

Use, access, and initial outcomes of off-label ivosidenib in patients with IDH1 mutant glioma

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Abstract

Background. Isocitrate dehydrogenase (IDH) is commonly mutated (mIDH) in gliomas, and this mutant enzyme produces the oncometabolite 2-hydroxyglutarate (2HG). 2HG promotes gliomagenesis and is implicated in epileptogenesis. Ivosidenib (IVO), a small molecule oral mIDH1 inhibitor, is FDA-approved for mIDH1 newly diagnosed and relapsed/refractory acute myeloid leukemia. Moreover, IVO has efficacy in clinical trials for recurrent mIDH1 gliomas. Given the lack of targeted treatments for gliomas, we initiated off-label IVO for mIDH glioma patients in October 2020.

Methods. Retrospectively, we sought to assess early outcomes in our patients and describe their experience on IVO from October 2020 through February 2022. Our objective was to report on the following variables of off-label use of IVO: radiographic response, seizure control, tolerability, and access to the medication. All patients initially received single-agent IVO dosed at 500 mg orally once daily.

Results. The cohort age range was 21–74 years. Tumor types included astrocytoma ($n = 14$) and oligodendroglioma ($n = 16$), with most being grade 2 ($n = 21$). The best radiographic response in nonenhancing disease ($n = 22$) was 12 stable diseases, 5 minor responses, 3 partial responses, and 2 progressive diseases. Seizure frequency was stable to improved for most patients (70%, $n = 21$). IVO was well-tolerated, with the most common toxicities being diarrhea, elevated creatine kinase, and QTc interval prolongation. Most patients (66.7%, $n = 20$) received drugs via the patient assistance program, with insurance initially covering a third of patients and with ongoing use, later covering 60%.

Conclusions. Targeted therapies like IVO are options for mIDH glioma patients and can provide positive oncologic and neurological outcomes.

Keywords

glioma | ivosidenib | isocitrate dehydrogenase | radiographic response

Glial tumors represent roughly 65% of all primary malignant central nervous system (CNS) tumors in adult patients.¹ A fundamental discovery in glioma was the observation that the isocitrate dehydrogenase (IDH) enzyme, a component of the Krebs cycle, is mutated in most low-grade gliomas and some high-grade gliomas.² When this enzyme is mutated (mIDH), α -ketoglutarate is converted into the oncometabolite, 2-hydroxyglutarate (2HG). 2HG leads to downstream effects that promote oncogenesis.³ Additionally, 2HG promotes seizure activity via glutamatergic neurons.⁴ The IDH mutation

is rarely lost when a glioma patient's tumor grows and progresses.^{5,6} Therefore, mIDH is responsible for the underlying oncologic and neurologic concerns in these mIDH glioma patients.

Whether a glioma harbors a wildtype IDH allele or a mutant IDH allele strongly predicts prognosis above and beyond other prognostic factors, including the Pignatti prognostic scoring system.^{7,8} These observations guided the World Health Organization's reclassification of gliomas by IDH genotype status.⁹ Now, treatment for glioma has the opportunity to

be directed by mIDH status of the tumor, giving patients and providers targeted therapy options. Historically, treatment of gliomas, particularly low-grade glioma, included maximal safe surgery along with the addition of radiation therapy and chemotherapy. The addition of radiation therapy with chemotherapy was usually reserved for patients considered “high risk.” Moreover, the relevance of IDH mutation status was not known at the time of conception of studies, such as RTOG 9802, and testing for mIDH was therefore not available for risk stratification.¹⁰

Other mIDH cancers, such as acute myelogenous leukemia, have benefited from the introduction of mIDH inhibitors, namely ivosidenib (IVO). Ivosidenib, an orally bioavailable mIDH1 inhibitor, was FDA-approved in 2018 for relapsed/refractory mIDH1 acute myeloid leukemia.¹¹ Two clinical trials evaluated the safety and efficacy of IVO in mIDH1 glioma. In the manuscript by Mellinshoff and colleagues, 66 patients with recurrent mIDH1 gliomas (Grades 2–4) received escalating doses of IVO.¹² In this phase I clinical trial, IVO was found to be safe with no dose-limiting toxicities, and a maximum (and recommended) oral dose of 500 mg once daily was achieved. The drug appeared to control tumor growth in nonenhancing gliomas better than in enhancing gliomas. In a second trial, IVO was explored in a similar patient population but included perioperative analysis of the tumor. Although the drug was found to achieve a reduction of 2HG at the dose of 500 mg orally once a day in obtained tumor tissue, the IVO’s penetration of the blood–brain barrier was not superior to the penetration of a second-generation agent vorasidenib, an orally bioavailable mIDH1/2 inhibitor.¹³ Therefore, vorasidenib became the lead compound in the pivotal phase III clinical trial (NCT04164901) that recently demonstrated a significant improvement in progression-free survival over placebo in newly diagnosed mIDH low-grade glioma (WHO Grade 2).¹⁴ We will await full safety data results to understand vorasidenib tolerability and place in therapy.

Given the limited treatment options for mIDH1 gliomas, our practice began to utilize IVO in select patients with mIDH1 gliomas who did not meet the criteria for enrollment in the phase III clinical trial (NCT04164901). In 2021, we published our first 6 cases and showed that we could achieve both tumor control and seizure control in a small cohort of patients.¹⁵ The current manuscript will detail our experience with this agent regarding radiographic response, seizure control, safety, and accessibility. We chose the aforementioned factors to represent “real-world” considerations in obtaining the drug, managing toxicities, and caring for our patients. To date, we have initiated over 70 patients on IVO, and this manuscript represents our experience with the first 30 patients (including the original 6 patients) who received monotherapy with off-label IVO.

Methods

Population and Setting

The study population consisted of adult mIDH glioma patients seen at the Preston Robert Tisch Brain Tumor Center at Duke University, Durham, North Carolina who were

initiated on monotherapy with IVO 500 mg orally once daily from October 9, 2020, to February 18, 2022. A cut-off date of February 18, 2022, to allow patients to have the opportunity to be on IVO for approximately 1 year. Our clinical outpatient pharmacy team identified patients from the clinical medical record as part of standard-of-care chemotherapy prescribing practices. To be included in this analysis, patients had to receive monotherapy with IVO. The Duke University Institutional Review Board approved the retrospective analysis.

Demographic information was obtained from the medical record. In addition to standard demographics, other information collected included tumor histology, tumor grade, prior treatment with radiation therapy, temozolomide, other mIDH-targeted therapies, history of seizures, seizure frequency, type of insurance coverage, and acquisition method of IVO. The tumor grade for this study was reported based on World Health Organization (WHO) 2021 grading recommendations.

Radiographic Response

Response to treatment was assessed using Response Assessment in Neuro-Oncology-Low-Grade Glioma (RANO-LGG) criteria for nonenhancing tumors and RANO criteria for enhancing tumors.^{16,17} Standard MRI examinations were performed at 2–3 month intervals at the treating physician’s discretion. Two independent reviewers performed imaging evaluations. Statistical analyses were conducted using SAS software (Version 9.4; SAS Institute Inc., Cary, NC, USA) and plots were created in the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Adverse Events

We collected and evaluated specific adverse events of interest with IVO therapy. These included diarrhea, elevated creatine kinase levels, and QTc interval prolongation.

Results

Patient Characteristics

We identified 30 patients initiated on IVO 500 mg orally once daily between October 2020 and February 2022 (Table 1). The age range was 21–74 years at the time of off-label initiation of IVO therapy. Sixteen patients (53.3%) were female participants. Tumor grade distribution was 21 WHO Grade 2, 8 WHO Grade 3, and 1 WHO Grade 4. Tumor types included 14 patients with astrocytoma and 16 patients with oligodendroglioma. Most patients had nonenhancing disease ($n = 22$, 73.3%), with 8 patients having primarily enhancing disease. Most patients had received prior treatments for their disease beyond surgical resection, including radiation therapy ($n = 8$), temozolomide ($n = 18$), bevacizumab ($n = 1$), and even mIDH-targeted therapies ($n = 2$). Most patients had a history of seizures ($n = 25$, 83.3%).

Most patients had coverage with private insurance plans ($n = 24$, 80%).

Treatment Factors

We evaluated the factors associated with IVO therapy, including time to initiation and duration of therapy, the rationale for initiation and discontinuation of IVO, adverse events of interest, seizure frequency while on therapy compared with before therapy, and access to IVO. The median time from diagnosis to initiation of treatment was 7.2 years with a wide range from 1.68 months to 19.5 years. The median time on IVO was 43.7 weeks (5.5 weeks to 74.1 weeks; [Figure 1](#)). At the time of publication, most patients are still on IVO, and only 6 patients (20%) have discontinued

treatment. Reasons for discontinuation included progressive disease ($n = 4$), adverse event/poor tolerance ($n = 2$), and patient choice ($n = 1$). A dose reduction to IVO 250 mg orally once daily due to toxicity was necessary in 5 patients ([Table 2](#)). Adverse events of interest include diarrhea (26.7%, $n = 8$), elevated creatine kinase (33.3%, $n = 10$), and QTc prolongation (16.7%, $n = 5$). These events were considered Grade 1 by CTCAE 5.0 terminology criteria and were self-limiting. One patient did experience a flare of chronic pancreatitis during treatment but it was deemed unrelated to IVO therapy. Seizure frequency was determined to be stable for 50% of patients ($n = 15$), decreased in 20% ($n = 6$), and increased in 13.3% ($n = 4$). Interestingly, an observation of increased seizure frequency was accompanied by subsequent observation of radiographic progression in most cases.

Most patients ($n = 20$, 66.7%) initially experienced insurance denials of IVO coverage, however, they benefited from the patient assistance program to obtain IVO. The typical coverage period lasted for a 1-year period. During the re-enrollment process, some patients could get insurance coverage due to the continuation of therapy while showing stable to improved disease. The percentage of patients who received IVO through insurance coverage increased from 33.3% to 60% within the course of the study period.

Treatment Response

Treatment response to IVO is shown in the waterfall plots in [Figure 2A](#) and [B](#). According to the investigator's assessment of response for patients with enhancing disease, 5 patients (62.5%) had the best response to stable disease, and 3 patients (37.5%) had the best response to progressive disease. It is important to note that the % change from baseline for enhancing disease at complete reduction of enhancement (−100%) for 2 patients and over −50% for 1 patient, but there was continued presence of nonenhancing disease. Thus, these patients were deemed to have the best response to stable disease per RANO criteria.

For patients with nonenhancing disease, 3 patients (13.6%) had the best response of partial response, 5 patients (22.7%) had a best response of minor response, 12 patients (54.5%) had the best response of stable disease, and 2 patients (9.1%) had the best response of progressive disease.

In this retrospective cohort, some patients had received prior therapies, and prior exposure to temozolomide occurred in 18 patients. The best radiographic response for these patients was eleven with stable disease, 4 with minor response, and 3 with progressive disease. Eight patients had prior radiation therapy, including mostly grade 3 tumors ($n = 6$, 5-astrocytoma and 1-oligodendroglioma) along with 1 patient with Grade 2 astrocytoma and 1 patient with Grade 4 astrocytoma. Radiographic response for these 8 patients was 4 patients with stable disease, 3 with progressive disease, and 1 with minor response. Two patients had received prior temozolomide with a peptide vaccine targeted to mIDH1. Both of these patients were started on IVO for the progression of nonenhancing disease, and the best response for 1 was

Table 1. Patient Characteristics

	Number (%)
Total number	30 (100)
Woman	16 (53.3)
Grade	
2	21 (70)
3	8 (26.7)
4	1 (3.3)
Histology	
Astrocytoma	14 (46.7)
Oligodendroglioma	16 (53.3)
Disease type	
Nonenhancing	22 (73.3)
Enhancing	8 (26.7)
Prior radiation therapy	
Yes	8 (26.7)
No	22 (73.3)
Prior temozolomide	
Yes	18 (60.0)
No	12 (40.0)
Prior mIDH-targeted therapy	
Yes	2 (6.7)
No	28 (93.3)
Prior bevacizumab	
Yes	1 (3.3)
No	29 (96.7)
History of seizures	
Yes	25 (83.3)
No	5 (16.7)
Type of insurance	
Private	24 (80)
Government	3 (10)
VA	1 (3.3)
Self-pay	2 (6.7)

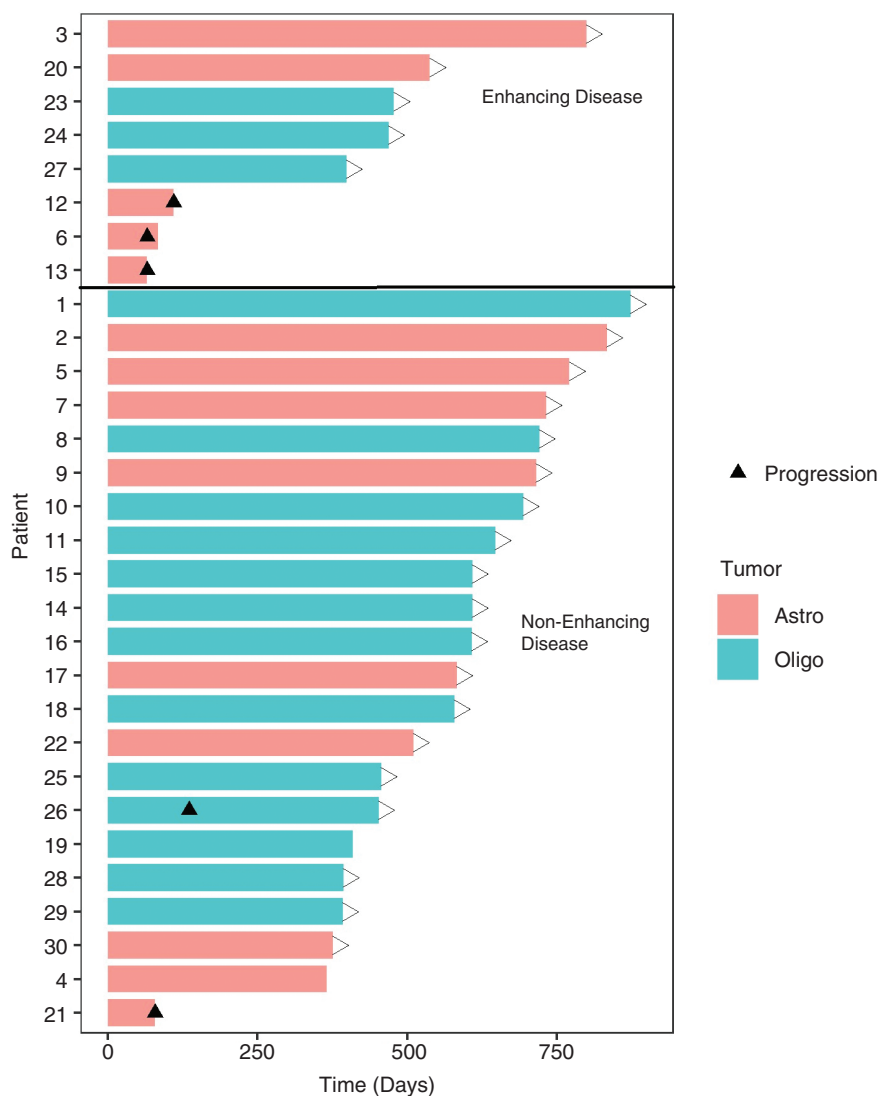


Figure 1. Treatment Duration for Patients on Monotherapy of Ivosidenib (Astro: Astrocytoma; Oligo: Oligodendroglioma) (Black Closed Triangle: Progression).

the minor response (-30.93% from baseline) and stable disease (-20.45% from baseline). It is important to note that all patients who had prior radiation therapy also received prior temozolomide.

In this cohort of 30 patients, 2 patients have died. One patient passed in the setting of progressive disease. Another patient passed after a prolonged hospitalization unrelated to their glioma diagnosis.

Discussion

Our retrospective analysis of 30 adult mIDH glioma patients shows that targeted IVO therapy can be safely used to treat this population. In patients with the nonenhancing disease, only 2 of 22 patients (9.1%) had progressive disease, with an overwhelming majority

(90.9%) having stable disease, minor response, or partial response. Seizure frequency was found to be stable in 50% of patients, with an additional 20% of patients having a decrease in seizure frequency. IVO therapy was well-tolerated overall, with only 2 patients (6.7%) discontinuing therapy due to intolerance. Insurance coverage challenges did delay therapy initiation; however, 20 patients (66.7%) were able to obtain drug access through the patient assistance program.

Our practical experience detailed in this paper highlights the complexities of prescribing and using off-label targeted therapeutics such as IVO. Our observations and practices can potentially assist other providers in utilizing off-label use of FDA-approved agents beyond IDH mutant targeted agents, particularly for even rarer CNS tumors. Although clinical trials are now being designed around cancer genetic drivers, there remains a need to describe outcomes in rare tumors when one cannot generate large

Table 2. Treatment Factors

Factors	Number
Total number (%)	30 (100)
Median time from diagnosis to initiation of IVO (range)	7.2 y (1.68 months to 19.5 y)
Median time on IVO (range)	43.7 weeks (5.5 weeks to 74.1 weeks)
Rationale for initiation of IVO	
Progression of nonenhancing disease	20 (66.7%)
Progression of enhancing disease	7 (23.3%)
Poor tolerance of temozolomide	3 (10%)
Adverse events of interest	
Diarrhea	8 (26.7%)
Elevated CK	10 (33.3%)
QTc prolongation	5 (16.7%)
IVO dose reduction to 250 mg daily	
Yes	5 (16.7%)
No	25 (83.3%)
IVO discontinuation	
Yes	6 (20%)
No	24 (80%)
Rationale for IVO discontinuation (n = 6)	
Progressive disease	4 (13.3%)
Adverse event/poor tolerance	2 (6.7%)
Patient choice	1 (3.3%)
Seizure frequency	
Stable	15 (50%)
Decrease	6 (20%)
Increase	4 (13.3%)
Not applicable	5 (16.7%)
Initial drug access	
Insurance	10 (33.3%)
Patient assistance program	20 (66.7%)

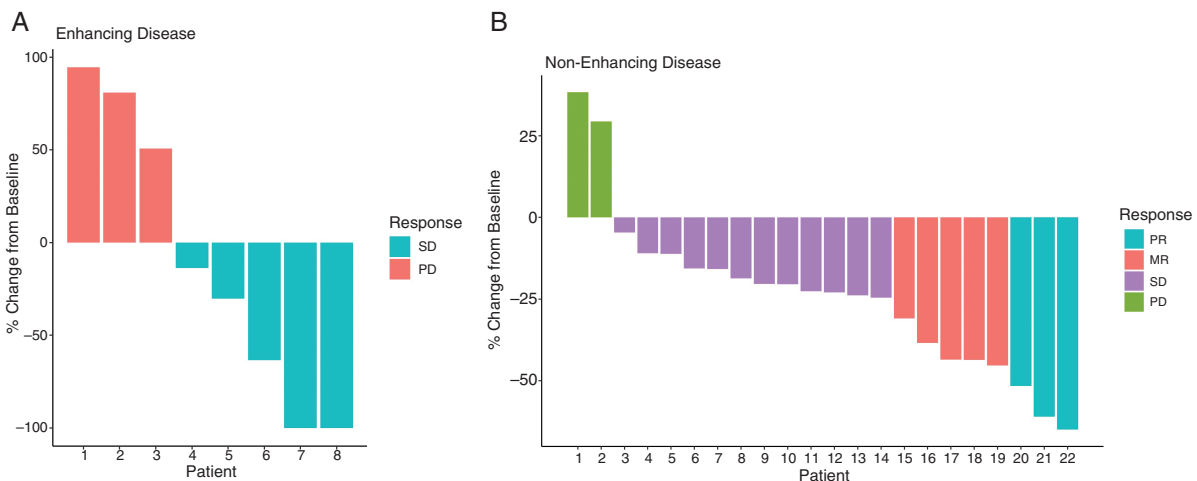


Figure 2. Best Percentage Change in Tumor Cross Product (SD: Stable Disease, PD: Progressive Disease, MR: Minor Response; PR: Partial Response, CR: Complete Response). In patients with primarily enhancing disease, best response was stable disease because non-enhancing disease did not meet criteria for MR, PR, or CR.

data sets. Of course, using off-label medications should never obfuscate the importance of enrolling patients in clinical trials.

Limitations of our study, include the retrospective nature of this single-center analysis as well as the heterogeneous population. Future studies may consider the investigation of combination therapies in the mIDH glioma population. Given the recent results of the mIDH1/2 inhibitor, vorasidenib, clinicians will need to elucidate further the role of IVO therapy. We sought to include all patients initiated on IVO monotherapy rather than excluding patients that were only 5 years post initial resection/diagnosis. In fact, our median time to IVO initiation was 7.2 years, thus most of our patients would not have been eligible for the INDIGO clinical trial. This observation demonstrates the utility of these mIDH inhibitors beyond the criteria prescriptive to published clinical trials. Perhaps further exploration of the toxicity profile of these agents in conjunction with comorbidities and concomitant medications, may help guide future utilization and optimal time to initiate IVO in the management of mIDH glioma.

Conflict of interest statement

K.B.P.: Advisory Board—Servier, Cordance Medical, Vivicitas Oncology, Sapience, Blue Earth Diagnostics, Ono Pharmaceuticals; Research Funding—Biomimetic; Varian; Servier. D.B.L.: Advisory Board—iADVISE, Roche. A.D.: Advisory Board—Orbus Therapeutics, Midatech LTD; Stock Options—Istari Oncology; Patents—Genetically modified poliovirus for the treatment of cancer. M.K.: Research Funding to Institution—BMS, AbbVie, Daiichi Sankyo, BioNTech, Celldex, Astellas, CNS Pharmaceuticals, Immorna Therapeutics, Immvira, Personalis; Honoraria—JAX lab for genomic research, Novocure, Servier, Johnson and Johnson, Voyager Therapeutics, George Clinical, and AnHeart Therapeutics; H.S.F.: Consulting or Advisory Role—Cancer Expert Now, Diverse Biotech, Istari Oncology; Stock Options—Cancer Expert Now, Diverse Biotech, Istari Oncology; Patents—Genetically modified poliovirus for the treatment of cancer.

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