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REVIEW ARTICLE

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Ivosidenib in the treatment of patients with *IDH1* mutated cholangiocarcinoma

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ABSTRACT

Metastatic cholangiocarcinoma (CCA) has poor prognosis. Chemotherapy in this indication demonstrated a limited benefit. Adding immunotherapy to standard chemotherapy is associated with an increase in median progressio.-free survival (mPFS) and increase in the response rate. An interesting therapeutic option for patients who have experienced progression during first line of treatment are targeted therapies. It is estimated that in over 50% of patients with CCA molecular tests based on next-generation sequencing (NGS) make it possible to identify genomic disorders, potentially enabling the use of targeted treatment. The most frequently reported disorders are fusions in the gene encoding fibroblast growth factor receptor 2 (FGFR2) and mutations in the *IDH1* gene encoding isocitrate dehydrogenase (IDH). Ivosidenib is an oral reversible inhibitor of the abnormal form of IDH1 enzyme. The use of ivosidenib in patients with CCA and the IDH1 gene mutation after failure of previous therapy was evaluated in a phase III ClarIDHy study. The results of the trial confirmed its beneficial effect in terms of both PFS and overall survival (OS).

Keywords: cholangiocarcinoma, *IDH1* mutation, ivosidenib

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Cholangiocarcinoma (CCA) includes a heterogeneous group of tumors originating from cells of intra- or extrahepatic bile ducts. The incidence of this cancer in Europe is estimated at 0.5/100 000 to 3.4/100 000 [1]. Extrahepatic bile duct tumors, due to their location, include perihilar CCA (perihilar eCCA, so-called Klatskin tumor) accounting for 50 to 70% of cases, and peripheral tumors (distal eCCA) diagnosed in 30–40% of patients. On the other hand, intrahepatic CCA (iCCA) is diagnosed in about 10% of patients [2]. The majority (60–70%) of tumors originating from the biliary tract are diagnosed in the local stage, without the possibility of radical resection, or in the metastatic stage. Median overall survival (mOS) in this group of patients usually does not exceed 12 to 15 months [3]. A possibility of surgical resection of the primary lesion slightly improves the prognosis, as disease recurrence is observed in over 60% of patients undergoing primary surgical treatment [4].

Treatment of patients with locally advanced disease without the possibility of primary surgical treatment and patients in the disseminated stage includes primarily systemic therapies and, in selected patients, palliative radiotherapy or local treatment [stereotactic radiotherapy, intra-arterial chemotherapy (IAC)]. A limited benefit from the use of chemotherapy in this indication was demonstrated, among others, by Glimelius et al. [5]. The use of regimens based on the combination of 5-fluorouracil with leucovorin and etoposide or, in the case of elderly patients, 5-fluorouracil with leucovorin, led to a slight improvement in the quality of life and increased mOS by 3.5 months in relation to patients receiving symptomatic treatment alone. The value of regimens based on the combination of gemcitabine and platinum derivatives has been confirmed, among others, in a meta-analysis of 104 studies involving a total of 2 800 patients diagnosed with CCA [6]. As it was shown,

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the use of doublet regimens increased the response rate and control of tumor growth. Very interesting conclusions can also be drawn from the study by Valle et al. [7] analyzing the effect of gemcitabine in combination with cisplatin versus gemcitabine alone in patients with locally advanced or metastatic CCA or gallbladder cancer. A total of 410 patients were included in the analysis. Median overall survival in the group of patients treated with the doublet regimen was 11.7 months, and it was 3.6 months longer than that observed in patients receiving gemcitabine monotherapy (8.1 months). The use of the combination of gemcitabine and cisplatin also led to a 36% reduction in the risk of cancer-related death (HR = 0.64; p < 0.001). Tolerability of treatment in both groups was similar; only in patients receiving the doublet regimen, neutropenia, as a complication of systemic treatment, was observed more often.

The introduction of immune checkpoint inhibitors anti-CTL4 antibodies, anti-programmed death receptor 1 (anti-PD1) and anti-programmed cell death ligand 1 (anti-PD-L1) antibodies into cancer therapy resulted in significant progress in the treatment of many cancers and initiated studies assessing the clinical effect and safety of immunotherapy in the treatment of patients with advanced CCA. One of them was the randomized multicenter phase III TOPAZ-1 study evaluating the efficacy and safety of chemoimmunotherapy based on a combination of doublet chemotherapy (cisplatin plus gemcitabine) with durvalumab versus chemotherapy alone in the first line of treatment in patients with advanced CCA. A total of 685 patients were included in the study. As compared to chemotherapy alone, the use of chemoimmunotherapy led to a 20% reduction in the risk of cancer-related death (HR = 0.80; p = 0.021) with a slight increase in mOS (12.8 months *vs*. 11.5 months, respectively). The benefit of adding immunotherapy to standard chemotherapy was also shown in the increased 2-year survival rate (24.9% *vs*. 10.4%, respectively) [8]. The use of combination therapy was also associated with an increase in median progression-free survival (mPFS) from 5,7 to 7.2 months with significant reduction (25%) in the risk of disease progression (HR = 0.75; p = 0.001), and an 8% increase in the response rate (26.7% *vs*. 16.7%) [9]. Importantly, the combination of chemotherapy and durvalumab led to a therapeutic effect regardless of the presence or absence of microsatellite instability and the number of genome mutations [10].

As mentioned above, cholangiocarcinomas have a poor prognosis, and the vast majority of patients, despite first-line treatment, experience disease progression. In some patients with good performance status or with mild organ impairment after first-line treatment, the use of regimens based on the combination of 5-fluorouracil with oxaliplatin or irinotecan in the next treatment line may be considered. As demonstrated in the ABC-06 study, the use of the FOLFOX regimen in the second treatment line, resulted in a 0.9-month increase in median overall survival (6.2 *vs*. 5.3 months, respectively) and a 31% reduction in the risk of death (HR = 0.69; p = 0.31) as compared to symptomatic therapy [11]. The results of irinotecan-based combination therapies used in the second treatment line were comparable to those observed in the group of patients receiving the FOLFOX regimen [12, 13]. Interesting results were also delivered by the NIFTY study, which showed the advantage of the regimen with liposomal irinotecan in combination with 5-fluorouracil and leucovorin over 5-fluorouracil and leucovorin in terms of increase in mPFS (7.1 months *vs*. 1.4 months, HR = 0.56; p = 0.0019) in the Asian population [14].

Another interesting therapeutic option is targeted therapies developed along with molecular research characterizing potential therapeutic targets. Cholangiocarcinoma is a genetically very diverse cancer. It is estimated that in over 50% of patients, molecular tests based on next-generation sequencing (NGS) make it possible to identify genomic disorders, potentially enabling the use of targeted treatment [15, 16]. The most frequently reported disorders are fusions in the gene encoding fibroblast growth factor receptor 2 (FGFR2) and mutations in the *IDH1* gene encoding isocitrate dehydrogenase (IDH). This enzyme catalyzes decarboxylation of isocitrate, resulting in the formation of carbon dioxide and alpha-ketoglutarate (a-KG). Mutations in the genes encoding IDH1 and IDH2 occur in a variety of cancers, particularly frequently in acute myeloid leukemias and gliomas. These disorders do not deactivate the functions of encoded enzymes but lead to gain of new enzymatic activity, e.g. catalyzing the reduction of alpha-ketoglutarate to 2-hydroxyglutarate (2-HG), present in normal cells in low concentration [17]. Increased 2-HG concentration leads to increased DNA and histone methylation, genetic instability, impaired cell differentiation, and consequently neoplastic transformation [18].

Ivosidenib (AG-120) is an oral reversible inhibitor of the abnormal form of IDH1 enzyme. The mechanism of action of the drug involves inhibiting the enzymatic activity of the protein resulting from mutation in the *IDH1* gene and, consequently, reducing the intracellular concentration of 2-hydroxyglutarate [19]. The clinical effect and safety of ivosidenib were assessed in a phase I study [20], including 73 patients diagnosed with CCA with *IDH1* mutation. In this study, ivosidenib was

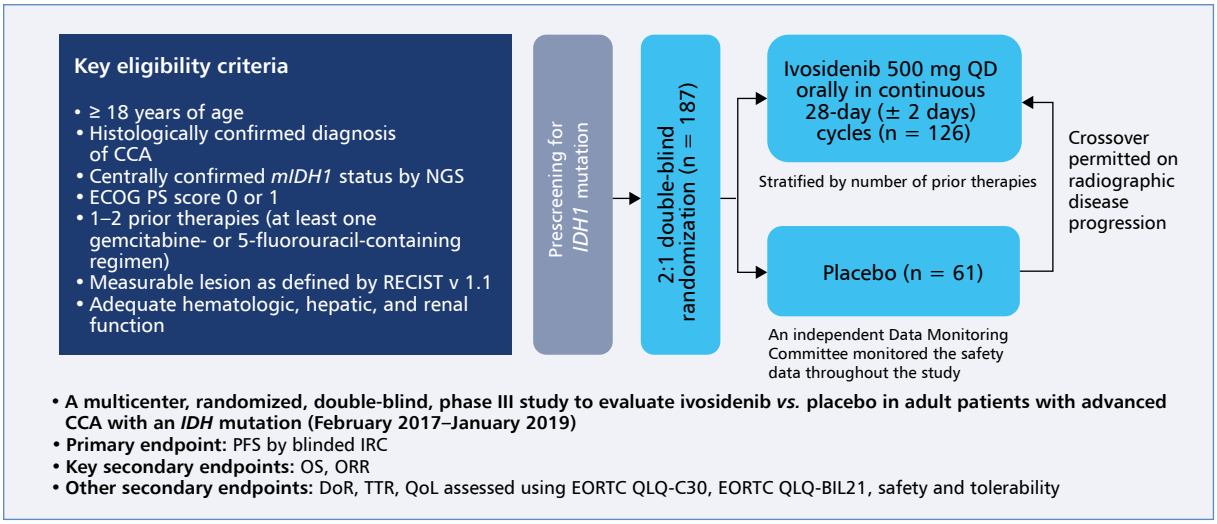
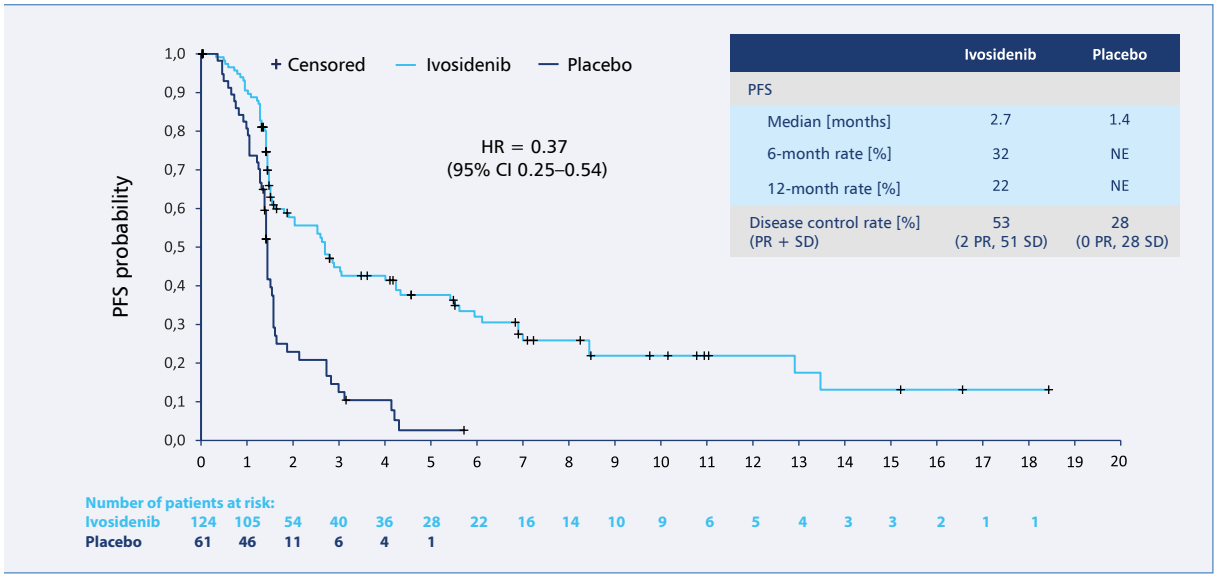


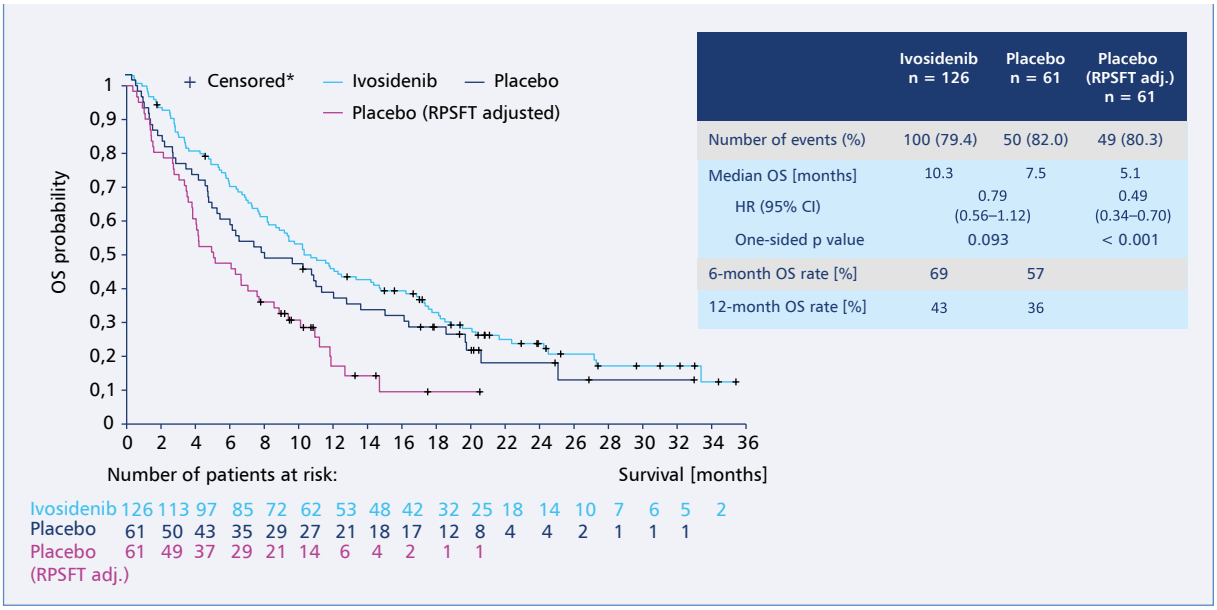
Figure 1. ClarIDHy study — design and endpoints (based on [22]); CCA — cholangiocarcinoma; DoR — duration of response; ECOG PS — Eastern Cooperative Oncology Group performance status; EORTC — European Organisation for Research and Treatment of Cancer; *IDH* — isocitrate dehydrogenase; IRC — independent radiology center; *mIDH* — mutant isocitrate dehydrogenase; NGS — next-generation sequencing; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; QD — once daily; QLQ-BIL21 — Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30 — Quality of Life Questionnaire Core 30; QoL — quality of life; RECIST — Response Evaluation Criteria in Solid Tumors; TTR — time to response

administered at doses ranging from 200 to 1200 mg/day without dose-limiting toxicities. The median time to disease progression for the dose of 500 mg/day was 3.8 months; the 6-month and 12-month progression-free survival rates were 40.1% and 21.8%, respectively; 4 patients (5%) achieved partial remission. Median overall survival was 13.8 months. The treatment was well tolerated. Common adverse events observed during treatment were fatigue (42%), nausea (34%), diarrhea (32%), abdominal pain (27%), loss of appetite (27%), and vomiting (23%). The most common adverse events grade 3 and higher by Common Terminology Criteria for Adverse Events (CTCAE) were ascites (5%) and anemia (4%). The results of a phase I study led to the design of randomized multicenter placebo-controlled phase III ClarIDHy study [21, 22] evaluating the efficacy and safety of ivosidenib in patients with *IDH1*-mutated CCA in the second and third lines of systemic treatment. The study included 187 patients with good performance status [Eastern Cooperative Oncology Group (ECOG) 0–1], who had received previously no more than 2 lines of gemcitabine or 5-fluorouracil-based chemotherapy. Patients were randomly assigned in a 2:1 ratio to the ivosidenib (n = 126) or placebo (n = 61) arms, and randomization was stratified by the number of prior treatment lines. The ClarIDHy study protocol allowed for crossover of patients in the placebo group to the experimental arm after disease progression. Following the results of previous studies, ivosidenib was administered in 28-day cycles, in a single daily dose of 500 mg, and the treatment was continued until disease progression or unacceptable or unmanageable toxicity. Radiological assessment of therapy effectiveness was performed every 6 weeks during the first 48 weeks of the treatment, and then every 8 weeks. The primary endpoint was PFS assessed using RECIST 1.1 criteria. The secondary endpoints were OS, duration of response (DoR), time to response (TTR), and quality of life (QoL) (Fig. 1 [22]). Based on the obtained data, the use of ivosidenib led to an increase in mPFS by 1.3 months (2.7 months *vs*. 1.4 months, respectively) and a 63% reduction in the risk of disease progression as compared to the control arm (HR = 0.37; $p < 0.0001$). The 6-month and 12-month PFS rates were 32% and 22%, respectively, and none of the patients in the control arm achieved PFS at 6 months (Fig. 2 [22]). Median overall survival was 10.3 months in the ivosidenib group and 7.5 months in the control group. The increase in mOS was accompanied by a 21% reduction in the risk of cancer-related death; however, with no statistical significance (HR = 0.79; p = 0.09). Taking into account the acceptable crossover of patients from the control arm to the ivosidenib arm after confirmed disease progression, mOS was assessed using rank preserving structural failure time (RPSFT) statistical analysis, based on which mOS in the control group was corrected from 7.5 months to 5.1 months (HR = 0.49; $p < 0.001$). Importantly, the benefit of



	Ivosidenib	Placebo
PFS		
Median [months]	2.7	1.4
6-month rate [%]	32	NE
12-month rate [%]	22	NE
Disease control rate [%] (PR + SD)	53 (2 PR, 51 SD)	28 (0 PR, 28 SD)

Figure 2. Primary endpoint — progression-free survival (PFS) (modified from [22] with permission from Elsevier). All randomized patients as of January 31, 2019; CI — confidence interval; HR — hazard ratio; IRC — independent radiology center; NE — not estimable; PR — partial response; SD — stable disease



	Ivosidenib n = 126	Placebo n = 61	Placebo (RPSFT adj.) n = 61
Number of events (%)	100 (79.4)	50 (82.0)	49 (80.3)
Median OS [months]	10.3	7.5	5.1
HR (95% CI)	0.79 (0.56–1.12)		0.49 (0.34–0.70)
One-sided p value	0.093		< 0.001
6-month OS rate [%]	69	57	
12-month OS rate [%]	43	36	

Figure 3. Overall survival and treatment duration in the intent-to-treat population (modified from [21]). All randomized patients as of May 31, 2020; *Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier; adj. — adjusted; CI — confidence interval; HR — hazard ratio; OS — overall survival; RPSFT — rank-preserving structural failure time

ivosidenib treatment was independent of the number of previous treatment lines used before study enrollment (Fig. 3 [21]).

Data related to treatment toxicity showed a relatively good tolerance of ivosidenib administered in a single dose of 500 mg. The most commonly observed adverse events were grades 1 and 2 diarrhea, nausea, and fatigue. Serious adverse events were experienced by 30% of patients treated with ivosidenib and 22% of patients in the placebo group. The most frequent grade 3 or higher adverse event by CTCAE was ascites, reported in 7% of patients in both analyzed groups. Grade 4 by CTCAE hyperbilirubinemia, grade 3 by CTCAE cholestatic jaundice, grade 2 by CTCAE QT interval prolongation, and

grade 3 by CTCAE pleural effusion (1 case each) were considered treatment-related. There were 4 (3%) deaths reported in the ivosidenib group, due to pneumonia, sepsis, intestinal obstruction, and pulmonary embolism (1 case each), but none of them were considered by the investigators as treatment-related. In the placebo group, all deaths were due to disease progression. Dose reduction and treatment discontinuation due to toxicity were required in 4 (3%) and 7 (6%) patients treated with ivosidenib, respectively.

The use of ivosidenib in patients with CCA and the *IDH1* gene mutation after failure of previous therapy seems to be an attractive therapeutic option. This treatment has a relatively good toxicity profile and the results of the ClarIDHy study confirmed its beneficial effect in terms of both PFS and OS. Patients with advanced CCA should be routinely tested for the presence of mutations in the *IDH1* gene to identify those who may benefit from ivosidenib therapy. Questions regarding the sequential targeted therapies and the benefits of combining them with other forms of anticancer therapies remain open.

Article Information and Declarations

Author contributions

Authors contributed equally.

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Conflict of interest

A.C.: declares no conflict of interest.
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Supplementary material

None.

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