

Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Safety and Clinical Activity in Patients With Advanced Chondrosarcoma

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PURPOSE Surgery is the primary therapy for localized chondrosarcoma; for locally advanced and/or metastatic disease, no known effective systemic therapy exists. Mutations in the isocitrate dehydrogenase 1/2 (IDH1/2) enzymes occur in up to 65% of chondrosarcomas, resulting in accumulation of the oncometabolite D-2-hydroxyglutarate (2-HG). Ivosidenib (AG-120) is a selective inhibitor of mutant IDH1 approved in the United States for specific cases of acute myeloid leukemia. We report outcomes of patients with advanced chondrosarcoma in an ongoing study exploring ivosidenib treatment.

PATIENTS AND METHODS This phase I multicenter open-label dose-escalation and expansion study of ivosidenib monotherapy enrolled patients with mutant *IDH1* advanced solid tumors, including chondrosarcoma. Ivosidenib was administered orally (100 mg twice daily to 1,200 mg once daily) in continuous 28-day cycles. Responses were assessed every other cycle using RECIST (version 1.1).

RESULTS Twenty-one patients (escalation, n = 12; expansion, n = 9) with advanced chondrosarcoma received ivosidenib (women, n = 8; median age, 55 years; range, 30-88 years; 11 had received prior systemic therapy). Treatment-emergent adverse events (AEs) were mostly grade 1 or 2. Twelve patients experienced grade \geq 3 AEs; only one event was judged treatment related (hypophosphatemia, n = 1). Plasma 2-HG levels decreased substantially in all patients (range, 14%-94.2%), to levels seen in healthy individuals. Median progression-free survival (PFS) was 5.6 months (95% CI, 1.9 to 7.4 months); the PFS rate at 6 months was 39.5%. Eleven (52%) of 21 patients experienced stable disease.

CONCLUSION In patients with chondrosarcoma, ivosidenib showed minimal toxicity, substantial 2-HG reduction, and durable disease control. Future studies of ivosidenib monotherapy or rational combination approaches should be considered in patients with advanced mutant *IDH1* chondrosarcoma.

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INTRODUCTION

Chondrosarcomas are rare primary malignancies of bone. Approximately 85% are of the conventional subtype and comprise a matrix of hyaline and/or myxoid cartilage; the remaining 15% include dedifferentiated, mesenchymal, and clear cell subtypes that have distinct clinicopathologic features.^{1,2} Conventional chondrosarcomas are categorized as central, peripheral, or periosteal according to anatomic location, and 90% are low or intermediate histologic grade at presentation.³ Current treatment options are limited, with surgery being the mainstay for most patients with localized disease.¹ Chemotherapy is ineffective in conventional chondrosarcoma, and although chemotherapy options exist for dedifferentiated and mesenchymal subtypes, they provide minimal benefit.¹ Therefore, new therapies are urgently needed for unresectable, metastatic, and refractory disease.

Isocitrate dehydrogenase (IDH) is a metabolic enzyme that catalyzes the oxidative decarboxylation of isocitrate, producing α -ketoglutarate (α -KG). Gain-of-function mutations in *IDH1* and *IDH2* have been described in several malignancies, including glioma,^{4,5} acute myeloid leukemia (AML),⁶⁻⁸ and cholangiocarcinoma.⁹ *IDH1/2* mutations are also documented in cartilaginous neoplasms, including up to 65% of conventional chondrosarcomas and up to 57% of dedifferentiated chondrosarcomas, as well as sporadic central cartilaginous tumors, periosteal chondromas, and enchondromas (a manifestation of the Ollier and Maffucci syndromes, which progress to chondrosarcoma in approximately 40% of cases).^{2,10-14}

IDH mutations result in the neomorphic enzyme activity of reduction of α -KG to the oncometabolite D-2-hydroxyglutarate (2-HG).¹⁵ Elevated 2-HG levels have been reported in cells from mutant *IDH* glioma,¹⁵ chondrosarcoma,¹⁶ cholangiocarcinoma,⁹ and AML.⁶

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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The accumulation of 2-HG contributes to malignancy via epigenetic pathways, although the precise mechanism remains unclear. 2-HG competitively inhibits α -KG-dependent dioxygenases, such as the methylcytosine dioxygenase TET2, and histone lysine demethylases; these enzymes regulate DNA and histone methylation, respectively, and control gene expression epigenetically.¹⁷⁻²² The induced hypermethylated phenotype has been reported in leukemias, gliomas, and enchondromas.^{11,17,18,23}

In a preclinical study, mutant *IDH1* mice showed impaired chondrocyte differentiation and developed enchondromas.²⁴ Furthermore, mutant *IDH1* inhibition in chondrosarcoma cell lines decreased 2-HG production in a dose-dependent manner and inhibited tumor cell growth.¹⁶ These data provide a biologic rationale for mutant *IDH1* inhibition as a clinical strategy in mutant *IDH1* chondrosarcoma.

Recently, agents targeting mutant *IDH1*²⁵ and *IDH2*²⁶ have received US Food and Drug Administration (FDA) approval for adults with specific cases of AML with a susceptible *IDH* mutation as detected by an FDA-approved test. The mutant *IDH1* inhibitor ivosidenib is currently under investigation in an ongoing phase I clinical study in patients with mutant *IDH1* advanced solid tumors; here we report results for the chondrosarcoma cohort in this study.

PATIENTS AND METHODS

Study Design and Treatment

We performed a phase I multicenter open-label dose-escalation and expansion study of ivosidenib monotherapy in patients with advanced solid tumors with an *IDH1* mutation, including cholangiocarcinoma, chondrosarcoma, and glioma. The primary objectives were to assess safety and tolerability and to determine the maximum tolerated dose and recommended phase II dose of ivosidenib.

Ivosidenib was administered orally in continuous 28-day cycles. For dose escalation, a standard 3 + 3 design was used, and doses tested were 100 mg twice daily and 300, 400, 500, 600, 800, 900, and 1,200 mg once daily. Patients were subsequently enrolled into four expansion cohorts: chondrosarcoma, cholangiocarcinoma, glioma, and other solid tumors not otherwise eligible for the other tumor-specific cohorts. On the basis of safety, tolerability, and pharmacokinetic/pharmacodynamic data from the dose-escalation phase, the 500 mg once daily dose was selected for all expansion cohorts.

Here, we report data from patients with chondrosarcoma enrolled in the dose-escalation and expansion cohorts. Inclusion criteria for this cohort in the escalation phase included known mutant *IDH1* advanced chondrosarcoma that had recurred or progressed during or not responded to standard therapy (or for which the investigator felt there

was no standard therapy) and measurable disease by RECIST (version 1.1)²⁷; in the expansion phase, criteria were mutant *IDH1* chondrosarcoma that was either locally advanced or metastatic and not amenable to complete surgical excision and an Eastern Cooperative Oncology Group performance status of 0 to 1. Key exclusion criteria included a heart rate-corrected QT interval \geq 450 ms or other factors that would increase the risk of QT prolongation or arrhythmic events and use of medications known to prolong the QT interval. Mutant *IDH* status for enrollment was determined by participating sites and confirmed retrospectively by centralized tissue testing.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice. The protocol, amendments, and informed consent form were approved by the institutional review board or independent ethics committee of each study site before study start. Informed consent was obtained from each participant or a legally authorized representative.

Pharmacokinetic and Pharmacodynamic Assessments

Serial blood samples were drawn before and after dosing at multiple time points in both the escalation and expansion phases to determine circulating plasma concentrations of ivosidenib and 2-HG. Additional details are provided in the Data Supplement and the published pharmacokinetic/pharmacodynamic report.²⁸

Levels of 2-HG were also measured in tumor biopsy samples performed when feasible at baseline, cycle 3 day 1, cycle 7 day 1 (if the patient had stable disease [SD] or a partial response [PR]), at any time disease progression (PD) was suspected, and/or at the end of treatment. 2-HG was extracted from tissue and evaluated using liquid chromatography and mass spectrometry (Data Supplement).

Study Assessments

Adverse events (AEs) were assessed at every visit and reported per the Common Terminology Criteria for Adverse Events (version 4.03; Data Supplement provides additional details). Prolongation of QT interval on ECG was specified as an AE of special interest because it is a known effect associated with ivosidenib.²⁵

Clinical activity of ivosidenib was evaluated with serial radiographic evaluations to determine response to treatment based on RECIST (version 1.1).²⁷ Computed tomography (CT) or magnetic resonance imaging (MRI) was conducted at screening and approximately every 56 days (8 weeks) during study treatment (independent of dose delays and/or dose interruptions) and/or at any time when PD was suspected. Radiographic assessment was also conducted at the end-of-treatment visit for patients who discontinued the study for reasons other than

PD. Responses were classified as complete response (CR), PR, SD, or PD. End points of clinical activity included progression-free survival (PFS) and best overall response.

Exploratory assessments included confirmation of baseline mutant *IDH1* status and identification of cooccurring mutations. Archival formalin-fixed paraffin-embedded samples were collected for analysis by next-generation sequencing using the FoundationOne panel (Foundation Medicine, Cambridge, MA),²⁹ which includes 361 genes. Fresh-frozen tumor samples were also collected at baseline and analyzed by next-generation sequencing using the ACE Extended Cancer Panel (Personalis, Menlo Park, CA), which includes 1,642 genes.

Statistical Analysis

The safety and full analysis sets for chondrosarcoma both comprised all patients who had received at least one ivosidenib dose (dose-escalation and expansion phases combined). The data cutoff date for the analyses reported here was January 16, 2019. Time-to-event end points were estimated using the Kaplan-Meier method. Descriptive statistics were used for other clinical, pharmacokinetic, and pharmacodynamic parameters.

RESULTS

Patients

This trial was initiated in March 2014, with a total of 168 patients with mutant *IDH1* advanced solid tumors receiving study treatment, of whom 21 had chondrosarcoma (dose escalation, n = 12; expansion, n = 9 [closed because of slow accrual]). Enrollment is complete, and the study is ongoing. Doses received in patients with chondrosarcoma were 100 mg twice daily (n = 1), 400 mg once daily (n = 4), 500 mg once daily (n = 11), 800 mg once daily (n = 3), and 1,200 mg once daily (n = 2). Of the 21 patients, four (19%) were still receiving treatment at the time of data cutoff (ivosidenib doses of 500, 800, 1,200, and 1,200 mg, respectively). Reasons for treatment discontinuation were PD (n = 10; 47.6%), AEs (n = 2; 9.5%), death (n = 2; 9.5%), withdrawal by patient (n = 1; 4.8%), clinical progression (n = 1; 4.8%), and other (transitioned to single-patient investigational new drug application, n = 1; 4.8%). Median age was 55 years, and most patients (n = 14) had grade 2 or 3 chondrosarcoma at screening (grade 1 chondrosarcoma, n = 2); six had dedifferentiated histology. Eleven patients (52%) had received prior systemic therapy (Table 1 lists demographic characteristics).

Pharmacokinetics and Pharmacodynamics

In patients with chondrosarcoma, ivosidenib was rapidly absorbed, with a half-life of 72 to 297 hours after a single dose (day -3), supporting a daily dosing regimen. Steady state was achieved within 14 days of dosing. Plasma

TABLE 1. Demographic and Baseline Clinical Characteristics of Full Analysis Set (N = 21)

Characteristic	No. (%)
Sex	
Female	8
Male	13
Age, years	
Median	55
Range	30-88
ECOG performance status	
0	9 (42.9)
1	12 (57.1)
Dedifferentiated histology	
Yes	6 (28.6)
No	13 (61.9)
Unknown	2 (9.5)
Tumor grade at screening	
1	2 (9.5)
2	8 (38.1)
3	6 (28.6)
Unknown	5 (23.8)
Locally reported <i>IDH1</i> mutation ^a	
Yes	20 (95.2)
No	1 (4.8)
Locally reported <i>IDH1</i> mutation type	
R132C	13 (61.9)
R132G	3 (14.3)
R132L	1 (4.8)
R132S	1 (4.8)
Other ^a	3 (14.3)
Prior systemic therapy	11 (52.4)
Median No. of lines (range)	1 (1-5)
Prior surgery	16 (76.2)
Prior radiotherapy	7 (33.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *IDH1*, isocitrate dehydrogenase 1.

^aOne patient had an *IDH2* mutation that was erroneously captured as *IDH1*.

exposure increased less than proportionally to dose with increasing doses.

Maximal 2-HG inhibition in plasma was achieved during the first 28-day cycle in patients receiving 500 mg once daily, with no additional inhibition observed at higher doses, in all tumor types. Plasma 2-HG was inhibited in all patients with chondrosarcoma, with consistent and substantial inhibition (median, 56.7%; range, 14%-94.2%) after multiple doses of ivosidenib, to levels consistent with those seen in healthy volunteers (Data Supplement). Similar plasma 2-HG

inhibition was also observed in patients with cholangiocarcinoma.²⁸ In two patients with chondrosarcoma who underwent tumor biopsies during the study, substantial reduction in 2-HG was also observed in tumor compared with baseline (85.4% and 98.6% inhibition, respectively). Additional details for all solid tumor types assessed in this study are provided in the full pharmacokinetic and pharmacodynamic report.²⁸

Safety

The maximum tolerated dose was not established in this study for the entire patient population (including all solid tumors), because there were no dose-limiting toxicities. On the basis of findings from the pharmacokinetic and pharmacodynamic analyses, including less than dose proportional increases in exposure beyond 500 mg and maximum suppression of plasma 2-HG at 500 mg, the 500 mg once-daily dose level was selected for the expansion phase.²⁸ Here we report safety results from the chondrosarcoma cohort only; the safety profile in this cohort was generally consistent with that observed in the cholangiocarcinoma and glioma cohorts in this study, with fatigue, diarrhea, and nausea among the most common AEs.^{30,31} The most common treatment-emergent AEs in the chondrosarcoma cohort (Table 2) were mostly grade 1 or 2. Of the grade ≥ 3 AEs in 12 patients (57.1%; Data Supplement), only one was judged to be treatment related by the investigator (hypophosphatemia, n = 1). One patient

TABLE 2. Most Common AEs ($\geq 10\%$ of patients) Regardless of Attribution in Safety Analysis Set (N = 21)

AE	No. (%)	
	Any Grade	Grade ≥ 3
Diarrhea	9 (42.9)	0
Nausea	7 (33.3)	0
Fatigue	6 (28.6)	0
Edema peripheral	5 (23.8)	1 (4.8)
ECG QT prolonged	5 (23.8)	0
Upper respiratory tract infection	5 (23.8)	0
Constipation	4 (19.0)	0
Decreased appetite	4 (19.0)	0
Pain in extremity	4 (19.0)	1 (4.8)
Anemia	3 (14.3)	1 (4.8)
Arthralgia	3 (14.3)	0
Blood alkaline phosphatase increased	3 (14.3)	1 (4.8)
Headache	3 (14.3)	0
Dizziness	3 (14.3)	0
Dyspnea	3 (14.3)	0
Vomiting	3 (14.3)	0

NOTE. Adverse Events (AE) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

had an AE leading to permanent drug discontinuation (hydronephrosis at 500 mg), which was not considered treatment related, and two had AEs leading to drug hold (anemia at 400 mg and confusion at 500 mg, respectively). There were no AEs leading to dose reductions. Grade 1 or 2 ECG QT prolongation occurred in five patients (23.8%); there were no grade ≥ 3 events, and no dose modifications were required for QT prolongation. There were two deaths during treatment resulting from serious AEs: acute respiratory failure at 400 mg and respiratory failure at 500 mg, respectively, both considered unrelated to study treatment by the investigator.

Clinical Efficacy

All 21 patients with chondrosarcoma were included for efficacy evaluation; 11 (52%) experienced SD as the best overall response by RECIST, six (29%) had PD, one (5%) had a response of unknown, and three (14%) were not assessed. There were no CRs or PRs. As of the data cutoff, median PFS for all patients (n = 21) was 5.6 months (95% CI, 1.9 to 7.4 months), with 3- and 6-month PFS rates of 62.1% (95% CI, 36.4% to 79.9%) and 39.5% (95% CI,

TABLE 3. Best Overall Response in Full Analysis Set (N = 21)

Best Response	No. (%)
SD	11 (52.4)
PD	6 (28.6) ^a
Unknown ^b	1 (4.8)
Not evaluable or not assessed ^c	3 (14.3)
PFS rate, % (95% CI)	
Overall population (N = 21)	
3 months	62.1 (36.4 to 79.9)
6 months	39.5 (17.9 to 60.6)
Nondifferentiated tumors (n = 13) ^d	
3 months	76.9
6 months	53.8
Dedifferentiated tumors (n = 6) ^d	
3 months	30.0
6 months	0

Abbreviations: PD, progressive disease; PFS, progression-free survival; SD, stable disease.

^aOne patient with PD had an *IDH2* mutation that was erroneously captured as *IDH1*.

^bPatient had SD at only postbaseline assessment; per RECIST, this was designated unknown because it occurred < 6 weeks after first dose.

^cNot assessed denotes patients who discontinued before response assessment or were missing RECIST assessment of target lesion at the time of data cutoff: one patient discontinued treatment on day 44 because of an AE; one discontinued treatment on day 14 because of death resulting from progressive disease; one had postbaseline assessment, but target lesion was not assessed.

^dOutcome by histologic subtype was not a prespecified analysis.

17.9% to 60.6%), respectively (Table 3; Data Supplement). Although the number of patients with dedifferentiated histology was small (n = 6), their outcomes were poor, with only 30% of patients progression free at 3 months and none by 6 months. In comparison, the 3-, 6-, and 12-month PFS rates for patients with nondifferentiated tumors (n = 13) were 76.9%, 53.8%, and 30.8%, although outcome by histologic subtype was not a pre-specified analysis. Six patients (28.6%) experienced PD as the best overall response, one of whom had an *IDH2* mutation (originally erroneously reported as mutant *IDH1* positive in the local pathology report, which was later corrected).

Duration of therapy is shown in Figure 1. Four patients (19%) have continued therapy for ≥ 2.5 years with a best response of SD. Of these, one patient previously had radiation therapy and therapy with the hedgehog pathway inhibitor saridegib for 1 year until PD in October 2011, followed by resection in November 2011. Further PD was detected in May 2014, followed by resection in January 2015 after progression of remaining sites; ivosidenib then commenced in late January 2015. Another patient had previously received saridegib therapy (4 months) followed by pazopanib (15 months to October 2013) until PD; a scan in September 2014 revealed metastasis, and ivosidenib commenced in September 2014. One patient diagnosed in October 2014 had documented PD in 2015 and commenced ivosidenib in July 2016. Several patients with SD experienced a reduction in tumor size (Fig 2). An example is shown in the Data Supplement, and according to the treating investigator, this patient reported resolution of pain, was able to discontinue analgesics, and had

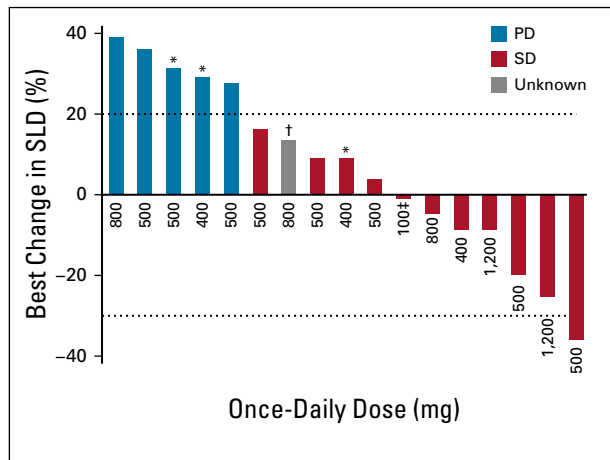


FIG 2. Best percentage change in the sum of the longest diameter (SLD) of the target lesions (full analysis set; patients classified according to assigned dose level). Dashed lines represent RECIST thresholds for progressive disease (PD; 20% increase) and partial response (30% decrease). Postbaseline assessments were not available for three patients; also excluded is the patient with an *IDH2* mutation that was erroneously captured as *IDH1*. SD, stable disease. (*) Patients with dedifferentiated disease. (†) Patient had one post-baseline assessment of target lesion; per RECIST, this was designated unknown because it occurred < 6 weeks after first dose. (‡) Administered twice daily.

a > 60% decrease in T2 hyperintense tumor volume by MRI; the patient received therapy for > 3 years. Additionally, the Data Supplement illustrates improvement in fluorodeoxyglucose-avid disease after four cycles of ivosidenib in a patient with metastatic chondrosarcoma who continued the study drug for 343 days.

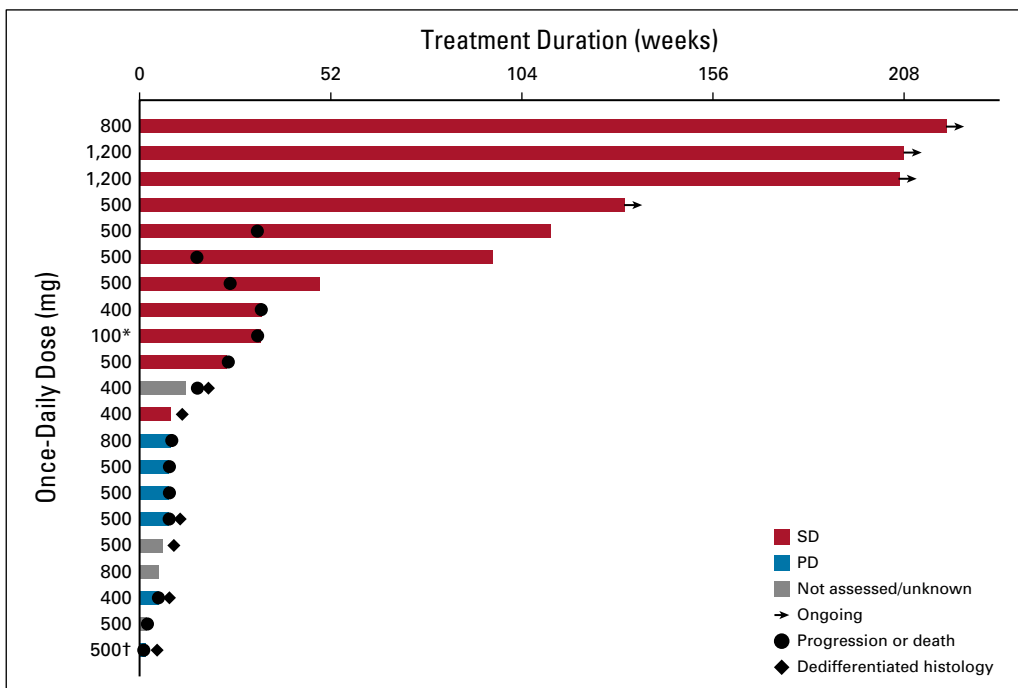


FIG 1. Duration of treatment and best overall response (full analysis set; patients classified according to assigned dose level). Patients could continue to receive therapy beyond disease progression (PD) if they were experiencing clinical benefit in the investigator's opinion. (*) Administered twice daily. (†) One patient with PD had an *IDH2* mutation that was erroneously captured as *IDH1*. SD, stable disease.

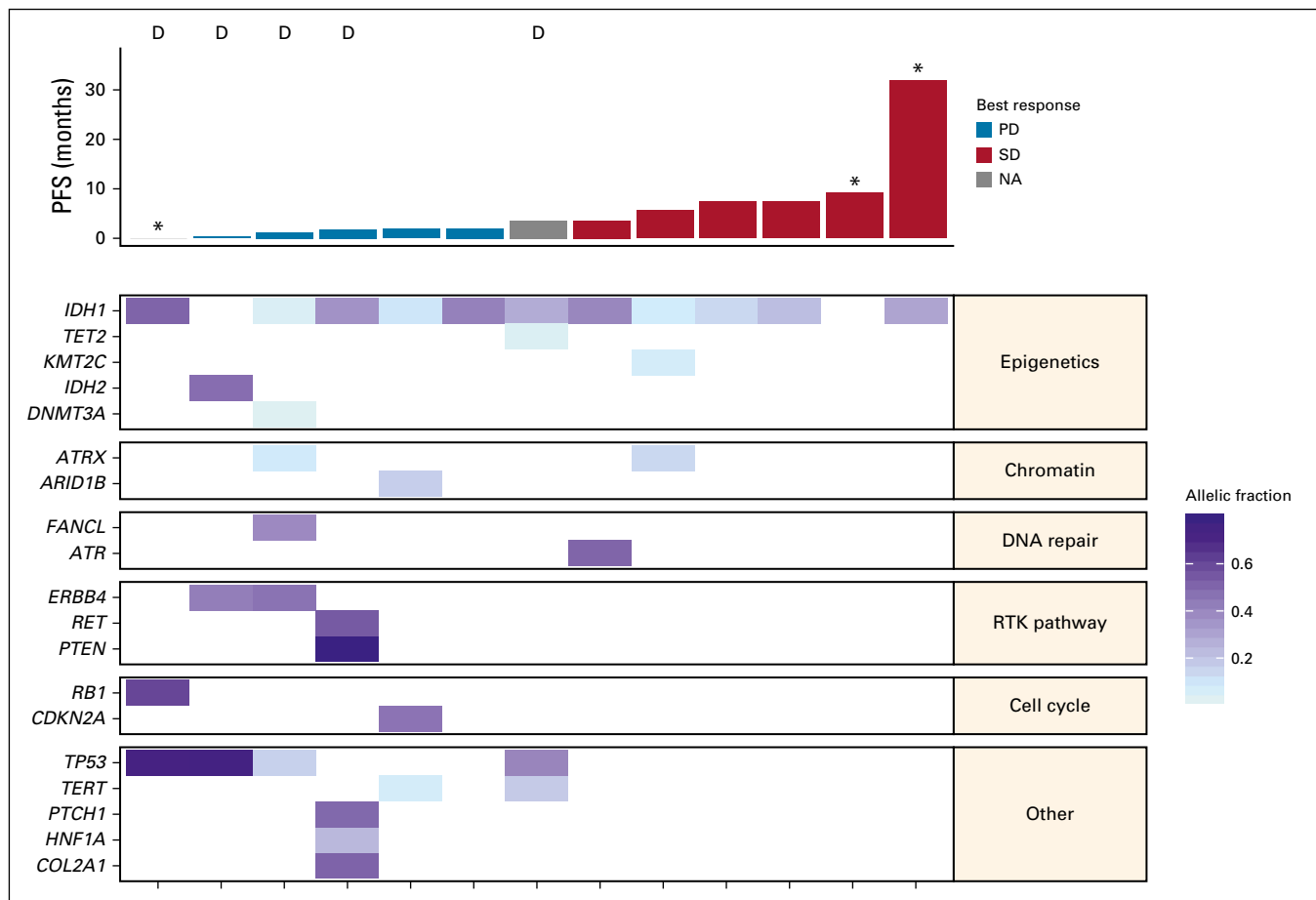


FIG 3. Cooccurring mutations (n = 13). The heatmap shows the allelic fraction of known or likely oncogenic mutations that were detected at baseline, with patients ordered by progression-free survival (PFS). Only genes present in both FoundationOne and Personalis panels are included. D, dedifferentiated histology at baseline; NA, not assessed; PD, progressive disease; RTK, receptor tyrosine kinase; SD, stable disease. (*) Denotes censoring.

Translational Analyses

Baseline cooccurring mutation profiling was conducted for 13 patients with available tumor tissue. Figure 3 shows the known or likely oncogenic mutations that were detected at baseline, with patients ordered by PFS. In this limited data set, patients with shorter PFS were more likely to have dedifferentiated histology and mutations in *TP53* or receptor tyrosine kinase pathway genes at baseline, and patients without cooccurring mutations as detected by these panels had longer PFS. One patient who was known to have a locally positive *IDH1* R132H mutation did not have central confirmation.

DISCUSSION

A majority of patients with chondrosarcoma have subtypes that are resistant to standard chemotherapy. Therefore, novel therapies are urgently needed for patients with metastatic or locally advanced chondrosarcoma. The observation that *IDH* mutations are commonly detected in chondrosarcomas offers hope that targeted mutant *IDH* inhibitors, such as ivosidenib, may provide a novel treatment strategy and improve outcomes for these patients.

In this phase I study, ivosidenib was well tolerated in a chondrosarcoma population. A majority of AEs were consistent with those seen in other mutant *IDH* solid tumors in this study.^{30,31} There was a low frequency of grade ≥ 3 treatment-related AEs. The AE of interest of ECG QT prolongation was reported in five patients (23.8%; no grade ≥ 3); guidelines for the management of such events were provided to all investigators. Ivosidenib resulted in significant reductions in plasma and tumor 2-HG, indicating an on-target pharmacodynamic effect.

Ivosidenib also demonstrated clinical activity, with an SD rate of 52%, median PFS of 5.6 months, and 6-month PFS rate of 39.5%. Moreover, the higher PFS rates in patients without dedifferentiated histology suggest that ivosidenib may be more effective in conventional chondrosarcoma. Dedifferentiated chondrosarcomas are clinically aggressive, with previous literature reporting that patients with these tumors have worse outcomes.³²⁻³⁴ The additional molecular aberrations seen in dedifferentiated tumors may explain the lack of response. However, several of the patients with conventional chondrosarcoma had evidence

of progression after prior interventions and went on to experience prolonged disease control and clinical benefit with ivosidenib. Diverse treatment regimens have been studied in patients with advanced chondrosarcoma. The hedgehog pathway, which is important for regulating chondrocyte proliferation and differentiation, is deregulated in chondrosarcoma. Hedgehog pathway inhibitors (eg, GDC-0449 and saridegib) have shown mixed results, with one GDC-0449 study reporting a median PFS of approximately 3.5 months in advanced chondrosarcoma,³⁵ whereas a subsequent global phase II randomized placebo-controlled trial of saridegib in chondrosarcoma showed no improvement in PFS, and the trial was ultimately stopped after a planned futility analysis.³⁶ In a study comparing outcomes of first-line systemic treatments for unresectable conventional chondrosarcoma, mean PFS included: doxorubicin, 2.5 months (n = 2); doxorubicin with either cisplatin or ifosfamide, 3.6 months (n = 10); gemcitabine and docetaxel, 2 months (n = 3); pazopanib with or without trametinib, 3.7 months (n = 7); dasatinib, 2.2 months (n = 4); vorinostat and hydroxychloroquine, 5 months (n = 4); and antihormonal therapy, 6.7 months (n = 7).³⁷ In our study, four patients treated with ivosidenib received the study drug for ≥ 2.5 years without PD, despite experiencing an overall shorter treatment duration with prior therapy. This signal of disease control is exceptional for patients with previously treated advanced chondrosarcoma. One could posit that these favorable outcomes with ivosidenib, seen in selected patients with mutant *IDH1* tumors, occurred because mutant *IDH1* tumors are clinically indolent compared with wild-type *IDH1* tumors. Currently available literature is mixed in this regard, suggesting both worse and favorable outcomes among mutant *IDH* chondrosarcomas based on retrospective reports.^{38,39}

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Our study also highlights the limitation of using RECIST to meaningfully assess tumor response in patients with chondrosarcoma. Specifically, durable progression-free intervals were seen in several patients treated with ivosidenib despite lack of response on RECIST. Interestingly, there were other imaging features noted in some cases, including reduction in MRI signal enhancement, increased calcifications on CT scans, and reduction in fluorodeoxyglucose avidity over the course of therapy. Similar limitations with RECIST have been reported in clinical trials for patients with other types of sarcoma.⁴⁰ There is therefore a need to develop additional methods to quantify treatment benefit in these tumor types.

Although the results of this phase I trial are encouraging and provide hope for patients with chondrosarcoma, this analysis focused primarily on tolerability in a limited number of patients with chondrosarcoma. Overall survival was also not captured in this patient cohort, and therefore, it was not possible to draw conclusions on whether there is a survival benefit with ivosidenib. Patient samples were also limited for translational studies, and therefore, longitudinal mutational analysis could not be performed to determine the emergence of resistant clones during treatment.

In conclusion, ivosidenib showed durable disease control in patients with mutant *IDH1* conventional chondrosarcoma. In addition to minor tumor regression by RECIST, four patients received treatment for ≥ 2.5 years without PD, and substantial reductions in 2-HG were reported in the plasma and available tumor biopsies. Importantly, ivosidenib was well tolerated, with no dose-limiting toxicities and few grade ≥ 3 treatment-related AEs. The recommended phase II dose was determined to be 500 mg once daily. The development of ivosidenib has the potential to offer therapy to patients with mutant *IDH1* chondrosarcoma who have no treatment options.

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EQUAL CONTRIBUTION

W.D.T. and V.M.V. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.02492>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Safety and Clinical Activity in Patients With Advanced Chondrosarcoma**

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