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Clinical development of IDH1 inhibitors for cancer therapy

Mehrdad Zarei [a,b,1], Jonathan J. Hue [b,1], Omid Hajihassani [a], Hallie J. Graor [a], Erryk S. Katayama [c], Alexander W. Loftus [b], David Bajor [d], Luke D. Rothermel [a,b], Ali Vaziri-Gohar [a], Jordan M. Winter [a,b,*]

[a] Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, United States
[b] Department of Surgery, Division of Surgical Oncology, University Hospitals Cleveland Medical Center, Cleveland, OH, United States
[c] Case Western Reserve University, Cleveland, OH, United States
[d] Department of Medicine, Division of Oncology, University Hospitals Cleveland Medical Center, Cleveland, OH, United States

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ABSTRACT

Isocitrate dehydrogenase 1 (IDH1) has been investigated as a promising therapeutic target in select cancers with a mutated version of the enzyme (mtIDH1). With only one phase III trial published to date and two indications approved for routine clinical use by the FDA, we reviewed the entire clinical trial portfolio to broadly understand mtIDH1 inhibitor activity in patients. We queried PubMed.gov and ClinicalTrials.gov to identify published and ongoing clinical trials related to IDH1 and cancer. Progression-free survival (PFS), overall survival (OS), 2-hydroxyglutarate levels, and adverse events were summarized. To date, ten clinical trials investigating mtIDH1 inhibitors among patients with diverse malignancies (cholangiocarcinoma, acute myeloid leukemia, chondrosarcoma, glioma) have been published. Almost every trial (80%) has investigated ivosidenib. In multiple phase I trials, ivosidenib treatment resulted in promising radiographic and biochemical responses with improved survival outcomes (relative to historic data) among patients with both solid and hematologic mtIDH1 malignancies. Among patients enrolled in a phase III trial with advanced cholangiocarcinoma, ivosidenib resulted in a PFS rate of 32% at 6 months, as compared to 0% with placebo. There was a 5.2 month increase in OS with ivosidenib relative to placebo, after considering crossover. The treatment-specific grade ≥3 adverse event rate of ivosidenib was 2%-26% among all patients, and was just 3.6% among 284 patients who had a solid tumor across four trials. Although <1% of malignancies harbor IDH1 mutations, small molecule mtIDH1 inhibitors, namely ivosidenib, appear to be biologically active and well tolerated in patients with solid and hematologic mtIDH1 malignancies.

Introduction

Since the validation of targeted cancer therapies in the late 1990s, numerous active agents have been developed against a variety of different cancer types. Rituximab and trastuzumab were among the first examples, which proved to be highly effective against B-cell lymphoma and HER2-positive breast cancer, respectively [1,2]. In the last seven years alone, 83 drugs aimed at 56 different targets have been approved by the United States Food & Drug Administration (FDA) for the treatment of solid and hematologic malignancies [3]. From this list of therapeutic targets, only two core metabolic enzymes have been targeted: isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2). Ivosidenib is approved to inhibit mutant (mt) IDH1 in patients with relapsed or refractory mtIDH1 acute myeloid leukemia (AML) and advanced or metastatic mtIDH1 cholangiocarcinoma [4,5]. Enasidenib is approved to target mtIDH2 in patients with relapsed or refractory mtIDH2 AML [6]. Metabolic enzymatic targets such as these are actionable and therefore represent attractive therapeutic opportunities when research efforts validate them as metabolic dependencies or vulnerabilities specific to tumors.

IDH1 is a cytosolic enzyme and the most commonly mutated metabolic enzyme in cancer [7]. The wild-type (wtIDH1) enzyme catalyzes a reversible reaction that interconverts isocitrate and alpha-ketoglutarate (αKG), with NADP+ and NADPH as cofactors (Fig. 1) [8-10]. Both reaction products of the oxidative conversion are important for cancer biology. Alpha-ketoglutarate is able to enter the tricarboxylic acid cycle

* Corresponding author.
E-mail address: Jordan.Winter@UHHospitals.org (J.M. Winter).
[1] These authors contributed equally to this manuscript.

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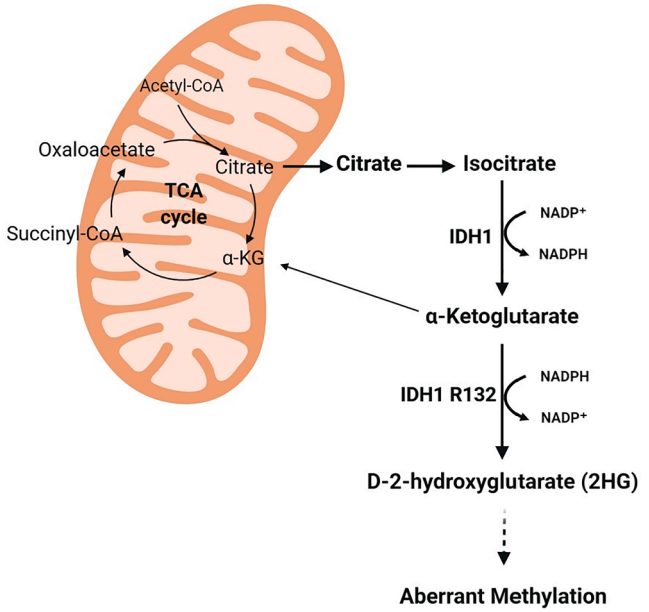

Fig. 1. Schematic of IDH1 activity.

as an anaplerotic metabolite, and therefore contributes to mitochondrial energy production. NADPH is important for detoxification of reactive oxygen species (ROS) and macromolecule synthesis. Mutations in IDH1 result in a loss of these functions, but the neomorphic mtIDH1 confers a selective advantage in certain cancer types (Fig. 1) [11,12]. The classic mutation occurs at arginine 132 (R132), creating an altered catalytic pocket [9]. This mutational change drives the conversion of αKG into an oncometabolite, 2-hydroxyglutarate (2-HG). This reaction consumes NADPH to regenerate $NADP^+$, which could impair a cancer's antioxidant capabilities. However, increased levels of 2-HG have pro-tumor effects. The oncometabolite promotes carcinogenesis and blocks cellular differentiation by inhibiting protein and DNA demethylating enzymes, thereby promoting methylation and epigenetic marks [11,13,14]. Thus, the oncometabolite promotes tumor dedifferentiation and a stem cell-like behavior [15].

Reported gain-of-function IDH1 mutations occur in secondary glioblastomas (~70% [16]), low grade or anaplastic gliomas (~70% [17,18]), central chondrosarcomas (>55% [19]), intrahepatic cholangiocarcinomas (13% [20]), AML (10–20% [16,18,21]), malignant melanoma (~10% [22]), and anaplastic thyroid cancer (~10% [23]) (Fig. 2). The presence of mtIDH1 has a variable impact on prognosis across these cancers. Reported outcomes do not differ based on IDH1 mutation status among patients with genotyped cholangiocarcinoma [24]. One prior study of patients with AML demonstrated that complete remission rates and overall survival were not associated with IDH1 mutation status [25]; however, a second study identified an association between mtIDH1 and poor outcomes [26]. IDH1 (or IDH2) mutations have been associated with prolonged relapse-free and metastasis-free survival among patients with chondrosarcoma [27], while another study reported an association between IDH1 mutations and worse overall survival [28]. There is a consensus that patients harboring low grade gliomas with mtIDH1 have prolonged survival as compared to wtIDH1 tumors [29].

Several small molecule inhibitors have been developed that are selective for mtIDH1, including ivosidenib (AG-120), BAY1436032, LY3410738, DS-1001b, IDH305, and olutasidenib (FT-2102). Out of this list of compounds, ivosidenib (previously referred to as AG-120 in preclinical drug development) has progressed through numerous clinical trials and is the only one granted FDA approval [30]. This drug binds to

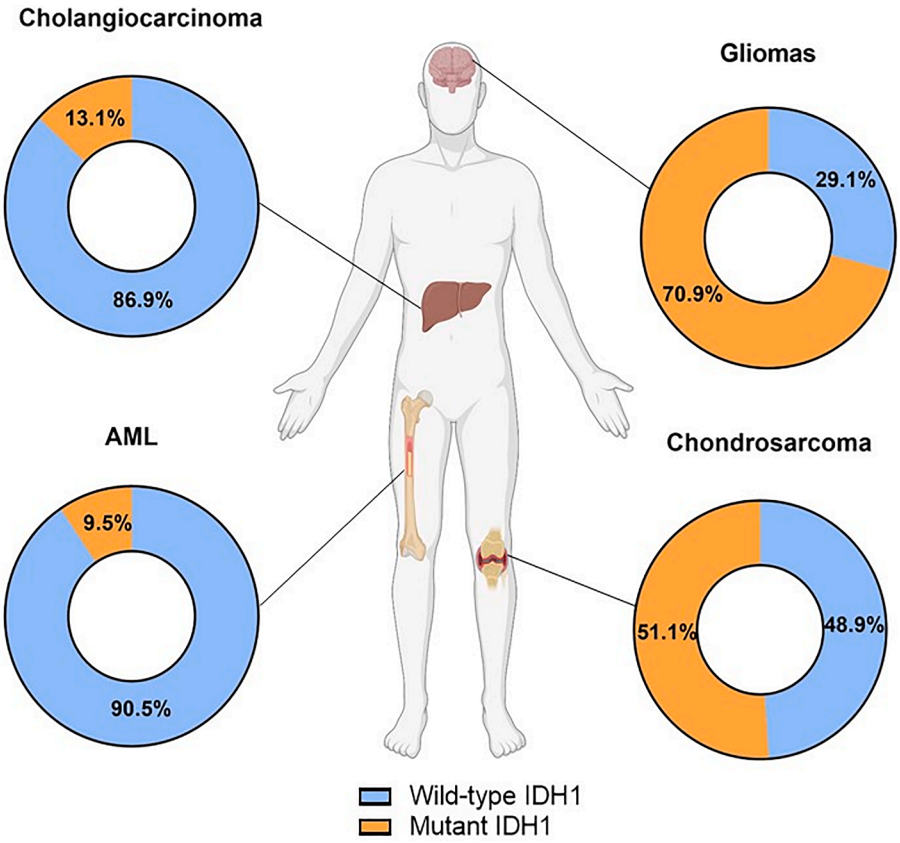

Fig. 2. Proportion of patients with wtIDH1 and mtIDH1, across several solid and hematologic malignancies, including cholangiocarcinoma, acute myeloid leukemia (AML), gliomas, and chondrosarcoma.

an allosteric pocket and disrupts conversion between open and closed forms of mtIDH1. As a result, the mtIDH1 enzyme is unable to effectively toggle between an open binary (IDH1 R132-NADP+) and a closed ternary (IDH1 R132-NADP+-αKG) complex, which prevents efficient enzyme turnover [31]. The activities of multiple mtIDH1 inhibitors are well characterized in pre-clinical studies [32-37]. Herein, we analyze all available clinical trial experience to determine the efficacy of mtIDH1 inhibitors in cancer.

Methods

The ClinicalTrials.gov registry was queried in September 2021. Separate searches were performed including the search terms "IDH1 and cancer" and "mutant IDH1 and cancer". Trials exclusively focusing on isocitrate dehydrogenase 2 (IDH2) inhibitors or pan-IDH inhibitors were excluded from this analysis. All cancer types and clinical trial phases (I, II, III) were included. Trials were classified as "Completed", "Recruiting", "Active, not recruiting", "Not yet recruiting", or "Withdrawn". Additionally, PubMed.gov was queried for published trials using the search terms "IDH1" and "clinical trial". Further, PubMed.gov was queried for additional published clinical trials using individual names of existing mtIDH1 inhibitors.

For each trial, we abstracted the type of cancer and stage of disease, other prior or concurrent therapies administered, progression-free survival (PFS), overall survival (OS), adverse effects or toxicity data, response rates, and biochemical responses (2-HG levels), when available. For later phase trials, survival comparisons with patients receiving placebo were included. Where these comparisons were not available, such as in early phase trials, comparisons were made with historical control groups as a reference or benchmark of expected clinical activity. Toxicity grading was based on the Common Terminology Criteria for Adverse Events. Grade 3 (severe) and 4 (life-threatening) toxicities were considered to be significant adverse events. When possible, rates of treatment-specific significant adverse events (i.e., those deemed related to the mtIDH1 inhibitor) were reported.

Results

Published trials

To date, ten clinical trials have published outcome data on survival (Table 1a), response rates (Table 1b), and toxicities (Table 2) of patients administered mtIDH1 inhibitors. Eight of the ten trials (80%) have used

Table 1a
Summary of reported survival outcomes across published clinical trials investigating the efficacy of mtIDH1 inhibitors.

Malignancy & trial reference	mtIDH1 inhibitor & concurrent therapies	Previous therapies	Number of patients & trial phase	Overall survival	Overall survival, control	Progression-free survival	Progression-free survival, control
Cholangio-carcinoma [41]	Ivosidenib	Chemotherapy	73 patients Phase I	- Median: 13.8 months	- Median: 6.7 months [40]	- Median: 3.8 months – 40.1% at 6 months – 21.8% at 12 months	Median: 3.2 months [40]
Cholangio-carcinoma [42,43]	Ivosidenib	Chemotherapy	185 patients – 126 ivosidenib – 61 placebo Phase III	- Median: 10.3 months - HR 0.49, p < 0.001	- Median: 5.1 months (without crossover)	- Median: 2.7 months – 32% at 6-months - HR 0.37, p < 0.0001	- Median: 1.4 months – 0% at 6-months
Chondro-sarcoma [19]	Ivosidenib	Systemic therapy, surgery, radiotherapy	60 patients Phase I	–	–	- Median: 5.6 months – 39.5% at 6-months	- Median: 3.5–4.7 months [44,45]
Glioma [17]	Ivosidenib	Systemic therapy, radiotherapy	27 patients Phase I	–	–	- Median: 13.6 months, non-enhancing tumors - Median: 1.4 months, enhancing tumors	- Median: 7 months [29]
AML (refractory or relapsed) [21]	Ivosidenib	Bone marrow transplantation, chemotherapy, other	125 patients* Phase I	- Median: 8.8 months	- Median: 3.3–3.5 months [47]	–	
AML (chemotherapy ineligible) [46]	Ivosidenib	Hypomethylating agents	66 patients Phase I	- Median: 12.6 months	- Median: 6 months [51]	–	
AML (chemotherapy ineligible) [52]	Ivosidenib (with azacitidine)	None	23 patients Phase I	- Median: not reached (16.1 months of follow-up) – 82% 12-month survival	- Median: 7.7–10.4 months [53,54]	–	
AML (treatment naive) [55]	Ivosidenib (with multiagent chemotherapy)	None	34 patients Phase I	- Median: not reached (9.3 months of follow-up) – 78% predicted 12-month survival	- Historic data not available	–	
Multiple solid tumors [56]	BAY1436032	Systemic therapy, radiotherapy	81 patients Phase I	–	–	– 25% at 3 months	–
AML (refractory or relapsed) [57]	BAY1436032	Systemic therapy, allogeneic transplantation	23 patients Phase I	- Median: 6.6 months	- Median: 3.3–3.5 months [47]	–	–

* Represents the primary efficacy population of this trial (those with refractory or relapsed AML with at least 6 months of follow-up).

Table 1b
Summary of reported radiographic and biochemical responses across published clinical trials investigating the efficacy of mtIDH1 inhibitors.

Malignancy & trial reference	mtIDH1 inhibitor & concurrent therapies	Previous therapies	Stable disease	Stable disease, control	Partial response	Partial response, control	Complete response/ remission	Complete response/ remission, control	2-HG response
Cholangio-carcinoma [41]	Ivosidenib	Chemotherapy	56.2%	37.6% [40]	5.5%	11.8% [40]	0%	0% [40]	– 94.5% of patients
Cholangio-carcinoma [42]	Ivosidenib	Chemotherapy	51%	28%	2.4%	0%	0%	0%	– 97% decrease from baseline
Chondro-sarcoma [19]	Ivosidenib	Systemic therapy, surgery, radiotherapy	52.4%	41% [44]	0	14% [44]	0	1% [44]	– 100% of patients – 14%-94% decrease from baseline
Glioma [17]	Ivosidenib	Systemic therapy, radiotherapy	– 66.7%, overall – 85.7%, non-enhancing – 45.2%, enhancing	–	0	–	0	–	–
AML (refractory or relapsed) [21]	Ivosidenib	Bone marrow transplantation, chemotherapy, investigational therapies	35.2%	–	0	–	30.4%	19.4% [47]	–
AML (chemotherapy ineligible) [46]	Ivosidenib	Hypomethylating agents	30.3%		3.0%		42.4%		–
AML (chemotherapy ineligible) [52]	Ivosidenib (with azacitidine)	None	17.4%	24.2–29.5% [53,54]	–	1.2–3.7% [53,54]	60.9%	17.8–27.8% [53,54]	–
AML (treatment naive) [55]	Ivosidenib (with multiagent chemotherapy)	None	–	–	–	–	68%	–	90.6%
Multiple solid tumors [56]	BAY1436032	Systemic therapy, radiotherapy	40.8%	–	4.2%	–	1.4%	–	– 76% median maximal decrease
AML (refractory or relapsed) [57]	BAY1436032	Systemic therapy, allogeneic transplantation	66.7%	–	3.7%	–	11.1%	19.4% [47]	– 100% of patients – 66% median maximal decrease

the mtIDH1 inhibitor, ivosidenib. Patients in the other two published trials (20.0%) received BAY1436032. Data from the trials are summarized below, and are categorized by the target malignancy.

Ivosidenib

Cholangiocarcinoma: The median OS of patients with advanced or metastatic biliary cancer treated with first-line cisplatin and gemcitabine in the landmark ABC-02 trial was 11.7 months, and PFS was 8.0 months [38]. Patients with advanced or metastatic biliary tract cancers who progressed on cisplatin and gemcitabine were randomized to FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or symptomatic management in the ABC-06 trial [39]. The median OS was 6.2 months among patients who received FOLFOX and 5.3 months in the cohort who received symptomatic management [39]. Similarly, the previously reported median OS and PFS among patients with advanced biliary cancers on second-line chemotherapy were just 6.7 and 3.2 months, respectively, in a retrospective analysis [40].

Two published clinical trials tested ivosidenib in patients with mtIDH1 cholangiocarcinoma, including an initial phase I trial [41] and a follow-up phase III trial [42] with recently published long-term results [43]. In the phase I trial, 73 patients with advanced, unresectable, or metastatic mtIDH1 cholangiocarcinoma (89% intrahepatic, 11% extrahepatic) who received previous gemcitabine- or fluorouracil-based chemotherapy were administered ivosidenib to determine safety and tolerability (i.e., second-line) [41]. The median PFS was 3.8 months and the median OS was 13.8 months (**Table 1**), both of which are remarkable advances over historical controls [39,40]. Almost all patients (94.5%) experienced reductions in plasma 2-HG levels in the phase I ivosidenib study, reflecting robust biologic and pharmacodynamic activity [41]. In this trial, ivosidenib was well tolerated at all doses, as only 5.5% of patients experienced a grade $\geq$ 3 complication attributed to ivosidenib (Table 2) [41].

Results from the international phase III "ClarIDHy" trial of ivosidenib utilization in patients with advanced or metastatic, chemotherapy-resistant cholangiocarcinoma (91% intrahepatic) were recently published [42,43]. Among previously treated patients randomized to receive ivosidenib, the median PFS was 2.7 months, as compared to 1.4 months for patients who received placebo in the same study (hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.25–0.54, **Table 1**) [42]. Importantly, 32% of patients receiving ivosidenib were free of disease progression at 6 months, as compared to 0% of patients receiving placebo [42]. In the intention-to-treat population, the median OS of patients receiving ivosidenib was 10.3 months and was 7.5 months in those

Table 2
Summary of adverse events.

Malignancy	mtIDH1 inhibitor	Grade ≥ 3 adverse event rate	Common toxicities	Ref
Cholangiocarcinoma	Ivosidenib	5.5%*	Fatigue (2.7%), hypophosphatemia (1.4%), increased alkaline phosphatase (1.4%)	[41]
Cholangiocarcinoma	Ivosidenib	2.4%*	Jaundice (<1%), hyperbilirubinemia (<1%), pleural effusion (<1%)	[42]
Chondrosarcoma	Ivosidenib	4.8%*	Hypophosphatemia (4.8%)	[19]
Glioma	Ivosidenib	3.0%*	Neutropenia (1.5%), Weight loss (1.5%), Hyponatremia (1.5%), Arthralgia (1.5%)	[17]
AML	Ivosidenib	25.6%*	QTc prolongation (7.0%), IDH1 differentiation syndrome (4.7%), anemia (2.3%), thrombocytopenia (1.9%), leukocytosis (1.2%), febrile neutropenia (1.2%), diarrhea (1.2%), or hypoxia (1.2%)	[21,46]
AML	Ivosidenib (with azacitidine)	100%**	Thrombocytopenia (61%), anemia (44%), febrile neutropenia (44%), neutropenia (30%), sepsis (22%), QTc prolongation (13%)	[52]
AML	Ivosidenib (with multiagent chemotherapy)	96.7%**	Hypophosphatemia (16.7%), hypokalemia (11.7%), QTc prolongation (10.0%), decreased appetite (8.3%), fever (6.7%), increased aspartate aminotransferase (6.7%), increased alanine aminotransferase (6.7%), hyperbilirubinemia (6.7%), hypocalcemia (5.0%), rash (5.0%), stomatitis (5%)	[55]
Multiple solid tumors	BAY1436032	12.0%*	Increased lipase (3.8%), increased alanine aminotransferase (3.8%), nausea (1.9%), rash (1.9%)	[56]
AML	BAY1436032	25.9%*	Hyperamylasemia (4%), IDH1 differentiation syndrome (4%), fatigue (4%), febrile neutropenia (4%), hyponatremia (4%), lung infiltrate (4%), peripheral edema (4%), pneumonitis (4%), leukopenia (4%), anemia (4%), ileus (4%), neutropenia (4%), thrombocytopenia (4%), sepsis (4%)	[57]

* Grade ≥ 3 adverse event rate that were deemed related to the mtIDH1 inhibitor.
** Grade ≥ 3 adverse event rate of any causality.

receiving placebo (HR 0.79, 95% CI 0.56–1.12) [43]. The similarity is likely attributable to trial crossover from placebo to ivosidenib, which occurred in 70% of patients initially randomized to the placebo arm [43]. Using a rank-preserving structural failure time method to estimate survival if crossover had not occurred, the predicted median survival of the placebo group was 5.1 months (HR 0.49, 95% CI 0.34–0.70, when comparing patients who received ivosidenib to those who received placebo without crossover) [43]. As in the phase I trial, ivosidenib was extremely well tolerated. Serious adverse events occurred in 34% of patients receiving ivosidenib and 24% of patients receiving placebo: importantly, just three patients (2.4%) experienced a grade ≥ 3 adverse event directly related to ivosidenib (Table 2), as compared to zero patients in the placebo arm [42,43].

Chondrosarcoma: A retrospective analysis of patients with advanced chondrosarcoma who received first-line chemotherapy reported a median PFS of 4.7 months [44]. A past phase II trial of patients with progressive chondrosarcoma reported a PFS of 3.5 months among those who received a Hedgehog inhibitor (GDC-0449) [45]. With these studies as background, 21 patients with advanced mtIDH1 chondrosarcoma received ivosidenib in a published phase I trial [19]. Patients enrolled in this study had recurrent disease, progressed on standard therapy, did not respond to standard therapy, or were deemed inappropriate for standard treatment options [19]. The median PFS was 5.6 months (>50% better than the abovementioned phase II trial [45]), with almost 40% of patients still without progressive disease at the 6-month mark (**Table 1**) [19]. Although there were no complete or partial radiographic responses, 52% of patients achieved radiographic stable disease during the study [19]. Three patients (14.3%) who achieved stable disease remained without progression after nearly four years of therapy, and treatment was ongoing at the time of trial publication [19]. 100% of patients experienced a reduction in 2-HG levels [19]. Only one patient (4.8%) in this phase I trial had an adverse event deemed to be secondary to ivosidenib (Table 2) [19].

Glioma: A total of 66 patients with advanced mtIDH1 glioma (including oligodendroglioma, astrocytoma, oligoastrocytoma, glioblastoma) received ivosidenib in a phase I trial [17]. All patients had recurrent disease after resection, or progressed with chemotherapy or radiotherapy [17]. Outcomes varied based on the presence or absence of contrast enhancement in the tumor on cross-sectional imaging, as enhancing tumors are more biologically aggressive [17]. For patients with non-enhancing gliomas, 85.7% of patients achieved stable disease with a median PFS of 13.6 months (**Table 1**) [17]. Historically, PFS is around 7 months for similar patients who received chemotherapy [29]. Patients with enhancing gliomas fared worse: only 45.2% achieved stable disease and the median PFS was just 1.4 months [17]. In the total cohort of patients, only 3% of patients experienced a grade ≥ 3 adverse event attributed to ivosidenib (Table 2) [17].

AML: A large phase I trial (n = 258) was recently completed among patients with mtIDH1 AML who received ivosidenib and results were reported in two separate publications [21,46]. This trial included two groups of patients; one with relapsed or refractory mtIDH1 AML (n = 179) [21] and another group with newly diagnosed mtIDH1 AML (n = 34) [46].

Of the 179 patients with relapsed or refractory mtIDH1 AML, the primary efficacy population included 125 patients with at least 6 months of follow-up [21]. The rate of complete remission or complete remission with partial hematologic recovery was over 30% and the overall response rate was nearly 42% [21]. The median OS of this group was 8.8 months (**Table 1**) [21]. Although the trial was not randomized, the results appear to indicate a strong activity signal for ivosidenib, as historic outcomes for patients with relapsed or refractory AML are generally poor. A previous international phase III clinical trial demonstrated an OS of between 3.3 and 3.5 months after treatment with either monotherapy elacytarabine (a cytarabine derivative) or investigator's choice of one of multiple regimens (high-dose cytarabine, low-dose cytarabine, MEC [mitoxantrone, etoposide, cytarabine], FLAG/FLAG-Ida [fludarabine, cytarabine, granulocyte colony-stimulating factor with or without idarubicin], hypomethylating agents, hydroxyurea, or supportive care) [47]. Several retrospective studies have reported variable survival data, with some series reporting favorable outcomes. A study of 25 patients with relapsed or refractory AML who received venetoclax combined with a hypomethylating agent reported a median OS of 5.5 months [48]. A separate study of patients in their first relapse who received intensive chemotherapy reported a median OS of 9.0 months [49]. A population-based study of 199 patients published in 2020 reported a median OS of 13.6 months for patients who received intensive chemotherapy (regimen not specified), and 9.4 months for patients who received non-intensive chemotherapy [50]. Just 23% of patients (n = 46) in that study were able to receive intensive chemotherapy [50], and this group was notably younger with more favorable disease biology, suggesting a potential selection bias. This study in particular highlights an ongoing need for effective, yet well-tolerated, therapeutics for all patients with

relapsed or refractory AML.

The aforementioned phase I trial also administered ivosidenib to 34 patients with newly diagnosed AML (i.e., not relapsed or refractory) who were deemed ineligible for standard therapy [46]. The median age of this cohort was 76 years [46]. The median OS of this group was 12.6 months and over 42% of patients achieved complete remission or complete remission with partial hematologic recovery (**Table 1**) [46]. In the subset of patients who had never received a hypomethylating agent for a preceding hematologic disorder, the rate of complete remission or complete remission with partial hematologic recovery was over 55% and the median duration of this remission was not reached during the trial [46]. A previous administrative database analysis reported an overall survival of approximately 6 months among patients age 65 years and older (median 78 years) who received any form of treatment for AML [51]. Although direct comparisons are difficult to make, the doubling of OS suggests ivosidenib is promising in this challenging group of patients.

Ivosidenib has also been administered in combination with approved agents. A phase I trial of 23 patients with treatment-naïve AML who were deemed ineligible for intensive chemotherapy were trialed with first-line combination ivosidenib and azacitidine [52]. Azacitidine, and other hypomethylating agents, are often utilized in elderly or comorbid patients as this patient population rarely tolerates intensive chemotherapy [53,54]. Ivosidenib and azacitidine resulted in complete remission in 61% of patients [52]. Additionally, after a median follow-up of over 16 months, the median survival was not reached (95% CI 17.0 months - not reached), with a predicted 12-month survival rate of 82% (**Table 1**) [52]. This compares favorably to experience with similar patients who receive a hypomethylating agent (azacitidine or decitabine) as monotherapy, who historically have complete remission rates around 18–28% and a median survival of 7.7–10.4 months [53,54]. Again, these data suggest a potential doubling of OS with ivosidenib. 100% of patients experienced a grade $\geq$ 3 adverse event, but this rate was not treatment-specific (i.e., adverse events of any causality) [52]. Approximately 87% of patients experienced any adverse event attributed to ivosidenib (grade $\geq$ 1) (Table 2) [52], yet the overall adverse event rate in a past phase III study of azacitidine monotherapy was 99.2%, suggesting azacitidine may be the driver to toxicity [54].

Patients with treatment-naïve mtIDH1 AML were administered ivosidenib in addition to multiagent chemotherapy in a phase I trial (n = 60) [55]. The complete remission rate was 68%, which is similar to rates reported in the literature (**Table 1**) [25]. The median overall survival was not reached after a median follow-up period of 9.3 months, but the predicted 12-month survival rate was 78% [55]. To our knowledge, historic survival data for comparison are not available to date. A significant proportion of patients in this study were $\geq$ 60 years old, where the published experience with multiagent induction chemotherapy is modest [55]. Similar to the other experiences, 96.7% of patients experienced a grade $\geq$ 3 adverse event, but these were not specific to ivosidenib (Table 2) [55].

BAY1436032

Multiple solid tumors: Eighty-one patients with mtIDH1 solid tumors (32% astrocytoma (low grade glioma), 20% secondary glioma, 20% intrahepatic cholangiocarcinoma, 16% oligodendroglioma (low grade glioma), 12% other tumor types) received BAY1436032 in a phase I trial [56]. Among patients with intrahepatic cholangiocarcinoma or secondary glioma, 0 patients achieved a complete or partial response (**Table 1**). Most patients with these tumor types experienced disease progression (58% and 71%, respectively), and the rates of PFS at 3 months were 10% and 22% [56]. Patients with low grade gliomas fared slightly better: 11% of patients had a complete or partial response. Over 45% of patients experienced disease progression and the PFS rate at 3 months was 31% [56]. Approximately 12% of patients experienced a grade $\geq$ 3 adverse event related to BAY1436032 (Table 2) [56].

AML: Patients with relapsed or refractory mtIDH1 AML or who were deemed ineligible for standard therapies were administered BAY1436032 in a phase I trial [57]. The overall response rate was 16% and median overall survival was 6.6 months (**Table 1**) [57]. As mentioned above, the overall response rate among a similar patient population who received ivosidenib was 42% and median overall survival was 8.8 months [21]. Approximately 26% of patients experienced a grade $\geq$ 3 adverse event related to BAY1436032 (Table 2) [57].

Pooled adverse events

Solid tumors: Of the four published trials examining ivosidenib monotherapy in patients with mtIDH1 solid tumors (cholangiocarcinoma, glioma, chondrosarcoma) [17,19,41,42], the pooled overall grade $\geq$ 3 adverse treatment-related event rate was 3.6% among 284 total patients who received ivosidenib. The adverse events were variable: electrolyte derangements (1.1%; hyperphosphatemia, hypophosphatemia, hyponatremia), biliary tract abnormalities (1.1%; cholestatic jaundice, increased alkaline phosphatase, hyperbilirubinemia), fatigue (0.7%), neutropenia (0.4%), arthralgia (0.4%), weight loss (0.4%), pleural effusion (0.4%).

Hematologic malignancies: The overall grade $\geq$ 3 adverse event rate deemed related to ivosidenib was 25.6% among patients with mtIDH1 AML [21,46]. The most common adverse events were QTc prolongation (7.0%), IDH1 differentiation syndrome (4.7%), anemia (2.3%), thrombocytopenia (1.9%), leukocytosis (1.2%), febrile neutropenia (1.2%), diarrhea (1.2%), or hypoxia (1.2%).

Ongoing trials

mtIDH1 inhibitor monotherapy: A total of 19 additional trials utilizing monotherapy mtIDH1 inhibitors were identified on ClinicalTrials.gov (Table 3). Eight trials (42.1%) are currently recruiting patients and another eight trials (42.1%) are listed as "Active, not recruiting." Three trials (15.8%) have been withdrawn, all of which aimed to test the mtIDH1 inhibitor, IDH305. Across all trials, five different mtIDH1 inhibitors are currently under investigation (BAY1436032, ivosidenib, LY3410738, DS-1001b, IDH305). These drugs are each assets of different pharmaceutical companies, including Bayer, Servier, Eli Lily and Company, Daiichi Sankyo, and Novartis, respectively. Seven of the listed trials (36.8%) are focused on AML or related hematologic malignancies, eight (42.1%) include patients with gliomas, three (15.8%) with chondrosarcoma, and three (15.8%) with cholangiocarcinoma. Five trials (26.3%) target multiple types of advanced mtIDH1 tumors. Most of the trials are in phase I testing (58%), with no new phase III trials of ivosidenib monotherapy currently underway [42,43].

mtIDH1 inhibitors, combination therapy: In total, 16 trials testing mtIDH1 inhibitors in combination with other therapies were identified (Table 4). The preponderance of these trials (81.2%) utilize ivosidenib as the index mtIDH1 inhibitor. As above, most trials (81.2%) are in patients with AML or related hematologic malignancies. Active trials also examine the efficacy of mtIDH1 inhibitors among patients with gliomas (12.5%), cholangiocarcinoma (12.5%), or chondrosarcoma (6.3%). Most trials are listed as "Recruiting" (43.8%) or "Active, not recruiting or Not yet recruiting" (43.8%). Two trials have been withdrawn (12.5%). Almost all trials (87.5%) are in either phase I or II testing. Two trials in patients with mtIDH1 AML are classified as phase III (12.5%) and are evaluating ivosidenib. Across these trials, concurrent treatments include diverse standard and experimental agents including chemotherapy (azacitidine, cisplatin, gemcitabine, cytarabine, etc.), IDH2 inhibitors (enasidenib), immunotherapies (nivolumab), or other targeted therapies (fedratinib, glasdegib).

Discussion

Herein, we summarize the landscape of clinical trials examining the efficacy of pharmacologic mtIDH1 inhibitors. There are at least six different mtIDH1 inhibitors under clinical investigation, each manufactured by a different company. However, the actual number of mtIDH1 inhibitors with actively resourced clinical drug development programs is difficult to ascertain. To date, only ivosidenib has been thoroughly investigated in multiple published human trials, leading to

Table 3
Summary of ongoing clinical trials using mtIDH1 inhibitor monotherapy across different malignancies.

mtIDH1 inhibitor	Pharma-ceutical company	Malignancy	Trial phase	Trial title	Trial status	Trial identification	Enrollment	Ref
Ivosidenib	Servier Pharmaceuticals	Cholangiocarcinoma	III	Study of AG-120 in Previously Treated Advanced Cholangiocarcinoma with IDH1 Mutations (ClarIDHy)	Active, not recruiting	NCT02989857	187	[42]
Ivosidenib	Servier Pharmaceuticals	Chondrosarcoma	II	AG-120 in People with IDH1 Mutant Chondrosarcoma	Recruiting	NCT04278781	17	–
Ivosidenib	Servier Pharmaceuticals	Solid tumors, lymphoma	II	Ivosidenib in Treating Patients with Advanced Solid Tumors, Lymphoma, or Histiocytic Disorders with IDH1 Mutations (A Pediatric MATCH Treatment Trial)	Recruiting	NCT04195555	49	–
Ivosidenib	Servier Pharmaceuticals	Glioma	I	Study of AG-120 and AG-881 in Subjects with Low Grade Glioma	Active, not recruiting	NCT03343197	49	** [88]
Ivosidenib	Servier Pharmaceuticals	Solid tumors	I	Study of Orally Administered AG-120 in Subjects with Advanced Solid Tumors, Including Glioma, with an IDH1 Mutation	Active, notrecruiting	NCT02073994	170	[17,19,41]
Ivosidenib	Servier Pharmaceuticals	AML, Myelodysplastic Syndrome	II	IDH1 (AG 120) Inhibitor in Patients with IDH1 Mutated Myelodysplastic Syndrome	Recruiting	NCT03503409	68	–
Ivosidenib	Servier Pharmaceuticals	AML	I, II	Study of Biomarker-Based Treatment of Acute Myeloid Leukemia	Recruiting	NCT03013998	2000	[89]
Ivosidenib	Servier Pharmaceuticals	Hematologic malignancies	I	Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation	Recruiting	NCT02074839	291	[21,46]
Ivosidenib	Servier Pharmaceuticals	Myeloid neoplasms	I	IDH1 Inhibition Using Ivosidenib as Maintenance Therapy for IDH1-mutant Myeloid Neoplasms Following Allogeneic Stem Cell Transplantation	Recruiting	NCT03564821	22	–
Ivosidenib	Servier Pharmaceuticals	AML	I	A China Bridging Study of Ivosidenib in r/r AML Subjects with an IDH1 Mutation	Active, notrecruiting	NCT04176393	30	–
BAY1436032	Bayer	Solid tumors	I	Phase I Study of BAY1436032 in IDH1-mutant Advanced Solid Tumors	Active, not recruiting	NCT02746081	81	–
LY3410738	Eli Lilly and Company	Solid tumors	I	Study of LY3410738 Administered to Patients with Advanced Solid Tumors with IDH1 Mutations	Recruiting	NCT04521686	180	* [90]
LY3410738	Eli Lilly and Company	Hematologic malignancies	I	Study of Oral LY3410738 in Patients with Advanced Hematologic Malignancies with IDH1 or IDH2 Mutations	Recruiting	NCT04603001	220	* [91]
DS-1001b	Daiichi Sankyo, Inc.	Glioma	II	A Study of DS-1001b in Patients with Chemotherapy- and Radiotherapy-Naive IDH1 Mutated WHO Grade II Glioma	Active, not recruiting	NCT04458272	25	–
DS-1001b	Daiichi Sankyo, Inc.	Glioma	I	Study of DS-1001b in Patients with Gene IDH1-Mutated Gliomas	Active, not recruiting	NCT03030066	47	** [92]
IDH305	Novartis Pharmaceuticals	Glioma	II	Trial of IDH305 in IDH1 Mutant Grade II or III Glioma	Withdrawn	NCT02977689	0	–
IDH305	Novartis Pharmaceuticals	Glioma	II	II Study of IDH305 in Low Grade Gliomas	Withdrawn	NCT02987010	0	–
IDH305	Novartis Pharmaceuticals	Multiple	I	A Study of IDH305 in Patients with Advanced Malignancies That Harbor IDH1R132 Mutations	Active, not recruiting	NCT02381886	166	–
IDH305	Novartis Pharmaceuticals	AML	I	A Dose Finding Study of IDH305 With Standard of Care in IDH1 Mutant Acute Myeloid Leukemia	Withdrawn	NCT02826642	0	–

* Indicates references related to study design and methods (i.e., trial still in progress).
** Abstract only.

FDA-approval for two indications (AML and cholangiocarcinoma). In total, published experience reflects 599 patients who received ivosidenib as of October 2021. Patients all had mtIDH1 tumors and pathologies included AML, glioma, chondrosarcoma, and cholangiocarcinoma. Taken together, the published experience suggests that ivosidenib likely has clinically relevant and appreciable activity against mtIDH1 tumors. Early data on the efficacy of BAY1436032 appear less promising; however, just over 100 patients with numerous cancer subtypes have been administered, thus, this particular mtIDH1 inhibitor requires further investigation before any conclusion could be rendered.

These studies reveal that ivosidenib is very well tolerated. Among patients with a hematologic malignancy, the treatment-related grade $\geq$ 3 adverse event was 25.6% and was significantly lower among patients with solid malignancies (3.6%). IDH1 differentiation syndrome, which is of particular interest when treating mtIDH1 hematologic malignancies with an IDH1 inhibitor, occurred in approximately 5% of patients with

Table 4
Summary of clinical trials using mtIDH1 inhibitors in combination with other therapies across different malignancies.

mtIDH1 inhibitor	Pharma-ceutical company	Other concurrent therapies	Malignancy	Trial phase	Trial title	Trial status	Trial identification	Enrollment	Ref
Ivosidenib	Servier Pharmaceuticals	Nivolumab	Solid Tumors	II	Ivosidenib (AG-120) with Nivolumab in IDH1 Mutant Tumors	Recruiting	NCT04056910	35	–
Ivosidenib	Servier Pharmaceuticals	Cisplatin, Gemcitabine,	Cholangiocarcinoma	I	Gemcitabine and Cisplatin with Ivosidenib or Pemigatinib for the Treatment of Unresectable or Metastatic Cholangiocarcinoma	Recruiting	NCT04088188	40	–
Ivosidenib	Servier Pharmaceuticals	Chemotherapy	AML, Myelodysplastic Syndrome	III	A Study of Ivosidenib or Enasidenib in Combination with Induction Therapy and Consolidation Therapy, Followed by Maintenance Therapy in Patients with Newly Diagnosed Acute Myeloid Leukemia or Myedysplastic Syndrome EB2, with an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy	Recruiting	NCT03839771	968	–
Ivosidenib	Servier Pharmaceuticals	Azacitidine	AML	III	Study of AG-120 (Ivosidenib) vs. Placebo in Combination with Azacitidine in Patients with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation	Active, not recruiting	NCT03173248	148	*&** [62,63]
Ivosidenib	Servier Pharmaceuticals	Nivolumab	AML, Myelodysplastic Syndromes	II	A Study of the IDH1 Inhibitor AG-120 in Combination with the Checkpoint Blockade Inhibitor, Nivolumab, for Patients with IDH1 Mutated Relapsed/ Refractory AML and High Risk MDS	Withdrawn	NCT04044209	0	–
Ivosidenib	Servier Pharmaceuticals	Decitabine, Cedazuridine, Venetoclax	AML	I, II	Decitabine/ Cedazuridine and Venetoclax in Combination with Ivosidenib or Enasidenib for the Treatment of Relapsed or Refractory Acute Myeloid Leukemia	Recruiting	NCT04774393	84	–
Ivosidenib	Servier Pharmaceuticals	Azacitidine, Venetoclax	Hematologic Malignancies	I, II	Ivosidenib and Venetoclax with or without Azacitidine in Treating Patients with IDH1 Mutated Hematologic Malignancies	Recruiting	NCT03471260	30	** [93]
Ivosidenib	Servier Pharmaceuticals	Azacitidine	AML	I, II	A Safety and Efficacy Study of Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus Subcutaneous Azacitidine in Subjects with Newly Diagnosed Acute Myeloid Leukemia (AML)	Active, not recruiting	NCT02677922	131	[52]
Ivosidenib	Servier Pharmaceuticals	Chemotherapy (Cytarabine, Fludarabine)	AML	I	Ivosidenib and Combination Chemotherapy for the Treatment of IDH1 Mutant Relapsed or	Not yet recruiting	NCT04250051	25	–

(*continued on next page*)

Table 4 (*continued*)

mtIDH1 inhibitor	Pharmaceutical company	Other concurrent therapies	Malignancy	Trial phase	Trial title	Trial status	Trial identification	Enrollment	Ref
					Refractory Acute Myeloid Leukemia				
Ivosidenib	Servier Pharmaceuticals	Cytarabine, Daunorubicin, Idarubicin, Mitoxantrone, Etoposide	AML, Myelodysplastic Syndrome	I	Safety Study of AG-120 or AG-221 in Combination with Induction and Consolidation Therapy in Participants with Newly Diagnosed Acute Myeloid Leukemia (AML) with an IDH1 and/or IDH2 Mutation	Active, not recruiting	NCT02632708	153	[55]
Ivosidenib	Servier Pharmaceuticals	Fedratinib	Myeloproliferative neoplasms	I	A Study of Fedratinib With IDH Inhibition in Advanced-Phase, IDH-Mutated Ph-Negative Myeloproliferative Neoplasms	Not yet recruiting	NCT04955938	50	–
Ivosidenib	Servier Pharmaceuticals	Glasdegib	AML	I	Glasdegib-Based Treatment Combinations for the Treatment of Patients With Relapsed Acute Myeloid Leukemia Who Have Undergone Hematopoietic Cell Transplantation	Not yet recruiting	NCT04655391	36	–
Olutasidenib (FT-2102)	Forma Therapeutics	Azacitidine, Nivolumab, Gemcitabine, Cisplatin	Solid Tumors	I, II	A Study of FT 2102 in Participants with Advanced Solid Tumors and Gliomas with an IDH1 Mutation	Active, not recruiting	NCT03684811	200	** [94]
Olutasidenib (FT-2102)	Forma Therapeutics	Cytarabine, Azacitidine	AML Myelodysplastic Syndrome	I, II	Open-label Study of FT-2102 with or without Azacitidine or Cytarabine in Patients with AML or MDS with an IDH1 Mutation	Recruiting	NCT02719574	500	** [95]
Olutasidenib (FT-2102)	Forma Therapeutics	ASTX727	AML, Myelodysplastic Syndrome	I, II	ASTX727 and FT-2102 in Treating IDH1-Mutated Recurrent/Refractory Myelodysplastic Syndrome or Acute Myeloid Leukemia	Withdrawn	NCT04013880	0	–

* Indicates references related to study design and methods (i.e., trial still in progress).
** Abstract only.

mtIDH1 AML who received ivosidenib [21,46]. This clinical syndrome can occur with various targeted therapies, but was first described among patients with mtIDH1 AML receiving ivosidenib in a case series from 2016 [58]. It is known that myeloid neoplasms (e.g., AML) often originate from disrupted or stunted cellular differentiation [59]. While the exact pathophysiology of IDH1 differentiation syndrome is unknown, it is hypothesized to occur as a result of a rapid increase in the number of circulating and differentiated neutrophils after treatment is initiated and suppression of normal cellular differentiation is lifted. Common signs and symptoms are nonspecific, and include leukocytosis (predominately neutrophils), fever, hypotension, fluid shifts (pericardial or pleural effusions), weight gain, edema, and renal dysfunction. Differentiation syndrome can be fatal if it is not recognized and promptly treated. To our knowledge, IDH1-related differentiation syndrome has only been described in hematologic malignancies; however, the concept of solid tumor differentiation syndrome has been described in the past [60]. Differentiation syndrome has also been described in patients with mtIDH2 AML who received enasidenib, a mtIDH2 inhibitor [55,61].

The combination of ivosidenib with the demethylating agent, azacitidine, is particularly promising and does not appear to worsen toxicity beyond expected toxicities associated with azacitidine [52,54]. The phase III AGILE trial randomized patients with mtIDH1 AML to receive ivosidenib and azacitidine vs. placebo and azacitidine, and was terminated early due to convincing efficacy in the ivosidenib arm [62,63]. Mechanistically these drugs cooperate to block the dedifferentiating effect of mtIDH1 by suppressing methylation through two related, but independent mechanisms: inhibition of 2-HG (by ivosidenib [64]), and directly removing epigenetic marks on DNA (by azacitidine [65]).

Studies have demonstrated that solid and hematologic malignancies may acquire resistance to mtIDH1 (or mtIDH2) inhibitors. One potential mechanism involves isotype switching, in which patients with a mtIDH1 (cytosolic) cancer develop an IDH2 mutation (mitochondrial) after treatment with a mtIDH1 inhibitor [66]. The opposite switch can also occur: mtIDH2 tumors develop a mutation in IDH1 after pharmacologic mtIDH2 inhibition [66]. Alternatively, one study described a patient with mtIDH1 AML who received ivosidenib, and then developed a second-site mutation in IDH1. The second mutations conferred clinical resistance, leading to disease progression [67]. Again, this phenomenon has also been observed in patients with mtIDH2 AML [67]. Additionally, alterations in oncogenes beyond IDH1 and IDH2 have been reported to drive resistance to IDH1 inhibitors, including certain receptor tyrosine kinases [68].

In 2021, there will be an estimated 1.9 million new cancer diagnoses in the United States [69]. AML [70], cholangiocarcinoma [71], chondrosarcoma [72], and glioma [73], are predicted to account for

approximately 50,000 cases, or less than 3% of new cancer cases. Extrapolating from published series of IDH1 mutation rates [20,74-79], less than 1% of all cancers in the United States, or 19,000 per year, are likely to harbor a mutation in the IDH1 gene and are potential candidates for mtIDH1 inhibition therapy. For these tumors, the oral mtIDH1 inhibitor, ivosidenib, appears to be particularly promising.

Recent work by our group and others suggests that wtIDH1 may also be a compelling therapeutic target [8,10,80-83]. For instance, we observed increased expression of wtIDH1 in primary and metastatic pancreatic cancer, and determined that the enzyme is important for pancreatic cancer cell survival under cancer-associated stress (e.g., nutrient deprivation or chemotherapy) [81]. Further, we showed that wtIDH1 may even be more important for cancer cell survival than the mutant isoenzyme in heterozygous IDH1-mutant tumors [84]. Studies show that drugs developed to target mtIDH1 have some cross-reactivity against the wild-type enzyme and may have anti-cancer effects against some wtIDH1 tumors [10,85,86]. Both forms of IDH1 possess an allosteric pocket where IDH1 inhibitors bind to the enzyme [37]. Activity studies of mtIDH1 inhibitors demonstrate selectivity for mtIDH1 over wtIDH1, with drug potency differences approaching two-orders of magnitude [18,84]. However, evidence suggests that magnesium cations play a key role in this selectivity, and lower levels may enable mtIDH1 inhibitors to inhibit wtIDH1 [87]. Future studies will determine if this class of drugs or novel agents can be utilized to expand the number of patients eligible for IDH1 inhibition therapy.

Conclusion

Small molecule IDH1 inhibitors, namely ivosidenib, appear to have legitimate biological activity across mutant-IDH1 tumors. They are extremely well tolerated. Determining the role of wild-type IDH1 in these and other tumors, mechanisms of resistance to IDH1 inhibitors, and synergistic therapeutic combinations are crucial next steps.

CRediT authorship contribution statement

Mehrdad Zarei: Data curation, Writing – original draft. **Jonathan J. Hue:** Data curation, Writing – original draft. **Omid Hajihassani:** Writing – review & editing. **Hallie J. Graor:** Writing – review & editing. **Erryk S. Katayama:** Writing – review & editing. **Alexander W. Loftus:** Writing – review & editing. **David Bajor:** Writing – review & editing. **Luke D. Rothermel:** Writing – review & editing. **Ali Vaziri-Gohar:** Writing – review & editing. **Jordan M. Winter:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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