Ivosidenib in IDH1-mutated cholangiocarcinoma: Clinical evaluation and future directions

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ABSTRACT

To date, treatment options for patients with chemorefractory cholangiocarcinoma (CCA) are limited. However, the advancements in molecular techniques have recently increased the opportunity to offer molecularly targeted therapies to patients with several cancer types and some targetable oncogenic alterations have been identified also in CCA.

Among these potentially actionable molecular alterations, isocitrate dehydrogenase-1 (IDH1) mutations have been detected in approximately 10–20% of intrahepatic CCA (iCCA). IDH1 is responsible for the accumulation of oncometabolites inducing epigenetic changes that are involved in various signaling pathways. Ivosidenib is the first IDH1 inhibitor which significantly improved progression-free survival (PFS) (2.7 vs 1.4 months) and overall survival (OS) (10.3 vs 5.1 months [adjusted median OS]) compared with placebo in chemorefractory IDH1-mutated CCA. The very low incidence of grade (G) 3–4 adverse events (AEs) and treatment discontinuation due to toxicity, associated with a significantly less marked decline in health-related quality of life for patients in the ivosidenib group than in placebo group, facilitates patient adherence and clinician confidence.

Here, we review the development of ivosidenib in CCA patients and evaluate the clinical impact of the results of the phase III ClarIDHy trial which was responsible for the Food and Drug Administration (FDA) approval for patients with IDH1-mutated CCA whose disease progressed after standard chemotherapy (CT). We also discuss the known primary and secondary resistance mechanisms, including concomitant and acquired mutations in other genes (e.g. IDH2 mutations), second-site mutation in IDH1, and enhanced activation of other pathways (e.g. PI3K/AKT/mTOR pathway). Finally we examine the future directions, as the opportunity to combine ivosidenib with other synergistic agents, including standard chemotherapy (CT), immune checkpoint inhibitors (ICIs), and IDH2 inhibitors.

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Contents

1. Introduction

Cholangiocarcinoma (CCA) is a relatively rare cancer, with an annual incidence of 1–2 cases per 100,000 in Western countries. Mortality rates are rising worldwide (Bertuccio, Malvezzi, Carioli, et al., 2019). The symptoms are often late and diagnosis is commonly in advanced stages. Signs and symptoms include jaundice, impaired liver function, generalized itching, abdominal pain associated with progressive weight loss. Surgical resection offers the only potential chance of recovery from cholangiocarcinoma. In contrast, for unresectable cases, the 5-year survival rate is poor, ranging from 0 to 5% (Banales, Marin, Lamarca, et al., 2020). For about 20 years, the standard of care in patients with advanced CCA included cisplatin-based chemotherapy (CT) in combination with gemcitabine. This drug combination improved survival compared with gemcitabine monotherapy in a phase III trial conducted by Valle and colleagues (Valle, Wasan, Palmer, et al., 2010).

In recent years, the advancements in molecular techniques have increased the opportunity to offer molecularly targeted therapies to patients with chemorefractory disease. Several oncogenic alterations have been identified also in CCA (Lavacchi, Roviello, & D'Angelo, 2020) [Fig. 1].

Among all molecular alterations, those of the fibroblast growth factor receptor (FGFR)-2 have been the first to be suitable for targeted therapies. Being almost exclusively limited to intrahepatic CCAs (iCCAs) with an estimated incidence of 10–16%, FGFR2 fusions or rearrangements have been identified as strong oncogenic drivers (Banales et al., 2020; Lowery, Ptashkin, Jordan, et al., 2018). Pemigatinib, a selective, potent FGFR1, 2 and 3 kinase inhibitor, was the first targeted therapy approved by the Food and Drug Administration (FDA) in April 2020 for the treatment of chemorefractory CCA. Through inhibition of FGFR phosphorylation and signaling, pemigatinib decreases growth of tumor cell lines harboring FGFR alterations (e.g. point mutations, amplifications, and fusions or rearrangements) (Liu, Koblish, Wu, et al., 2020). The efficacy and safety of pemigatinib in patients with previously treated advanced CCA, with or without FGF/FGFR alterations, was evaluated in the multicentre, single-arm, multicohort phase II trial, FIGHT-202. Only patients with FGFR2 fusions or rearrangements achieved objective response to pemigatinib: the overall response rate (ORR) was 35% and disease control rate (DCR) 82%, respectively, while no patients with other FGF/FGFR alterations or no FGF/FGFR alterations achieved benefit from treatment. Progression-free survival (PFS) was 6.9 months in patients with FGFR2 fusions or rearrangements, while the overall survival (OS) data were not mature (Abou-Alfa, Sahai, Hollebecque, et al., 2020). Mutations in the BRAF gene have been described in approximately 5–7% of patients with CCA. (Jain & Javle, 2016) The multicenter, phase II ROAR basket trial evaluated the use of dabrafenib plus trametinib in patients with BRAF V600E-mutated biliary tract cancer. The reported ORR, PFS and OS were 47%, 9 months, and 14 months, respectively (Subbiah, Lassen, Élez, et al., 2020). Another promising targeted therapy for patients with HER2 (human epidermal growth factor receptor 2) -amplified CCA is represented by zanidatamab, a bispecific antibody that simultaneously binds the two distinct HER2 epitopes ECD2 and ECD4. Encouraging results for HER2 overexpressing biliary tract cancers derived from a phase I trial (NCT02892123), in which zanidatamab showed an ORR of 40% and a DCR of 60% (Meric-Bernstam, Hanna, El-Khoueiry, et al., 2021). Other molecular alterations deemed potentially actionable by targeted therapies include neurotrophic tropomyosin receptor kinase (NTRK) gene fusions and microsatellite instability (MSI), which have paved the way for tumor-agnostic treatments also in patients with CCA (Lavacchi, Roviello, & D'Angelo, 2020).

Isocitrate dehydrogenase-1 (IDH1) belongs to the IDH protein family which also includes IDH2, and IDH3. IDHs are key metabolic enzymes involved in the metabolic pathway of cellular aerobic respiration. IDH1 is located in peroxisomes and cytoplasm, while IDH2 and IDH3 are found in the mitochondrial matrix. IDH1 and IDH2 are nicotinamide adenine dinucleotide phosphate (NADP)-dependent enzymes which exert a critical role in the tricarboxylic acid cycle, catalyzing the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) to produce NADPH from NADP+, while IDH3 isozyme utilizes NAD+ as cofactor to generate NADH. The derived NADPH and NADH are essential reducing factors involved in the cellular defense against oxidative damage IDH hotspot missense mutations map to key structural arginine residues within active-binding sites of these enzymes (p.R132 in IDH1, p.R140
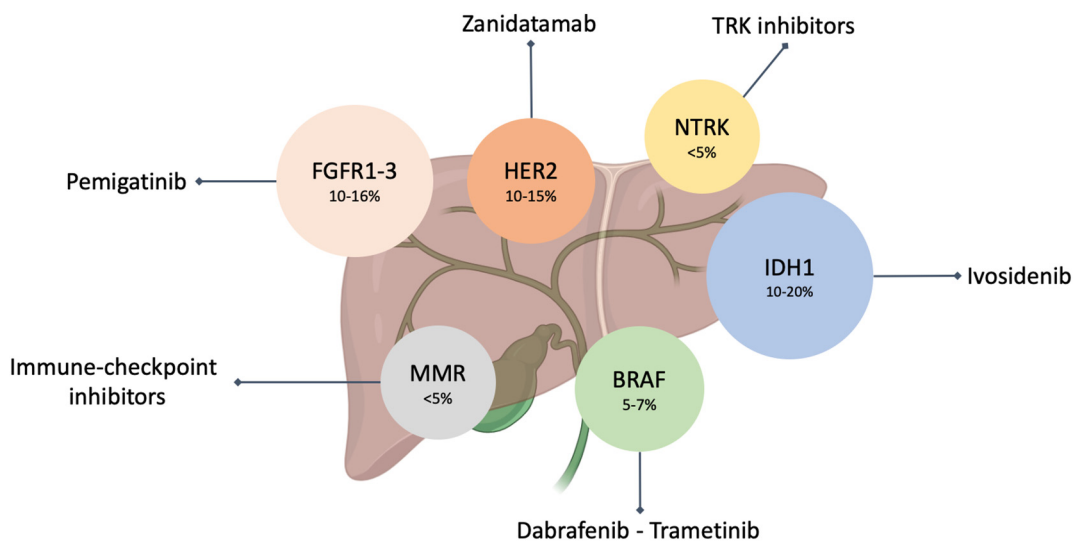

Fig. 1. Frequency of oncogenic alterations in CCAs and recent targeted therapies.

and p.R172 in IDH2). Mutant IDH enzymes have neomorphic activity and catalyze the reduction of the physiologic metabolite α-KG into the 2-hydroxyglutarate (2-HG). 2-HG acts as an oncometabolite and its accumulation leads to various epigenetic changes (i.e. DNA and histone hypermethylation and altered gene expression) which, in turn, are involved in the cell growth, hepatic stem cell differentiation, and hypoxia signaling (Dang, Yen and Attar, et al. 2016; Upadhyay, Brunner and Fathi, et al., 2017; Tommasini-Ghelfi, Murnan, Kouri, et al., 2019). [Fig. 2].

The IDH1 and IDH2 genes have been reported to be mutated in several neoplasms: IDH1 and, less frequently, IDH2 mutations have been detected in over 75% of grades II and III gliomas and secondary glioblastomas, in approximately 20% of acute myeloid leukemia (AML), in thyroid carcinomas (16%), cartilage cancers (75%), and occasionally in prostate cancers, B-cell acute lymphoblastic leukemias and paragangliomas. Gain-of-function IDH1 mutations are among the most common genetic alterations in biliary tree carcinomas: iCCAs have been reported to harbor IDH1 mutations in 10–20%, while less than 1% of extrahepatic CCAs are IDH1-mutated (Calvert, Chalastanis, Wu, et al., 2017; Lowery et al., 2018; Ye, Guan, & Xiong, 2018). Ivosidenib (AG-120) is a highly specific, allosteric, reversible inhibitor of mutant IDH1 enzyme, which can restore the normal cellular differentiation by decreasing 2-HG levels in tumor cells leading to the reversal of IDH mutation. (Popovici-Muller, Lemieux, Artin, et al., 2018) The first FDA approval for IDH1 inhibitor ivosidenib was in 2019 for the treatment of patients with IDH1-mutated AML (DiNardo, Stein, de Botton, et al., 2018) and in May 2021, it received the FDA approval for the treatment of patients with IDH1-mutated CCA whose disease has progressed to standard CT, basing on the results of the phase III ClarIDHy trial (Abou-Alfa, Macarulla, Javle, et al., 2020).

Here, we review the development of ivosidenib in CCA patients and evaluate the clinical impact of the results of the phase III ClarIDHy trial discussing the known resistance mechanisms and the future directions.

2. Development of ivosidenib in cholangiocarcinoma (CCA)

2.1. Phase I trial

Lowery and colleagues reported the results from the cohort of patients with IDH1-mutated CCA treated with ivosidenib within the phase I, multicentre, open-label, dose-escalation and dose-expansion NCT02073994 trial. The study population consisted of 73 patients previously treated with at least one gemcitabine-based line of CT. CCA was intrahepatic in 89% of patients and extrahepatic in 11%, with R132C and R132L as the most frequently reported mutant-IDH1 variants (77% and 11%, respectively).

In the dose-finding part of the trial, the starting dose of ivosidenib was 100 mg bid and a dose escalation method was used up to 1200 mg once daily. No dose-limiting toxicities were reported and the recommended dose of 500 mg once daily was established as appropriate for expansion on the basis of 2-HG levels decrease, pharmacokinetic parameters, safety, and activity data obtained from both the escalation and expansion phases. At this dose the maximal IDH1 inhibition (2-HG decrease) was achieved during the first course and no additional inhibition was observed with higher dose levels.

Ivosidenib was well tolerated and was associated with only non-serious toxicities. The most commonly reported grade (G) 3 adverse events (AEs) were ascites in 5% of patients and anemia in 4%. The prolongation of the QT interval was observed in 8 (11%) patients (G3 in 1 patient and G1–2 in 10). Dose withheld and reduction rates were 23% and 4%, respectively. Only one patient discontinued ivosidenib due to cystitis and hyponatraemia. No toxic death was reported. ORR and DCR were 5% and 61%, respectively; the median PFS was 3.8 months (95% CI 3.6–7.3) while 6- and 12-months PFS rates were 40.1% and 21.8%, respectively. Median OS was 13.8 months (95% CI 11.1–29.3). Of note, four patients have continued treatment for more than 1.5 years. Analysis of baseline genetic profile detected concomitant known or likely oncogenic mutations, including PBRM1 in 21%, ARID1A in 17%, PIK3CA in 13%, and KRAS in 11%, in most of the patients enrolled in the study. However, no additional mutation was identified to be predictive of response to ivosidentib. Moreover, new acquired co-mutations were found to develop during treatment, including IDH2-R172V and IDH1-R132F at disease progression (PD), and mutations in TP53, ARID1A, POLE, PIK3R1, and TBX3 (Lowery, Burris 3rd, Janku, et al., 2019) [Tables 1, 2].

Exploratory analyses suggested that mild or moderate renal impairment or mild liver impairment did not affect pharmacokinetic parameters and plasma clearance of ivosideinb, as well as baseline patient characteristics or concomitant administration of weak CYP3A4 inducers or inhibitors (Fan, Mellinghoff, Wen, et al., 2020).
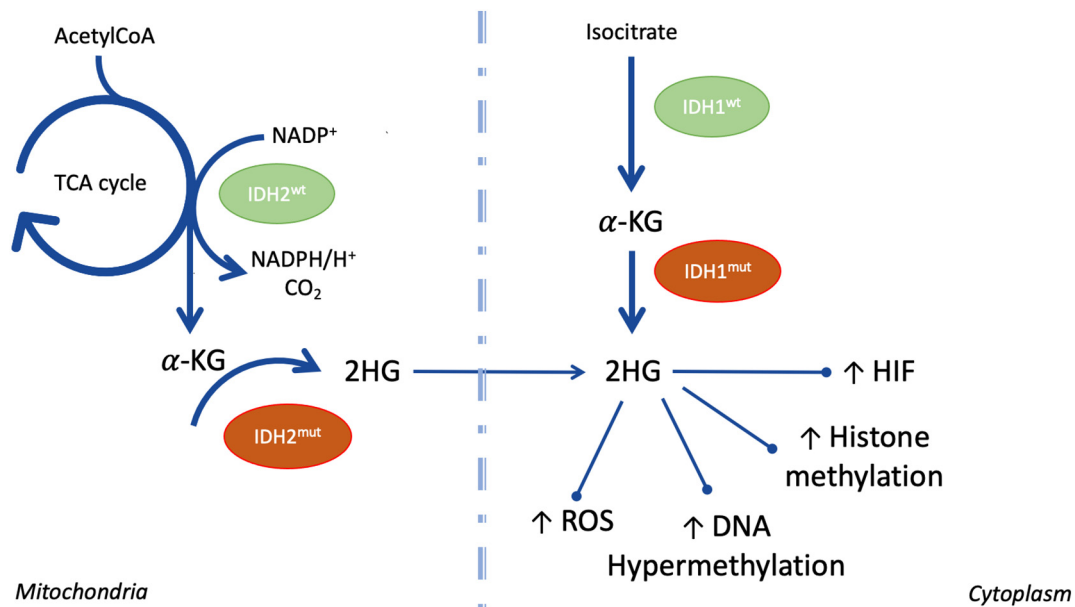

Fig. 2. Overview of IDH2 and IDH1 activity.

Table 1
Summary of the main trials of ivosidenib in cholangiocarcinoma (CCA) patients.

Trial	Phase	Treatment setting	Arms	Number of patients with CCA	Most frequent concomitant mutations at baseline (%)	Primary end-point	ORR (%)	DCR (%)	PFS (months)	OS (months)
ClarIDHy (Abou-Alfa, Macarulla, et al., 2020; Zhu et al., 2021)	III	After at least 1 and no more than 2 prior CT regimens	-Ivosidenib 500 mg in continuos	187	11% PIK3CA 7% KRAS 4% BRAF 4% FGFR2	PFS	2 vs 0	51 vs 28	2.7 vs 1.4	10.3 vs 7.5 (5.1 RPSFT-adjusted)
Lowery et al. (Lowery et al., 2019)	I	After at least 1 gemcitabine-based CTregimen	-Placebo Ivosidenib 200–1200 mg daily	73	21% PBRM1 17% ARID1A 13% PIK3CA 11% KRAS.	Safety, tolerability, maximum tolerated dose, and recommended dose for phase 2.	5%	61%	3.8	13.8

Abbreviations: CCA: cholangiocarcinoma; CT: chemotherapy; DCR: disease control rate; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RPSFT: prespecified rank-preserving structural failure time.

Table 2
Adverse events (AEs) of ivosidenib in cholangiocarcinoma (CCA) patients.

Trial	Arms	Nausea G ≥ 3 (%)	Vomiting G ≥ 3 (%)	Fatigue G ≥ 3 (%)	Anemia G ≥ 3 (%)	AST increase G ≥ 3 (%)	Blood bilirubin increase G ≥ 3 (%)	QT prolongation (%)	Dose reduction rate (%)	Discontinuation rate due to treatment-related AEs (%)
ClarIDHy (Abou-Alfa, Macarulla, et al., 2020; Zhu et al., 2021)	-Ivosidenib 500 mg (including crossover patients)	2 vs 2	2 vs 0	3 vs 2	7 vs 0	5 vs 2	6 vs 2	1 vs 0	4 vs 0	7 vs 8
Lowery et al. (Lowery et al., 2019)	-Placebo Ivosidenib 200–1200 mg daily	1	0	3	4	NR	NR	1	4%	1%

Abbreviations: AE: adverse event; CCA: cholangiocarcinoma; G: grade; NR: not reported.

2.2. Phase III trial

The selective mechanism of action and preliminary data from the phase I trial supported the development of ivosidenib within a phase III trial.

ClarIDHy was a randomized, multicentre (49 centers in 6 countries), double-blind trial comparing ivosidenib to placebo in patients with advanced IDH1-mutated CCA previously treated with up to two chemotherapy regimens. Eligibility included a life expectancy of at least 3 months and ECOG PS of 0 or 1. Patients were randomly assigned to ivosidenib 500 mg or placebo once daily in continuous 28-day cycles. Crossover from placebo to ivosidenib was permitted in case of PD. The primary endpoint was PFS; secondary endpoints included OS, ORR, safety, and quality of life (Abou-Alfa, Macarulla, et al., 2020).

At the data cut-off (May 2020 for the final OS analysis), 187 patients were randomly assigned to receive ivosidenib ($n = 126$) or placebo ($n = 61$); in contrast, 44 patients (19%) were ineligible because of the absence of documented IDH1-mutant disease or having an ECOG PS greater than 2. Patient characteristics were similar in the two groups. Most of patients (93%) had a stage IV disease, and 88 patients (47%) failed 2 prior lines of therapy. Primary tumor location was intrahepatic in 91% of cases. Among the IDH1 variants, the vast majority of patients (70%) had R132C mutation. The most frequent genes harboring co-mutations at baseline included PIK3CA (11%), KRAS (7%), BRAF (4%), and FGFR2 (4%). IDH2 co-mutation at baseline was detected in only 1% of patients (Zhu, Maraculla, Javle, et al., 2021).

The study met its primary endpoint: median PFS was 2.7 months in the ivosidenib arm and 1.4 months in the placebo arm (HR 0.37; 95% CI 0.25–0.54; $p < 0.0001$). PFS rates at 6 and 12 months were 32% and 22%, respectively; in contrast, all patients in the placebo group experienced PD within 6 months (Abou-Alfa, Macarulla, et al., 2020).

Final OS analysis showed a clinically significant benefit from ivosidenib over placebo: median OS was 10.3 months (95% CI, 7.8–12.4 months) in the ivosidenib group and 7.5 months (95% CI, 4.8–11.1 months) in the placebo group (HR, 0.79, 95% CI 0.56–1.12). At the data cut-off, 43 patients in the placebo group crossed over to ivosidenib. The difference in OS between the two groups was amplified when adjusted for crossover: adjusted median OS was 5.1 months in patients treated with placebo (HR 0.49; 95% CI, 0.34–0.70; 1-sided $p < 0.001$). With a median treatment duration of 2.8 months in the ivosidenib group and 1.6 months in the placebo group, the longest treatment durations were 34.4 and 6.9 months, respectively.

ORR was 2% in the ivosidenib group and 0% in the placebo group, while DCR was 53% vs 28%.

Overall, the safety profile of ivosidenib was favorable. The most common AEs in both groups, including crossover patients, were G1–2 nausea (36% in the ivosidenib group vs 27% in the placebo group), diarrhea (33% vs 17%), and fatigue (26% vs 15%). The most frequent G3–4 AEs in the ivosidenib arm were ascites in 9%, blood bilirubin increase in 5%, and anemia in 7%. Notably, G3–4 ascites and bilirubin increase occurred also in the placebo arm in 7% and 2%, respectively. Prolonged QT interval was reported in 13 patients (8%) receiving ivosidenib and 2 patients (3%) receiving placebo. Dose reduction due to AEs occurred in 5 patients (4%) in the ivosidenib group and ivosidenib discontinuation in 9 patients (7%) (Zhu et al., 2021) [Tables 1, 2].

3. Current perspectives and clinical evaluation

Treatment options for patients with chemorefractory biliary tract cancer are limited, and the chance for long-term disease control decreases across the treatment lines. The second-line treatment opportunities for CCA have not achieved satisfactory results. To date, the one-

size-fits-all approach includes a fluoropyrimidine-based CT combination (e.g. FOLFOX or FOLFIRI), but results are disappointing and toxicities deserve close attention (Benson, D'Angelica, Abbott, et al., 2021). In the ABC-06 trial, FOLFOX demonstrated a survival benefit over active symptom control in a molecularly unselected patient population, but clinical impact was quite small in magnitude, although statistically significant (6.2 months vs 5.3 months for OS, adjusted HR 0.69, $p = 0.031$), and only 5% of patients obtained an objective response. Overall, 69.0% of patients treated with FOLFOX experienced G ≥ 3 AEs (38% treatment-related G3–5 AEs), including treatment-related neutropenia in 12%, fatigue or lethargy in 11% and infective events in 10%. Three treatment-related deaths were reported. The ABC-06 study population was clearly different from that of the ClarIDHy trial: extrahepatic, gallbladder or ampulla tumor site was in 58% of patients in the FOLFOX arm of the ABC-06 study; in contrast, only 4% of patients in the ivosidenib arm of the CLARIDH study had extrahepatic location and this was consistent with the frequency of the IDH mutation in extrahepatic CCA. (Lamarca, Palmer, Wasan, et al., 2021; Zhu et al., 2021).

Targeting IDH1, the use of ivosidenib belongs to the tailored approach. However, several strengths and limitations have to be addressed. First of all, the ClarIDHy trial showed a clear survival benefit from ivosidenib in previously treated patients, with a prespecified rank-preserving structural failure time (RPSFT)-adjusted HR for OS of 0.49 (95% CI 0.34–0.70; 1-sided $p < 0.001$). More than two-thirds of patients, indeed, crossed over to ivosidenib upon PD. As previously reported, adjusting for patient crossover, median OS was 10.3 months with ivosidenib and 5.1 months with placebo. Secondly, the favorable safety profile makes ivosidenib a suitable option for previously treated patients. Only 7% of patients experienced G ≥ 3 treatment-related AEs with no toxic deaths. Overall, the low incidence of AEs and treatment discontinuation due to toxicity, associated with a significantly less marked decline in health-related quality of life for patients in the ivosidenib group, facilitate patient adherence and clinician confidence (Abou-Alfa, Macarulla, et al., 2020; Zhu et al., 2021).

Among the weaknesses, the numerically low rate of objective response is the main critical point and does not make ivosidenib the best candidate for tumor shrinkage (Aguado-Fraile, Tassinari, Ishii, et al., 2021). However, other CT regimens did not offer numerically higher rates of response in second- or further-line of treatment (Benson et al., 2021; Lamarca et al., 2021). In addition, the benefit offered by ivosidenib might not exclusively correlate with RECIST response, since pre-clinical and clinical evidence suggests that histological changes (i.e. decrease in the quantity of cytoplasm, cellular differentiation) might also have an impact on survival. Ivosidenib has been reported to promote a change from biliary differentiation to hepatocyte differentiation, as revealed by the increased expression of HNF-4α target genes and reduced bile duct markers (Aguado-Fraile et al., 2021; Saha, Parachoniak, Ghanta, et al., 2015). The study conducted by Aguado-Fraile et al. identified the expression of hepatocyte-specific genes and, simultaneously, downregulation of biliary lineage genes as factors associated with prolonged PFS in patients treated with ivosidenib (Aguado-Fraile et al., 2021).

Another limitation is the lack of a control arm with standard CT that precludes a precise estimate of the real benefit offered by ivosidenib in patients eligible for every second-line treatment (Abou-Alfa, Macarulla, et al., 2020). Cross trial comparison is not reliable since, as previously specified, there are also significant differences in primary tumor location between studies and these differences can have a significant impact on survival. (Lamarca, Ross, Wasan, et al., 2020) In addition, the cost of therapy is a very real concern, so the cost-effectiveness must be carefully evaluated by relating the magnitude of clinical benefit with the potential economic impact on health systems (Gervaso, Pellicori, & Fazio, 2020).

4. Resistance mechanisms

To date, the exact mechanisms of primary and acquired resistance to ivosidenib have not been completely explored.

In the study of DiNardo et al., the high co-mutational burden at baseline, specifically for mutations in receptor tyrosine kinase (RTK) pathway genes (e.g. NRAS, FLT3, PTPN11 and KRAS), was identified as predictive of suboptimal response in patients with IDH1-mutated relapsed or refractory AML. At baseline, the most frequently reported genes with co-occurring mutations likely involved in primary treatment resistance in IDH1-mutated AML were DNMT3A, NPM1, SRSF2, ASXL1, RUNX1, NRAS, and TP53 (Choe, Wang, DiNardo, et al., 2020; DiNardo et al., 2018). In contrast, although also in patients with IDH1-mutated CCA, enrolled in the phase I study conducted by Lowery et al., several concomitant mutations were detected at baseline, including those in PBRM1 (21%), ARID1A (17%), PIK3CA (13%), and KRAS (11%). None of them had a statistically significant association with primary resistance or response to ivosidenib, indicating that concurrent baseline mutations are not universal resistance mechanisms (Lowery et al., 2019). In a recent systematic review collecting 45 publications of which 11 with available data on concomitant alterations, ARID1A, BAP1 mutation or loss, and PBRM1 were the most frequently reported co-mutations, with incidence of 22.0%, 15.5%, and 13.3%, respectively, while other mutations were reported in less than 8% of cases (Boscoe, Rolland, & Kelley, 2019). Interestingly, ARID1A, BAP1 and PBRM1 are chromatin-remodeling genes and frequently harbor inactivating mutations in iCCA. These mutations have been identified as promising biomarkers for immune checkpoint inhibitors in several cancers (Jiao, Pawlik, Anders, et al., 2013; Lavacchi, Pellegrini, Palmieri, et al., 2020). However it is unclear whether incidence of co-mutations differ between IDH1-mutated and wild-type IDH1 iCCAs (Boscoe et al., 2019).

Acquired co-mutations that emerged during treatment, including those in RTK pathway genes, have been considered responsible for several cases of secondary resistance to IDH1 inhibitors. However, evidence derived mainly from studies on AML, while in solid tumors the real impact of specific acquired mutations in drug resistance requires further investigations (Lavacchi, Pellegrini, et al., 2020; Lowery et al., 2019). In the study of Aguado-Fraile et al., matching pre- and on-treatment biopsy samples, early PD was associated with enhanced activation of the PI3K/AKT/mTOR pathway, but no activating mutation has been observed to be directly responsible for drug resistance (Aguado-Fraile et al., 2021). Among acquired co-mutations, of particular interest is the development of IDH2 mutations. This results in restoration of 2-HG production, leading to altered histone and DNA demethylation and, as consequence, disruption of cellular differentiation. Harding et al. reported a case of a patient with IDH1 R132C-mutated CCA who experienced PD after initial response to ivosidenib. Remarkably, post-progression biopsy revealed several additional mutations including IDH2 R172V mutation and CDKN2A/B loss. Likewise, authors described the development of IDH2 mutation as an acquired resistance mechanism to ivosidenib also in patients with IDH1-mutated AML. A distinctive feature of the case series was the longitudinal monitoring of cell-free DNA (cfDNA) for IDH1 and IDH2 mutations. Specifically, the clearance of IDH1-mutant allele was associated with treatment response and the emergence of IDH2 mutations was strictly related to PD (Harding, Lowery, Shih, et al., 2018). This is really intriguing, as liquid biopsy might be a reliable biomarker for real-time monitoring of drug resistance and to guide the choice of treatment. However, a crucial issue is the interpretation of the polyclonal resistance mechanisms underlying PD (Choe et al., 2020). Another mechanism of secondary resistance has been supposed to be the acquisition of a second-site mutation in IDH1 that sterically hinders ivosidenib from binding to mutant IDH1 isoform. Although biologically reasonable and reported in AML patients

Table 3
Selected ongoing trials with ivosidenib in solid tumors.

Clinical trial identifier	Kind of tumor	Phase	Setting	Primary endpoint	Status
NCT04056910	IDH1-mutated gliomas and advanced solid tumors	II	Advanced disease in combination with nivolumab after appropriate standard of care treatment options.	ORR, 6mPFS	Recruiting
NCT04088188	IDH1-mutated CCA	I	First-line in combination with cisplatin plus gemcitabine after at least 3 cycles of CT alone without PD.	Safety, tolerability, maximum tolerated dose and/or recommended phase 2 dose.	Recruiting

Abbreviations: CCA: cholangiocarcinoma; CT: chemotherapy; IDH1: isocitrate dehydrogenase-1; ORR: overall response rate; 6mPFS: progression-free survival at 6 months.

at disease relapse, its real clinical impact has yet to be definitively assessed in CCA patients (Choe et al., 2020; Intlekofer, Shih, Wang, et al., 2018; Quek, David, Kennedy, et al., 2018; Oltvai, Harley, Koes, et al., 2021). Of note, the various mechanisms of acquired resistance are not mutually exclusive, but can occur in isolation or in combination, as described for two AML patients who developed second-site IDH1 mutation and IDH2 mutation during treatment and for other five patients in which secondary mutations were detected in both RTK pathway genes and IDH1 and/or IDH2 at PD (Choe et al., 2020). All together, these findings underline the complex cellular and molecular biology that drive resistance to IDH inhibitors and support the potential use of ivosidenib in combination with other therapies to prevent the emergence of new resistance mechanisms.

5. Future directions

Given the manageable safety profile, ivosidenib seems to be an excellent candidate for combination studies with other synergistic agents [Table 3]. A phase II trial (NCT04056910) is evaluating the combination of ivosidenib and nivolumab in patients with IDH1-mutated advanced solid tumor after failure of standard treatments, while a phase I trial (NCT04088188) is investigating ivosidenib in combination with cisplatin and gemcitabine in advanced IDH1-mutated CCA.

A promising approach for further developments could be represented by the IDH1/IDH2 dual inhibition. Since the mutant IDH isoform switching seems to be one of the main mechanisms of early resistance to IDH inhibition, the dual inhibition strategy aims at preventing the restoration of 2HG production (Harding et al., 2018). This could result in prolonging the duration of response and increasing the rate of responders. Unfortunately, the real frequency of mutant IDH isoform switching as secondary resistance to ivosidenib remains uncertain and translational studies including circulating tumor DNA sequencing in patients enrolled in the ClarIDHy trial are ongoing (Zhu et al., 2021). Two phase I trials are evaluating the safety of HMPL-306, a dual IDH1/IDH2 inhibitor, in patients with IDH-mutated advanced or metastatic solid tumors including CCA (NCT04762602) and in patients with IDH-mutated advanced hematological malignancies (NCT04764474). Another dual IDH1/IDH2 inhibitor, vorasidenib, is currently under investigation in the phase III AG881-C-004 trial (NCT04164901), including patients with IDH-mutated residual or recurrent grade 2 glioma, and in a phase I trial (NCT04603001), including patients with IDH-mutated advanced hematologic malignancies.

In conclusion, despite some issues highlighted above, the positive results in OS improvement, associated with the favorable safety profile, make ivosidenib one of the main option for second- or further line of treatment in IDH1-mutated CCA. In the ClarIDHy trial, quality of life assessed by the QLQ-C30 physical functioning score declined in patients receiving placebo, whereas it was preserved in those receiving ivosidenib (Zhu et al., 2021). Outside the clinical trial framework, ivosidenib seems to be a feasible therapy in non-favorably selected populations including elderly or frail patients who are not optimal candidates for intensive chemotherapy (Roboz, DiNardo, Stein, et al., 2020).

Advances in longitudinal monitoring of drug resistance, through liquid biopsy, and comprehensive knowledge of primary and secondary resistance mechanisms are expected.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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