado ou metastático, portadores da mutação IDH1 R132, previamente tratados com pelo menos uma linha de terapia sistêmica. **Método:** A busca por evidências foi realizada nas bases de dados eletrônicas Medline via PubMed, Embase, Cochrane e Lilacs, para identificar ensaios clínicos randomizados. Os desfechos analisados incluíram sobrevida livre de progressão (SLP), sobrevida global (SG), qualidade de vida e eventos adversos. Dois investigadores conduziram a busca, seleção dos estudos, extração de dados e avaliação da qualidade e do risco de viés utilizando a ferramenta Cochrane RoB2. A certeza das evidências foi analisada com o suporte da ferramenta GRADE. **Resultados**: Foram incluídas duas publicações derivadas do mesmo ensaio clínico randomizado pivotal, identificado como ClarIDHy. A mediana de SLP foi de 2,7 meses nos pacientes tratados com ivosidenibe, comparado a 1,4 meses naqueles que receberam placebo (HR = 0,37; IC95%: 0,25 a 0,54). As taxas de SLP em seis e doze meses foram de 32% e 22%, respectivamente. A análise final de SG indicou um benefício do ivosidenibe em comparação ao placebo. De modo geral, o perfil de segurança do ivosidenibe foi favorável, sendo náusea, diarreia e fadiga os eventos adversos mais comumente relatados em ambos os grupos. **Conclusão**: Em pacientes com colangiocarcinoma localmente avançado ou metastático portadores da mutação IDH1, o ivosidenibe desponta como alternativa terapêutica viável; entretanto, essa conclusão deve ser interpretada com cautela, uma vez que está fundamentada principalmente nos resultados de dois estudos derivados de único ensaio clínico pivotal, o que limita a robustez da evidência disponível.

Palavras-chave: Colangiocarcinoma; Neoplasia de Ducto Biliar; Colangiocarcinoma Intra-hepático; Colangiocarcinoma Extra-hepático; Ivosidenibe.

Introduction

Cholangiocarcinoma (CCA) is an aggressive and rare form of epithelial cancer of the bile ducts. It may originate from any site along the biliary tree.[1] Anatomically, it can be classified into categories according to its topography, being intrahepatic, arising from the intrahepatic biliary tract within the hepatic parenchyma, or extrahepatic. In Western countries, an annual incidence of 1 to 2 cases per 100,000 inhabitants has been reported.[2] In Brazil, the Instituto Nacional de Câncer (INCA) does not provide official statistics on the incidence of biliary tract cancer; however, for liver cancer, the estimated risk for the 2023, 2025 triennium is 4.9 cases per 100,000 inhabitants.[3]

Each subtype presents distinct characteristics and may require specific therapeutic approaches. The treatment of CCA depends on the anatomical location of the tumor, disease stage, and the patient's clinical condition. Among the therapeutic options, surgical resection stands out, offering the only potential chance of cure for CCA, as well as adjuvant systemic therapies, such as radiotherapy, chemotherapy, and, more recently, targeted therapy. However, due to its aggressive nature and frequently late diagnosis, many patients present with advanced tumors at the time of diagnosis, which limits treatment options and results in a less favorable prognosis.[4]

The advent of genomic sequencing and, consequently, knowledge of the molecular profile of tumors has led to a better understanding and identification of potentially treatable genomic alterations in patients with CCA, one of these mutations occurs in the gene called IDH1 (isocitrate dehydrogenase 1), an alteration that occurs mainly in the intrahepatic subtype of CCA, where it has been detected in approximately 14% of patients.[5,6]

Objective

To evaluate the efficacy and safety of ivosidenib as monotherapy in the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma harboring the IDH1 R132 mutation and who have already received at least one prior line of systemic treatment for the disease.

Methodology

This systematic review was reported in accordance with the checklist contained in PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and is registered in PROSPERO.[7]

Information sources consulted

The electronic databases consulted were Medline via PubMed, Embase, Cochrane, and Lilacs. In addition, a manual search of the references of relevant reviews on the topic and of the included studies was performed, as well as an investigation of the grey literature through consultation of the ClinicalTrials.gov clinical trial registry database and the Google Scholar search engine. The searches were completed on December 15, 2024. In Table 1, the information sources consulted, descriptors used, and search strategies developed according to the eligibility criteria can be verified.

Eligibility criteria

No restriction was applied regarding language or publication date. As inclusion criteria, only phase III randomized clinical trials (RCTs) for which the full text could be retrieved and in which the use of the drug ivosidenib was analyzed in the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma harboring the IDH1 R132 gene mutation and previously treated with at least one prior line of systemic therapy were selected.

Exclusion criteria

Studies with methodological designs incompatible with the inclusion criteria were excluded, such as those without a control group or that did not use placebo as a comparator, as well as investigations based on preliminary data or whose results could not be verified.

Table 1. Information sources consulted, descriptors, and search strategies

Medline via PubMed
#1: *(Cholangiocarcinoma* OR Cholangiocarcinomas OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinomas OR Extrahepatic Cholangiocarcinoma OR Cholangiocarcinoma, Extrahepatic OR Cholangiocarcinomas, Extrahepatic OR Extrahepatic Cholangiocarcinomas OR Intrahepatic Cholangiocarcinoma OR Cholangiocarcinoma, Intrahepatic OR Cholangiocarcinomas, Intrahepatic OR Intrahepatic Cholangiocarcinomas OR Bile Duct Neoplasms OR Bile Duct Neoplasm OR Neoplasm, Bile Duct OR Biliary tract cancers OR Perihilar cholangiocarcinoma OR Distal cholangiocarcinoma OR Neoplasms, Bile Duct OR Bile Duct Cancer OR Bile Duct Cancers OR Cancer, Bile Duct OR Cancers, Bile Duct OR Cancer of Bile Duct OR Cancer of the Bile Duct)* n=55.297

#2: *(Ivosidenib OR N-((1S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyano-2-pyridinyl)-N-(5-fluoro-3-pyridinyl)-5-oxo-L-prolinamide OR AG-120 OR AG120 OR Tibsovo OR Isocitrate Dehydrogenase* OR Pyridines)* n=347.946
Estratégia 1: #1 AND #2: n=553

Embase
#1: *('bile duct adenocarcinoma'/exp OR 'adenocarcinoma of the bile duct' OR 'cholangioadenocarcinoma' OR 'choledochal adenocarcinoma' OR 'bile duct adenocarcinoma' OR 'bile tract carcinoma' OR 'biliary carcinoma' OR 'biliary duct carcinoma' OR 'biliary tract carcinoma' OR 'carcinoma of bile duct' OR 'carcinoma of the biliary tract' OR 'cholangiocarcinoma' OR 'cholangiocellular carcinoma' OR 'cholangiolar carcinoma' OR 'gall duct carcinoma' OR 'malignant cholangioma' OR 'bile duct carcinoma' OR 'biliary cancer' OR 'biliary carcinogenesis' OR 'biliary malignancies' OR 'biliary malignancy' OR 'biliary system cancer' OR 'cancer of the biliary system' OR 'cancer of the biliary tract' OR 'malignancies of the biliary tract' OR 'malignancy of the biliary tract' OR 'malignant tumor of biliary tract' OR 'biliary tract cancer')* n=53.448

#2: *(Ivosidenib OR '1 (4 cyano 2 pyridinyl) 5 oxo prolyl 2 (2 chlorophenyl) n (3, 3 difluorocyclobutyl) n2 (5 fluoro 3 pyridinyl) glycinamide' OR '1 (4 cyano 2 pyridyl) 5 oxo prolyl 2 (2 chlorophenyl) n (3, 3 difluorocyclobutyl) n2 (5 fluoro 3 pyridyl) glycinamide' OR '1 (4 cyanopyridin 2 yl) 5 oxo prolyl 2 (2 chlorophenyl) n (3, 3 difluorocyclobutyl) n2 (5 fluoropyridin 3 yl) glycinamide' OR 'ag 120' OR 'ag120' OR 'cs 3010' OR 'cs3010' OR 'n [1 (2 chlorophenyl) 2 [(3, 3 difluorocyclobutyl) amino] 2 oxoethyl] 1 (4 cyano 2 pyridinyl) n (5 fluoro 3 pyridinyl) 5 oxo 2 pyrrolidinecarboxamide' OR 'n [1 (2 chlorophenyl) 2 [(3, 3 difluorocyclobutyl) amino] 2 oxoethyl] 1 (4 cyano 2 pyridinyl) n (5 fluoro 3 pyridinyl) 5 oxoprolinamide' OR 'n [1 (2 chlorophenyl) 2 [(3, 3 difluorocyclobutyl) amino] 2 oxoethyl] 1 (4 cyano 2 pyridyl) n (5 fluoro 3 pyridyl) 5 oxo 2 pyrrolidinecarboxamide' OR 'n [1 (2 chlorophenyl) 2 [(3, 3 difluorocyclobutyl) amino] 2 oxoethyl] 1 (4 cyanopyridin 2 yl) n (5 fluoropyridin 3 yl) 5 oxopyrrolidine 2 carboxamide' OR 's 95031' OR 's95031' OR 'tibsovo' OR 'tidhesco' OR 'tuoshuwo' OR 'ivosidenib' OR 'IDH inhibitor' OR 'isocitrate dehydrogenase inhibitor')* n=2.831

Estratégia 1: #1 AND #2: n=383

Central Cochrane
Cholangiocarcinoma AND (Ivosidenib OR Isocitrate Dehydrogenase*)* n=26

ClinicalTrials.gov
Cholangiocarcinoma AND Ivosidenib n=8

Lilacs
Cholangiocarcinoma AND Ivosidenib n=0

Source: Prepared by the authors.

Study identification

Two researchers (R.S.S. and J.C.N.M.) developed the search strategies and independently assessed the titles and abstracts of potentially eligible studies using the RAYYAN tool. The full texts of any potentially relevant articles were obtained and independently reviewed by the same authors, who applied the eligibility criteria that had been decided a priori. Discrepancies were discussed by the two reviewers until agreement was reached. Remaining discrepancies were resolved through a consensus decision with a third reviewer (J.S.C.G.).

Types of measures (response to treatment)

The efficacy of treatment in patients diagnosed with locally advanced or metastatic CCA with mIDH1 who received at least one prior line of systemic therapy is assessed according to the type of response:

- Progression-free survival (PFS);
- Overall survival (OS);
- Objective response rate;
- Duration and time to response;
- Quality of life;
- Adverse events.

Risk of bias assessment

For the assessment of risk of bias, the Cochrane Risk of Bias 2 (RoB2) tool was used. High risk, low risk, and some concerns were assessed based on five domains addressing the randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, and selection of the reported result.

Classification of the quality of evidence

The quality of evidence regarding the efficacy of the interventions on the outcomes overall survival, progression-free survival, and quality of life was assessed according to the recommendations contained in GRADE, Grades of Recommendation, Assessment, Development and Evaluation. The following domains were assessed: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Because this is a serious disease, any gains in OS and PFS were considered clinically significant. Gains in quality of life measured as 10 points or more on the scale were considered clinically significant.

Statistical analysis

Absolute risk reduction (ARR) and the number needed to treat (NNT) were estimated using the online StatPages tool (https://statpages.info). For all estimates, the respective 95% confidence intervals (95%CI) were calculated.

Results

After submitting the search strategies to the electronic information databases consulted, a total of 974 citations were identified. Following the title and abstract screening process, 17 potentially relevant studies were retrieved, of which only two were selected for full-text review and inclusion in this review (Flowchart). The main factor determining the exclusion of studies was articles that did not meet the selection criteria related to the clinical question.

Main characteristics of the included study

Two publications were included and reported results related to the pivotal study known as ClarIDHy (NCT02989857), which was a multicenter, double-blind, phase III trial in which patients diagnosed with locally advanced or metastatic CCA with mIDH1, treated with at least one prior line of systemic therapy, were randomized to receive ivosidenib as monotherapy or placebo.[9,10] The primary objective of the study was the assessment of PFS. In this trial, eligible patients were aged ≥18 years, had measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), documented disease progression after at least one and no more than two systemic treatment

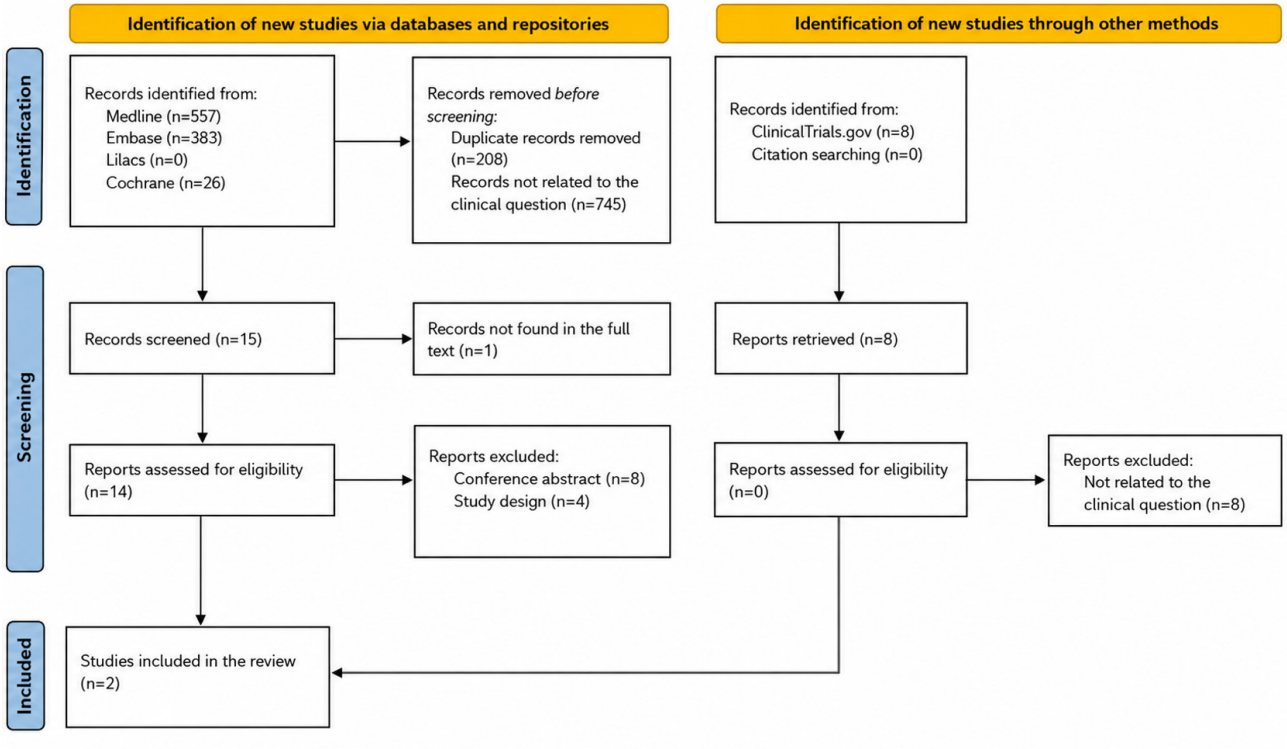
regimens, including at least one chemotherapy regimen containing gemcitabine or another fluorouracil-based regimen, and an Eastern Cooperative Oncology Group, ECOG, performance status of 0 or 1. Treatment was administered until the occurrence of intolerable toxicity or disease progression. Patients who had been randomized to the placebo arm and who continued to meet the eligibility criteria at the end of treatment had the opportunity to cross over to the investigational arm and receive ivosidenib (a total of 70% of patients who received placebo crossed over to ivosidenib after disease progression). Patient characteristics were similar in both groups. Most patients (93%) had stage IV disease, and n=88 patients (47%) had failed two prior lines of therapy. The primary tumor location was intrahepatic in 91% of cases. Among IDH1 variants, the vast majority of patients (70%) had the R132C mutation.

With a planned sample size of n=186 patients randomized in a 2:1 ratio to treatment with ivosidenib and placebo, and with 131 PFS events, the study had 96% power to detect a hazard ratio of 0.5. Regarding crossover, the rank-preserving structural failure time method, known as RPSFT, was used to reconstruct the survival curve (pre-specified exploratory analysis) for patients who received placebo as if crossover had never occurred. The RPSFT method is based on a common treatment assumption: the effect of treatment with ivosidenib is the same for all individuals, regardless of when the treatment is received.

Progression-free survival

At the time of the analysis, 126 PFS events had been observed. With a median follow-up of 6.9 months, the study demonstrated an improvement in PFS among patients randomized to treatment with ivosidenib, with a hazard ratio (HR) of 0.37 (95%CI: 0.25 to 0.54; p<0.0001). The estimated median PFS was 2.7 months (95%CI: 1.6 to 4.2) in the ivosidenib arm versus 1.4 months (95%CI: 1.4 to 1.6) in the placebo arm.[9] A subgroup of patients experienced prolonged disease control, with a 12-month PFS rate observed in 22% of patients treated with ivosidenib versus 0% in the placebo group.

Flowchart. Study selection process



Source: Prepared by the authors.

Overall survival

Median OS was 10.8 months (95%CI: 7.7 to 17.6) in the ivosidenib arm compared with 9.7 months (95%CI: 4.8 to 12.1) in the placebo arm (HR=0.69 [95%CI: 0.44 to 1.1]; p=0.06).[9] Based on the occurrence of 150 events, the estimate for median OS was higher among patients treated with ivosidenib (10.3 months versus 7.5 months for patients treated with ivosidenib and placebo, respectively), although with no difference between groups (HR=0.79 with 95%CI: 0.56 to 1.12).[10] However, after adjustment for the crossover effect, the mean survival in the placebo group was reduced to 5.1 months, revealing a difference in mean overall survival between the two treatment arms.[10]

Objective response rate

The objective response rate in the group treated with ivosidenib was 2%, comprising the occurrence of three partial responses compared with no responses among patients in the placebo group (ARR= -0.33 with 95%CI: -0.33 to 0.36). A total of n=63 patients treated with ivosidenib had stable disease, compared with n=17 patients who had been randomized to the placebo group (ARR= -0.2 with 95%CI: -0.3 to -0.06 and NNT=4 [95%CI: 3 to 16]).

Quality of life

At baseline, 113 patients (91%) in the ivosidenib group and 52 patients (85%) in the placebo group completed the EORTC QLQ-C30 assessment, while 107 and 51 patients completed the QLQ-BIL21 assessment, respectively. In the second cycle, change scores from baseline for the EORTC QLQ-C30 were available for 62 patients (55%) of 113 in the ivosidenib group and for 20 patients (38%) of 52 in the placebo group. Change scores from baseline for the EORTC QLQ-BIL21 were available for 60 patients (56%) of 107 in the ivosidenib group and for 19 patients (37%) of 51 in the placebo group. The reduction from baseline in the second cycle in the physical functioning subscale of the EORTC QLQ-C30 was smaller among patients treated with ivosidenib. Changes from baseline in the pain and appetite loss subscales showed no significant differences between groups.

Adverse events

The safety assessment was based on the analysis of 182 patients who received at least one dose of ivosidenib (n=123) or placebo (n=59). Comparative safety data in patients randomized to the placebo arm are included only from the placebo portion of the study (the analysis excludes data from these patients at the time of crossover to ivosidenib). The most commonly observed treatment-related adverse events were fatigue/asthenia (26% in the ivosidenib group versus 15% in the placebo group), nausea (36% versus 27%), diarrhea (33% versus 17%), abdominal pain, cough, anemia, and peripheral neuropathy. The incidence of adverse events leading to death during treatment was 4.9% in the ivosidenib arm and 0% in the placebo arm, with most deaths in the ivosidenib arm attributed to progressive disease.

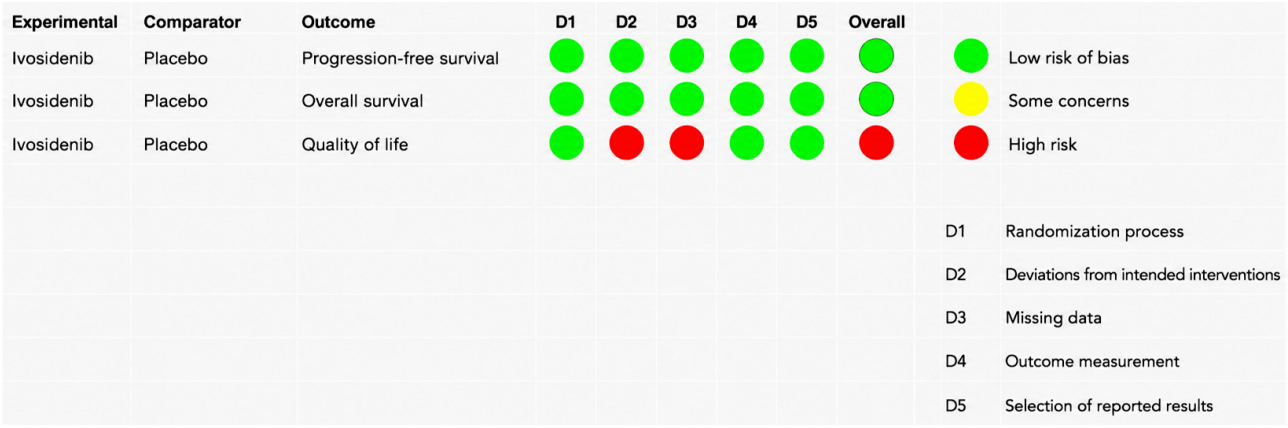
Risk of bias assessment

The overall risk of bias was considered low for the PFS and OS outcomes. Conversely, for the quality-of-life outcome, it was considered to have a high risk of bias, mainly due to missing data and deviations from the intended intervention (Chart 1).

Assessment of the quality of evidence

The classification of the quality of evidence is presented in Table 2 for the outcomes PFS, OS, and quality of life. It was classified as high for the PFS and OS outcomes. Conversely, the quality of evidence was classified as low for the quality-of-life outcome, mainly due to loss to follow-up of a significant proportion of the sample.

Chart 1. Risk of bias assessment



Source: Prepared by the authors.

Table 2. Classification of the quality of evidence

Certainty of the evidence							Summary of Findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence	Study event rates (%) With placebo	Study event rates (%) With ivosidenib	Relative effect (95% CI)	Potential absolute effects Risk with placebo	Potential absolute effects Risk difference with ivosidenib
Progression-free survival (follow-up: 6 months)											
185 (1 ECR)	not serious	not serious[a]	not serious	not serious	none	⊕⊕⊕⊕ High[a]	61 participants	124 participants	**HR 0.37** (0.25 to 0.54) [Progression-free disease] 1 por 1.000[b]	**High**	**76 more per 1,000** (from 23 more to 176 more)
Overall survival (follow-up: 6 months)											
185 (1 ECR)	not serious	not serious[a]	not serious	not serious	none	⊕⊕⊕⊕ High[a]	61 participants	124 participants	**HR 0.46** (0.28 to 0.75) [Overall survival] 5 por 1.000[c]	**High**	**84 more per 1,000** (from 14 more to 225 more)
Quality of life (follow-up: 1 month; assessed with: EORTC QLQ-C30; Scale: 0 to 100)											
82 (1 ECR)	serious[a]	not serious[a]	not serious	serious[e]	none	⊕⊕◯◯ Low[a,d,e]	20	62	-	20	MD **9.8 points higher** (2.8 higher to 16.7 higher)

CI: Confidence interval; **HR:** Hazard Ratio; **MD:** mean difference
Source: Prepared by the authors.

Discussion

The mechanism of action of ivosidenib involves reversible inhibition of the enzymatic activity of the protein resulting from the mutation in the IDH1 gene, which has neomorphic activity and, consequently, leads to a reduction in the intracellular concentration of 2-hydroxyglutarate, which acts as an oncometabolite whose accumulation leads to several epigenetic alterations. The clinical effect and safety of ivosidenib were evaluated in a phase I study (NCT02073994) that included 73 patients diagnosed with CCA harboring an IDH1 mutation. In this study, ivosidenib was administered at doses ranging from 200 to 1200mg/day without dose-limiting toxicities, and the mean time to disease progression for the 500mg/day dose was found to be 3.8 months, with progression-free survival rates

at six and 12 months of 40.1% and 21.8%, respectively.[11] The results of this study supported the development of the multicenter, randomized, phase III clinical trial known as ClarIDHy, which found that ivosidenib enabled a mean increase in progression-free survival of 1.3 months compared with placebo (2.7 months versus 1.4 months for patients treated with ivosidenib and placebo, respectively), as well as a 63% reduction in the risk of disease progression compared with the arm that received placebo. The 6- and 12-month PFS rates were 32% and 22%, respectively, and none of the patients in the placebo arm achieved PFS at six months.[9,10] Overall survival among patients treated with ivosidenib did not reach statistical significance compared with those who received placebo (10.3 months versus 7.5 months; $p=0.09$). This observation was mainly attributed to events related to crossover among patients originally assigned to the placebo group. However, after adjustment for this event, mean OS in the placebo group was reduced to 5.1 months, revealing a difference in mean survival between the two treatment arms ($p<0.001$).[10]

At this point, it is important to discuss the RPSFT method, which was used to estimate the difference in overall survival between groups in the study, had crossover not occurred. This method is based on the main assumption of the "common treatment effect", which implies that survival times are independent of the treatment group and requires, at least approximately, that the treatment effect be the same for all patients, regardless of the time at which treatment is administered. Nevertheless, it is relevant to consider that, if the patient crosses over after disease progression, the benefit obtained from treatment may not be equivalent to the benefit observed in patients who had initially been randomized to the experimental group. Thus, there is a potential risk of bias.

It is also important to highlight the favorable safety profile observed with the use of ivosidenib, which makes it a therapeutic option for patients who had already been treated with systemic therapy. It was possible to verify that only 7% of patients experienced grade ≥3 adverse events. Overall, the low incidence of adverse events and the reduction in discontinuations due to toxicity, associated with a significantly smaller decline in health-related quality of life in the group that received ivosidenib, contribute to better treatment adherence.

Among the limitations of this review, it is noteworthy that the identified evidence consists of two studies derived from a single randomized clinical trial. At first glance, this concentration of data may raise concerns regarding the diversity of the available evidence sources and suggest the possibility of potential publication bias, since favorable results tend to be reported more frequently. However, such an interpretation should be carefully contextualized. The assessment of the quality of evidence using the GRADE system indicated high certainty, reflecting the methodological rigor, adequate design, and consistency of the results of the pivotal study. Furthermore, in the context of innovative technologies, it is expected that the initial evidence base be grounded in a robust pivotal trial, which, in itself, does not compromise the solidity of the conclusions when methodological criteria are rigorously met. Thus, although the limitation related to the single origin of the evidence should be acknowledged, it neither invalidates nor substantially weakens the findings presented in this review. It should also be highlighted that the objective response rate, defined as the proportion of patients with a reduction in tumor size in a predefined dimension and for a minimum period of time, was numerically low and represents the main critical point, which prevents ivosidenib from being considered the best candidate for tumor reduction (2% versus 0% for ivosidenib and placebo, respectively, with no difference between groups). In addition, the benefit provided by ivosidenib may not be exclusively related to the RECIST response, since preclinical and clinical evidence indicates that histological changes, such as a reduction in the amount of cytoplasm and cellular differentiation, may also influence survival.[12] Another aspect to be highlighted refers to the outcome "quality of life". In our review, it was possible to observe the high risk of bias associated with this outcome, mainly due to missing data for analysis, which may have generated attrition bias. In our analysis, we were unable to determine whether the gain in PFS or OS was related/associated with an improvement

in quality of life or whether the increase in PFS resulted in better quality of life, with or without an overall survival benefit. These are fundamental points in the treatment of patients with cancer, especially in cases with a poor prognosis, particularly when modest or minimal gains in progression-free survival and overall survival are observed.

Another limitation is the absence of a control group receiving standard chemotherapy, which makes it difficult to accurately estimate the actual benefit offered by ivosidenib in patients eligible for each second-line treatment. It is worth noting that comparisons across trials are not reliable due to significant differences in the topography of the primary tumor.

It is also important to highlight the inevitable development of resistance to targeted therapies, as in the case of ivosidenib. Although data on acquired resistance in CCA are limited, cases of conversion from IDH1 R132C to IDH1 R132F and isoform switching to mutant IDH2 have been reported.[13,14]

Conclusions

In patients with locally advanced or metastatic intrahepatic cholangiocarcinoma, previously exposed to at least one line of systemic treatment, with a minimum life expectancy of three months, ECOG score 0, 1, and IDH1 R132 mutation, ivosidenib represents a viable therapeutic alternative. The ClarIDHy study demonstrated relevant clinical benefits, including improvement in progression-free survival and gain in overall survival, associated with a relatively favorable toxicity profile. However, these results should be interpreted in light of the inherent limitations of the available evidence, since they essentially derive from a single pivotal clinical trial, which reinforces the need for further studies to confirm and expand these findings.

Author Contributions
All authors contributed to: Conception and design or data analysis and interpretation; Drafting of the article or relevant critical revision of the intellectual content; Final approval of the version to be published; Accountability for all aspects of the text in ensuring the accuracy and integrity of any part of the work.

Conflicts of interest
All authors declare that they are consultants and work at Unimed do Brasil.

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Data Availability Statement
The contents underlying the research text are contained in the manuscript.

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