Phase I Assessment of Safety and Therapeutic Activity of BAY1436032 in Patients with IDH1-Mutant Solid Tumors

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ABSTRACT

Purpose: BAY1436032, an inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1), was active against multiple IDH1-R132X solid tumors in preclinical models. This first-in-human study was designed to determine the safety and pharmacokinetics of BAY1436032, and to evaluate its potential pharmacodynamics and antitumor effects.

Patients and Methods: The study comprised of dose escalation and dose expansion cohorts. BAY1436032 tablets were orally administered twice daily on a continuous basis in subjects with m*IDH1* solid tumors.

Results: In dose escalation, 29 subjects with various tumor types were administered BAY1436032 across five doses (150–1,500 mg twice daily). BAY1432032 exhibited a relatively short half-life. Most evaluable subjects experienced target inhibition as indicated by a median maximal reduction of plasma R-2-hydroxyglutarate levels of 76%. BAY1436032 was well tolerated and an MTD was not identified. A dose of 1,500 mg twice daily was selected for dose expansion, where 52 subjects were treated in cohorts representing four different tumor types [lower grade glioma (LGG), glioblastoma, intrahepatic cholangiocarcinoma, and a basket cohort of other tumor types]. The best clinical outcomes were in subjects with LGG ($n = 35$), with an objective response rate of 11% (one complete response and three partial responses) and stable disease in 43%. As of August 2020, four of these subjects were in treatment for >2 years and still ongoing. Objective responses were observed only in LGG.

Conclusions: BAY1436032 was well tolerated and showed evidence of target inhibition and durable objective responses in a small subset of subjects with LGG.

Introduction

Somatic hotspot mutations in isocitrate dehydrogenase 1 (*IDH1*) have been identified in a variety of cancers (reviewed in refs. 1, 2). In solid tumors, mutant *IDH1* (m*IDH1*) is found in >70% of lower grade gliomas (LGG; grades 2 and 3) and secondary glioblastoma (GBM; grade 4; ref. 3). *IDH1* mutations are also found at lower frequencies in a variety of other cancers, such as intrahepatic cholangiocarcinoma (4, 5) and chondrosarcoma (6). For gliomas, the updated World Health Organization (WHO) classification will strictly use *IDH* status to distinguish gliomas with and without this mutation, renaming what was previously known as secondary (m*IDH*) GBM to astrocytoma WHO grade 4 (7).

Tumor-associated mutations in IDH1 change the conserved arginine at codon 132 in the active site to a variety of alternative amino acids, and in doing so, confer a neomorphic activity to this enzyme. Whereas wild-type IDH1 (wtIDH1) catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG), mIDH1 converts α-KG to R-2-

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Translational Relevance

Mutations in isocitrate dehydrogenase 1 (m*IDH1*) have been identified in a variety of cancers and are therapeutically actionable in subjects with advanced acute myeloid leukemia, where inhibition of m*IDH1* induces a proper differentiation program in leukemic blasts. However, there are no approved therapies specifically for subjects with m*IDH1* solid tumors. This article describes the results of the first-in-human phase I clinical study of the m*IDH1* inhibitor, BAY1436032. In this multipart dose escalation and dose expansion study, BAY1436032 was administered to subjects with advanced m*IDH1* solid tumors. BAY1436032 was well tolerated and demonstrated target inhibition at the dose selected for evaluation in expansion cohorts. Evidence of clinical activity, including durable objective responses, was seen in a subset of heavily pretreated subjects with m*IDH1* lower grade glioma. These findings support the continued clinical evaluation of m*IDH1* inhibitors in this patient population and indicate that some solid tumors may be susceptible to differentiation therapy.

hydroxyglutarate (R-2HG), which inhibits α-KG–dependent enzymes, thereby leading to epigenetic alterations and ultimately impaired differentiation and altered cell growth (8–14).

BAY1436032 is an oral small-molecule inhibitor of all known activating IDH1-R132X mutations, which has shown efficacy in preclinical models of acute myeloid leukemia (AML) and glioma (11, 15). BAY1436032 is brain penetrant in mice and in models of intracranial m*IDH1* glioma, enhances survival, suppresses R-2HG production, and induces markers of differentiation (11, 16).

Supported by these encouraging preclinical findings, BAY1436032 was evaluated in a phase I clinical study in subjects with advanced m*IDH1* solid tumors (NCT02746081), the results of which are presented herein. The study was designed to determine the MTD or the recommended phase II dose (RP2D) of BAY1436032, and to characterize its safety, tolerability, pharmacokinetics, and preliminary pharmacodynamics and antitumor activity in subjects with mIDH1-R132X advanced solid tumors.

Patients and Methods

Study design

This study was an open-label, multicenter, first-in-human, phase I dose escalation trial conducted at a total of 13 sites in Denmark, Germany, Japan (dose expansion only), and the United States. The primary objective was to determine the safety, tolerability, and MTD or RP2D of BAY1436032 in subjects with mIDH1-R132X advanced solid tumors. Secondary objectives were to evaluate the pharmacokinetics of BAY1436032 (including evaluation of a standard, high-fat, and high-calorie meal on pharmacokinetics), and to assess pharmacodynamics effects and evidence of clinical efficacy associated with BAY1436032 administration.

The study consisted of dose escalation to determine MTD or RP2D, followed by dose expansion to further explore safety and clinical efficacy at the MTD or RP2D. Subjects with any type of mIDH1-R132X advanced solid tumor were eligible for dose escalation, while subjects in dose expansion were enrolled to one of four cohorts: LGG, GBM, intrahepatic cholangiocarcinoma, or a basket of "other tumor types" (OTT). The LGG cohort was initially termed the "anaplastic glioma" cohort in the protocol, but because subjects with tumors originally classified as grade 2 were also eligible for enrollment, the term LGG, which incorporates both grade 2 and 3 gliomas (3), more accurately reflected the composition of this cohort. BAY1436032 tablets were orally administered twice daily on a continuous basis in 21-day cycles.

The starting dose was 300 mg per day (150 mg twice daily). Subjects continued receiving BAY1436032 until disease progression, unacceptable toxicity, consent withdrawal, removal from the study at the investigator's discretion, or death. After implementation of an amendment during dose expansion, treatment postprogression was permitted upon agreement between the investigator and the study sponsor.

Dose escalation was conducted in sequential dose cohorts, with each cohort being comprised of a minimum of three and a maximum of nine subjects evaluable for dose-limiting toxicities (DLT). Treatment of a minimum of three DLT-free subjects was required prior to escalating to a higher dose. Cohort sample size of three to nine DLT evaluable subjects in dose escalation was chosen based on experience and simulation results from an adaptive Bayesian dose DLT model. This number of subjects is anticipated to provide sufficient safety information to help guide dose escalation decisions in a reasonable time frame, without exposing an excess number of subjects to potentially toxic or inactive doses of study drug. The details of the DLT evaluation period (21 days), and the consequences if a DLT was observed, are listed in Supplementary Materials and Methods. The MTD was defined as the highest dose of BAY1436032 that could be given such that ≤25% of subjects were predicted to experience a DLT. If MTD was not reached in dose escalation, a RP2D for use in dose expansion was to be selected on the basis of available pharmacokinetics, pharmacodynamics, safety, tolerability, and clinical efficacy data.

The study protocol was approved by the institutional review board of the participating institutions and complied with the Declaration of Helsinki, current Good Clinical Practice guidelines, and local laws and regulations. Written informed consent was provided by all participants prior to the initiation of any study-specific procedure. The study was sponsored by Bayer AG.

Subjects

Male and female subjects of ≥18 years of age with a histologically confirmed advanced solid tumor harboring a missense mutation in IDH1-R132X as assessed by a DNA-based test were eligible. Some additional important eligibility criteria include: (i) patients with advanced cancer who are refractory to, have demonstrated intolerance to, or have refused access to available standard therapies; (ii) disease must be evaluable as per RECIST 1.1 or response assessment in neuro-oncology (RANO; for gliomas), and at least one measurable target lesion was required in expansion cohort patients; and (iii) patients must be able to provide a formalin-fixed, paraffin-embedded tumor tissue specimen prior to treatment. The specimen may have been taken at any time during the course of the disease and may be from the primary tumor or from a metastasis.

Prior treatment with any therapy targeting mIDH1 (including BAY1436032) was exclusionary.

Assessments

Safety

Safety and tolerability were evaluated by analysis of adverse events (AE), physical examinations, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and various laboratory assessments. Weekly clinic visits were scheduled to monitor safety.

Cardiac function was assessed with triplicate 12-lead electrocardiogram at screening and at multiple timepoints during treatment as detailed in Supplementary Materials and Methods.

Severity of AEs was graded by investigators according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. AEs were presented by the Medical Dictionary for Regulatory Activities v22.0.

Subjects must have taken ≥80% of scheduled doses of study drug during C1 or have taken ≥1 dose of study drug and experienced a DLT in C1 to be considered DLT evaluable. A DLT was defined as any of the following events occurring in a DLT evaluable subject during C1 which was regarded as being at least possibly related to study drug. The hematologic events included: (i) absolute neutrophil count (ANC) $<0.5 \times 10^9$/L for ≥7 days; (ii) febrile neutropenia, defined as ANC <1,000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour; and (iii) platelets $<25 \times 10^9$/L for any length of time or $<50 \times 10^9$/L for ≥7 days or $<50 \times 10^9$/L for any length of time concurrent with grade ≥2 active bleeding.

The nonhematologic events included any grade ≥3 nonhematologic toxicity with the following exceptions: (i) nausea, vomiting, and diarrhea responsive to medical intervention within 7 days; (ii) transient fatigue (grade 3 for ≥ 3 days); and (iii) isolated asymptomatic elevations in biochemistry laboratory values lasting for ≥7 days (including electrolyte abnormalities responsive to medical intervention).

The miscellaneous events included: (i) missing >25% of doses of study drug due to any drug-related toxicity grade ≥2; (ii) delay of the start of C2 by >14 days due to any drug-related toxicity grade ≥2; (iii) any other toxicity that in the view of the investigator represented a clinically significant risk to the subject; and (iv) for certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and the sponsor would determine whether the AE should be classified as a DLT.

Therapeutic activity

Tumor assessment by CT scan or MRI was to be performed at screening, and approximately every 6 weeks (two cycles) thereafter until C11 (i.e., day 1 ± 3 days of C3, C5, C7, and C9). Starting with C11, tumor assessments could be performed every four cycles instead of every two. Tumor assessment was also performed at the end of treatment, if not performed within the prior 30 days. For subjects who are currently on treatment, tumor assessment is performed as per local standard of care.

Pharmacokinetics

Details on the procedure used to quantify BAY1436032 in plasma, timepoints of plasma collection, pharmacokinetics assessments that were conducted to evaluate a potential food effect, and population pharmacokinetic-pharmacodynamic modeling that was performed, are included in Supplementary Materials and Methods.

Pharmacodynamics

Plasma R-2HG concentrations were measured from samples collected at various timepoints as described in Supplementary Materials and Methods.

Mutational analysis

Only subjects with a tumor-associated IDH1-R132X mutation detected by a DNA-based test were eligible for enrollment. A subset of subjects with available tumor tissue was also retrospectively evaluated for alterations in genes other than *mIDH1*. Mutational analysis details are described in Supplementary Materials and Methods.

Results

Subject enrollment, baseline characteristics, and treatment

A total of 224 subjects were enrolled and 125 of these subjects failed prescreening because of the absence of an IDH1-R132X mutation and were deemed ineligible (**Fig. 1**). Of the 99 subjects who were eligible based on m*IDH1* testing, 18 failed main screening. Ultimately, 81 subjects received BAY1436032 treatment between July 15, 2016 and the data analysis cutoff date of November 8, 2018, at which time enrollment was complete and the study was ongoing with eight subjects still receiving study drug (Supplementary Table S1). All 81 treated subjects were included in the safety analysis set and 71 were evaluable for response via RANO or RECIST.

BAY1436032 tablets were orally administered twice daily on a continuous basis, and each treatment cycle was 21 days long. The dosing schedule and starting dose were selected on the basis of preclinical pharmacokinetics modeling and safety data. In dose escalation, 29 m*IDH1* subjects were treated across five cohorts at doses of 150 mg twice daily to 1,500 mg twice daily. Tumor types treated in dose escalation were LGG ($n = 14$), intrahepatic cholangiocarcinoma ($n = 9$), GBM ($n = 3$), and OTT ($n = 3$; two chondrosarcomas and one pancreatic adenocarcinoma). In dose expansion, 52 m*IDH1* subjects were treated at 1,500 mg twice daily (LGG, $n = 25$; GBM, $n = 13$; intrahepatic cholangiocarcinoma, $n = 7$; and OTT, $n = 7$).

Baseline demographics and disease characteristics of the 81 treated subjects are listed in **Table 1**. The majority of subjects were male (73%) and had a baseline ECOG <2 (98%). Median age and time since initial cancer diagnosis was 47 years (19–81) and 254 weeks (31–887), respectively. Subjects had a median of 2.5 (1–10) prior lines of systemic anticancer therapies. The most common tumor types were LGG (48%), GBM (20%), and intrahepatic cholangiocarcinoma (20%), and the most common *IDH1* mutations were R132**H** (64%) and R132**C** (23%).

Pharmacokinetics and target inhibition assessment

Pharmacokinetics analysis was performed on C1-D1 after single-dose oral administration and on C1-D15 following continuous twice daily dosing. For subjects participating in pharmacokinetics analyses, the evening dose was withheld on C1-D1, after which time twice daily dosing commenced. Following single-dose administration, BAY1436032 plasma concentrations were detectable 30 minutes after administration. Maximum plasma concentrations were observed approximately 2–3 hours after single-dose and continuous twice daily administration (Supplementary Fig. S1; Supplementary Table S2). In the dose range of 150–1,200 mg, BAY1436032 exposure was broadly dose proportional, with high intra- and intersubject variability. Although the half-life of BAY1436032 could not be accurately determined because of insufficient elimination phase data, it is apparent that maximal BAY1436032 plasma concentrations significantly decreased during the administration interval associated with twice daily dosing.

Results from a preliminary assessment conducted to evaluate a potential food effect on BAY1436032 exposure are described in Supplementary Results.

To evaluate potential effects of the study drug on target inhibition, R-2HG levels were measured in plasma samples obtained at baseline and at various timepoints during treatment. Circulating R-2HG levels in subjects with wt*IDH1* cancers are reported to be approximately 61 ng/mL, and the 97th percentile upper reference limit found in healthy individuals is approximately 138 ng/mL (17, 18).

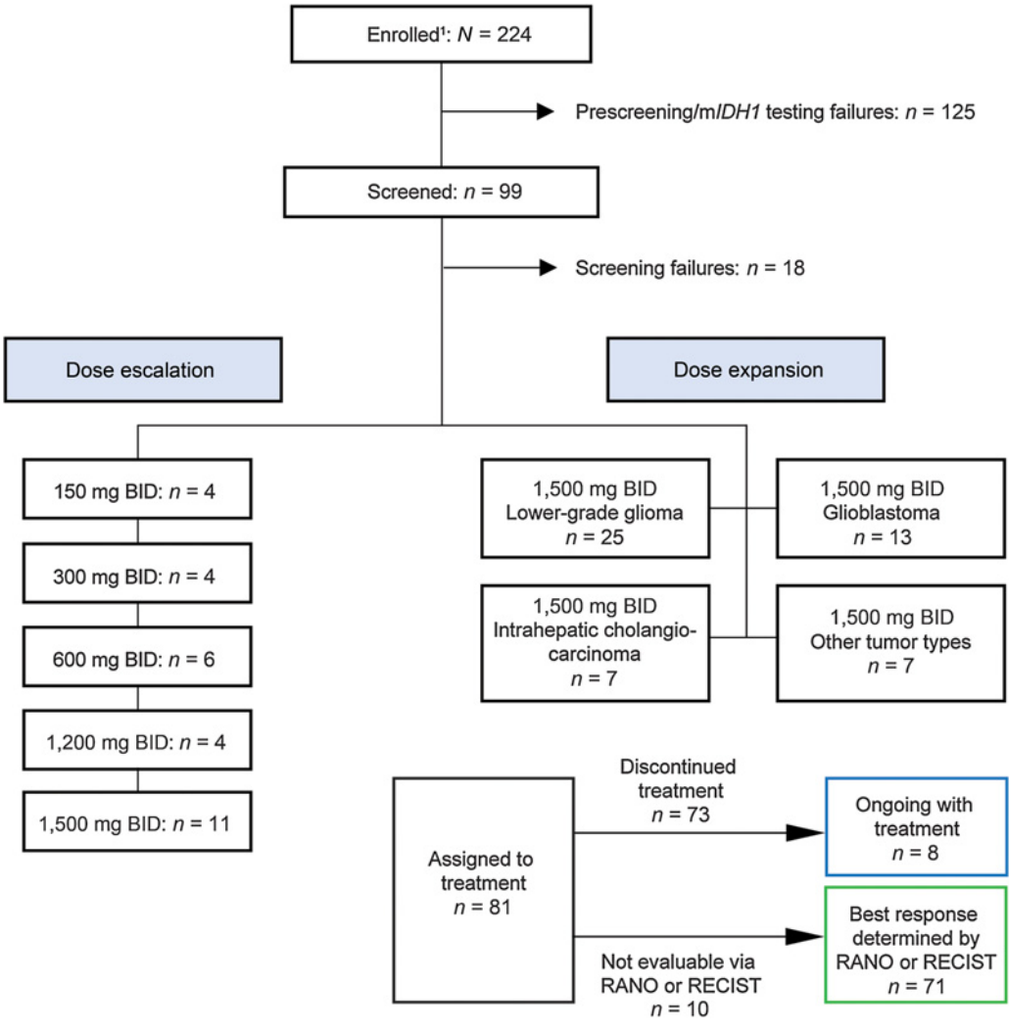

Figure 1.

Subject disposition at the time of database cutoff. This chart shows the number of subjects enrolled in the study and their subsequent allocation to dose escalation or dose expansion treatment cohorts. Also shown are the number of subjects treated, the number of subjects still ongoing in treatment at the time of data cutoff (November 8, 2018), and the number of subjects evaluable via RANO or RECIST and included in the best response analysis. The most common reasons for main screening failures were: (i) inability to meet inclusion criteria related to adequate bone marrow, liver, and renal function and (ii) meeting an exclusion criteria for a clinically relevant ECG finding. The 10 subjects who were not evaluable via RANO or RECIST had discontinued treatment before their first on-treatment scan. BID, twice daily; *n*, number of subjects. [1], enrolled = signed informed consent for prescreening (m*IDH1* testing) and/or screening.

As anticipated (19), subjects with glioma did not show elevated baseline plasma R-2HG levels, and thus potential effects of BAY1436032 on target inhibition could not be evaluated in this population. However, 76% (20/26) of the nonglioma subjects treated in this study showed a baseline R-2HG level >138 ng/mL. Subjects with intrahepatic cholangiocarcinoma had a median baseline R-2HG level of 452 ng/mL (134–1,782) and R-2HG levels for 15 of these subjects were evaluated during BAY1436032 treatment (Supplementary Table S3). Among these subjects, there was a median maximal decrease of 76% (0–98), with 67% (10/15) showing a decrease to <138 ng/mL. Suppression of plasma R-2HG was evident as soon as 4 hours after administration of the first dose of BAY1436032 and was sustained in some subjects over many cycles of treatment (**Fig. 2**; Supplementary Table S3). In some cases, R-2HG levels increased concurrently with disease progression.

Selection of dose for expansion cohorts

The decision to stop dose escalation at the 1,500 mg twice daily dose and to use this dose for expansion cohorts was based on the finding that C1-D1 pharmacokinetics did not show an increase in C_{max}, $AUC_{(0-12)}$, or $AUC_{(0-24)}$ for 1,500 versus 1,200 mg (Supplementary Fig. S1; Supplementary Table S2), and that a subject with intrahepatic cholangiocarcinoma treated at 1,200 mg twice daily showed an R-2HG decrease from 1,782 ng/mL at baseline to 32 ng/mL at C2-D1, representing target inhibition of 98% (Supplementary Table S3). In addition, a subject with LGG treated at 1,200 mg twice daily during dose escalation experienced a durable complete response (CR) and both 1,200 and 1,500 mg twice daily doses were safe and tolerable (see below). Finally, subjects treated at 1,500 mg twice daily were already taking a large number of tablets (20/day), and due to nonclinical safety

Table 1. Demographics and baseline clinical characteristics.

	Dose escalation					Dose expansion				
	150 mg BID ($n = 4$)	300 mg BID ($n = 4$)	600 mg BID ($n = 6$)	1,200 mg BID ($n = 4$)	1,500 mg BID ($n = 11$)	LGG 1,500 mg BID ($n = 25$)	GBM 1,500 mg BID ($n = 13$)	ICC 1,500 mg BID ($n = 7$)	OTT 1,500 mg BID ($n = 7$)	Total ($N = 81$)
Sex, *n* (%)										
Female	0	0	2 (33)	1 (25)	3 (27)	7 (28)	5 (39)	3 (43)	1 (14)	22 (27)
Male	4 (100)	4 (100)	4 (67)	3 (75)	8 (73)	18 (72)	8 (62)	4 (57)	6 (86)	59 (73)
Age										
Median, years (range)	31 (27–36)	51 (43–59)	47 (29–81)	46 (38–48)	53 (33–74)	44 (29–67)	43 (23–53)	65 (60–73)	58 (19–74)	47 (19–81)
Tumor type, *n* (%)										
LGG astrocytoma	1 (25)	1 (25)	4 (67)	3 (75)	1 (9)	16 (64)	0	0	0	26 (32)
LGG oligodendroglioma	0	3 (75)	0	0	1 (9)	9 (36)	0	0	0	13 (16)
GBM	2 (50)	0	0	0	1 (9)	0	13 (100)	0	0	16 (20)
ICC	0	0	1 (17)	1 (25)	7 (64)	0	0	7 (100)	0	16 (20)
OTT	1 (25)	0	1 (17)	0	1 (9)	0	0	0	7 (100)	10 (12)
ECOG performance status, *n* (%)										
0	1 (25)	1 (25)	1 (17)	1 (25)	7 (64)	8 (32)	6 (46)	3 (43)	5 (71)	30 (37)
1	3 (75)	3 (75)	4 (67)	3 (75)	4 (36)	16 (64)	7 (54)	4 (57)	2 (29)	49 (60)
2	0	0	1 (17)	0	0	1 (4)	0	0	0	2 (2)
Time since initial diagnosis										
Median, weeks (range)	250 (74–343)	230 (58–344)	200 (60–649)	406 (98–651)	153 (58–673)	425 (56–887)	296 (84–678)	56 (31–130)	139 (59–524)	254 (31–887)
IDH1 mutation[a], *n* (%)										
Unknown	0	0	0	0	0	0	1 (8)	0	0	1 (1)
R132H	2 (50)	4 (100)	5 (67)	3 (75)	3 (27)	22 (88)	12 (92)	0	1 (14)	52 (64)
R132C	1 (25)	0	1 (17)	0	5 (45)	2 (8)	0	6 (86)	4 (57)	19 (23)
R132G	0	0	0	0	1 (9)	0	0	1 (14)	1 (14)	3 (4)
R132L	1 (25)	0	0	1 (25)	1 (9)	0	0	0	0	3 (4)
R132S	0	0	0	0	1 (9)	1 (4)	0	0	1 (14)	3 (4)
Subjects who received prior radiotherapy										
n, (%)	4 (100)	4 (100)	4 (67)	3 (75)	4 (36)	23 (92)	13 (100)	1 (14)	3 (43)	59 (73)
Number of prior systemic anticancer therapies										
Median (range)	2 (1–4)	3 (2–5)	2.5 (1–2)	1.5 (1–2)	2 (1–3)	3 (1–7)	4 (1–10)	2 (1–4)	2 (1–3)	2.5 (1–10)

Abbreviations: BID, twice daily; ICC, intrahepatic cholangiocarcinoma; *n*, number.
[a]As determined by local and/or central DNA-based testing.

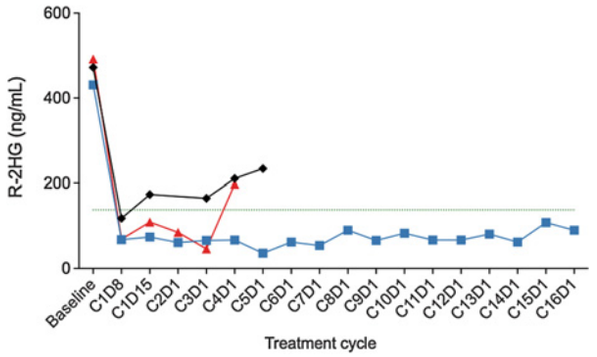

Figure 2.

Plasma R-2HG levels over time in a subset of subjects with intrahepatic cholangiocarcinoma. R-2HG levels are depicted for three representative subjects with intrahepatic cholangiocarcinoma. Each subject was treated with BAY1436032 at 1,500 mg twice daily and cycle length was 21 days. See Supplementary Table S3 for complete R-2HG data from all subjects with intrahepatic cholangiocarcinoma. Red triangles indicate a subject who showed best response of SD, with PFS of 2.3 months and maximum R-2HG inhibition of 91%. Blue squares indicate a subject who showed best response of SD, with PFS censored at 9.7 months (subject was ongoing at the time of data cutoff) and maximum R-2HG inhibition of 92%. Black diamonds indicate a subject who showed best response of SD, with PFS of 2.8 months and maximum R-2HG inhibition of 75%. The dotted line indicates R-2HG levels associated with healthy individuals (138 ng/mL).

results and the specificity of BAY1436032 for the mutant form of IDH1, identification of the MTD was not anticipated.

Safety assessments in dose escalation and expansion cohorts

Dose escalation cohorts

A total of 38% (11/29) of subjects experienced at least one treatment-emergent AE (TEAE) related to BAY1436032, and events occurring in ≥5% of subjects are listed in **Table 2**. All events were grade ≤2 and none were serious or led to dose modification or study drug discontinuation. No subject treated in dose escalation cohort experienced a DLT. MTD was not reached, and 1,500 mg twice daily was selected for use in dose expansion.

A total of 86% (25/29) of subjects experienced at least one TEAE irrespective of relationship to study drug, with a TEAE grade ≥3 being reported for 41% (12/29; Supplementary Table S4). TEAEs resulting in dose modification occurred in 17% (5/29), with 14% (4/29) discontinuing study drug as a result of TEAEs. A total of 14% (4/29) experienced fatal AEs, none related to study drug.

During dose escalation, there were no deaths attributable to study drug.

Dose expansion cohorts

BAY1436032 also exhibited a good safety profile in dose expansion (1,500 mg twice daily). A total of 33% (17/52) of treated subjects experienced at least one TEAE related to BAY1436032, most of mild or moderate severity (**Table 2**). A total of 12% (6/52) experienced a TEAE grade ≥3 related to study drug, one of which was grade ≥4 (grade 4 lipase increase). In addition, one subject treated with BAY1436032 in Japan experienced an AE of grade 3 maculopapular rash that was assessed as drug related and a DLT, as DLT criteria were also defined in dose expansion per local study protocol (Japan regulatory requirement). Following treatment and recovery, this subject resumed administration of study drug at a reduced dose (1,200 mg twice daily) and experienced a treatment-emergent serious AE (TESAE) of grade 3 hypersensitivity that was assessed as drug related. Study drug was then permanently discontinued, and the episode of hypersensitivity subsequently resolved.

A total of 94% (49/52) of subjects experienced at least one TEAE irrespective of relationship to study drug, with TEAE grade ≥3 being reported for 72% (28/52; Supplementary Table S4). TEAEs resulting in dose modification occurred in 31% (12/52), with 24% (9/52) discontinuing study drug as a result of TEAEs. A total of 15% (6/52) experienced fatal AEs, none related to study drug.

During dose expansion, there were no deaths attributable to study drug.

Therapeutic activity

Overall

Of the 81 treated subjects, 71 (26 from dose escalation and 45 from dose expansion) were evaluable via RANO or RECIST and included in the best response evaluation (**Table 3**). Among these 71 subjects, objective responses were experienced by 6% [one CR and three partial responses (PR)] and stable disease (SD) by 41%. The progression-free survival (PFS) rate at 3 months was 0.25 (0.15–0.35). As of August 2020, four subjects were still taking study drug and had been on treatment for >2 years (Supplementary Table S1). Results by tumor type are as follows:

LGG: Thirty-five subjects were evaluable via RANO across all dose levels and best responses were CR in 3% (1/35) and PR in 9% (3/35), for an objective response rate (ORR) of 11% (4/35). Two additional subjects showed tumor decreases of >30% from baseline, but did not reach a sufficient level of shrinkage to be considered an objective response. A best response of SD was achieved in 43% (15/35) and the PFS rate at 3 months was 0.31 (0.15–0.46; **Table 3**; Supplementary Table S5). Thirty-three of the 35 evaluable subjects with LGG had a measurable lesion (contrast enhancing) at study entry (Supplementary Table S5). Maximum change from baseline in the sum of target lesions is shown in **Fig. 3A** and treatment duration in **Fig. 3B**. Two of the subjects who experienced an objective response (OR; one CR and one PR), and two who had a best response of SD, were still receiving BAY1436032 treatment as of August 2020 and have been taking study drug for >2 years. Details on these four subjects, as well as the two other subjects with LGG who experienced an OR and are currently off study, are shown in Supplementary Table S9. Each of these subjects had undergone surgery and had received prior radiotherapy and temozolomide; most had also received additional prior systemic therapies. MRI scans from one of these subjects are shown in Supplementary Fig. S2. This subject had a diagnosis of oligodendroglioma, had initiated BAY1436032 treatment in July 2018, and was still taking the study drug as of August 2020. At the time of data cutoff, this subject had been on BAY1436032 treatment for 4.2 months and had experienced a maximal tumor decrease of 36%, and a best response of SD. A comparison of scans taken at screening with those taken during BAY1436032 treatment shows reduced contrast enhancement in the later scans.

OTT: Of the 10 subjects evaluable via RECIST across all dose levels, best response was SD in 50% (no OR) and the PFS rate at 3 months was 0.23 (0–0.51; **Table 3**; Supplementary Table S6). Maximum change from baseline in the sum of target lesions and treatment duration are shown in Supplementary Fig. S3.

Intrahepatic cholangiocarcinoma: Twelve subjects were evaluable via RECIST across all dose levels and best response was SD in 42%

Table 2. BAY1436032-related TEAEs occurring in ≥5% of subjects in dose escalation and dose expansion.

		Dose escalation					
TEAE	**CTCAE grade**	**150 mg BID ($n = 4$)**	**300 mg BID ($n = 4$)**	**600 mg BID ($n = 6$)**	**1,200 mg BID ($n = 4$)**	**1,500 mg BID ($n = 11$)**	**Total $N = 29$ (%)**
Diarrhea	Grade 1	0	0	0	0	2	2 (7)
Nausea	Grade 1	0	0	0	0	1	1 (3)
	Grade 2	0	0	0	0	1	1 (3)
Vomiting	Grade 1	1	0	0	0	1	2 (7)
Fatigue	Grade 1	0	1	1	1	0	3 (10)
	Grade 2	0	0	0	1	0	1 (3)
Dysgeusia	Grade 1	0	1	0	1	1	3 (10)
		Dose expansion					
TEAE	**CTCAE grade**	**1,500 mg BID $n = 52$ (%)**					
ALT increase	Grade 2	1 (2)					
	Grade 3	2 (4)					
AST increase	Grade 1	1 (2)					
	Grade 2	2 (4)					
Lipase increase	Grade 1	1 (2)					
	Grade 2	1 (2)					
	Grade 3	1 (2)					
	Grade 4	1 (2)					
Nausea	Grade 1	2 (4)					
	Grade 2	1 (2)					
	Grade 3	1 (2)					
Appetite decrease	Grade 1	1 (2)					
	Grade 2	2 (4)					

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; *n*, number of subjects.

(no OR). The PFS rate at 3 months was 0.10 (0–0.29; **Table 3**; Supplementary Table S7). Maximum change from baseline in the sum of target lesions and treatment duration are shown in Supplementary Fig. S3.

GBM: Fourteen subjects were evaluable via RANO across all dose levels and best response was SD in 29% (no OR). The PFS rate at 3 months was 0.22 (0–0.44; **Table 3**; Supplementary Table S8). Maximum change from baseline in the sum of target lesions and treatment duration are shown in Supplementary Fig. S3.

Dose escalation

Of the 26 subjects evaluable via RECIST or RANO, 4% had an OR (one CR) and 55% had a best response of SD. The PFS rate at 3 months was 0.25 (0.08–0.42; Supplementary Table S9). As of August 2020, the subject with LGG who had experienced a CR was the only subject from dose escalation still taking the study drug (1,200 mg twice daily; Supplementary Tables S1 and S10).

Dose expansion

Of the 45 subjects evaluable via RECIST or RANO, 7% had an OR (three PRs) and 33% had a best response of SD. The PFS rate at 3 months was 0.25 (0.12–0.38; Supplementary Table S11). As of August 2020, the only subjects from dose expansion still taking study drug were three subjects with LGG (one with PR and two with SD; Supplementary Tables S1 and S10). Of the four different tumor cohorts evaluated in dose expansion, subjects with LGG showed the best PFS rate at 3 months and LGG was the only tumor type in which ORs were achieved.

Table 3. Best overall investigator-reported response determined by RANO or RECIST.

	Tumor type[a]				
Best response	**OTT ($n = 10$)**	**ICC ($n = 12$)**	**GBM ($n = 14$)**	**LGG ($n = 35$)**	**Total ($N = 71$)**
CR	0	0	0	1 (3)	1 (1)
PR	0	0	0	3 (9)	3 (4)
SD	5 (50)[b]	5 (42)	4 (29)	15 (43)	29 (41)
PD	5 (50)	7 (58)	10 (71)	16 (46)	38 (54)
PFS rate at 3 months[a]	0.23 (0–0.51)	0.10 (0–0.29)	0.22 (0–0.44)	0.31 (0.15–0.46)	0.25 (0.15–0.35)

Abbreviations: ICC, intrahepatic cholangiocarcinoma; *n*, number of subjects; PD, progressive disease.
[a]Best response analysis includes 71 subjects from dose escalation and dose expansion who were evaluable via RANO or RECIST. PFS analysis includes these 71 subjects, in addition to three subjects who had clinical progression without radiological assessment and were not included in the best response analysis.
[b]Number of subjects (%).

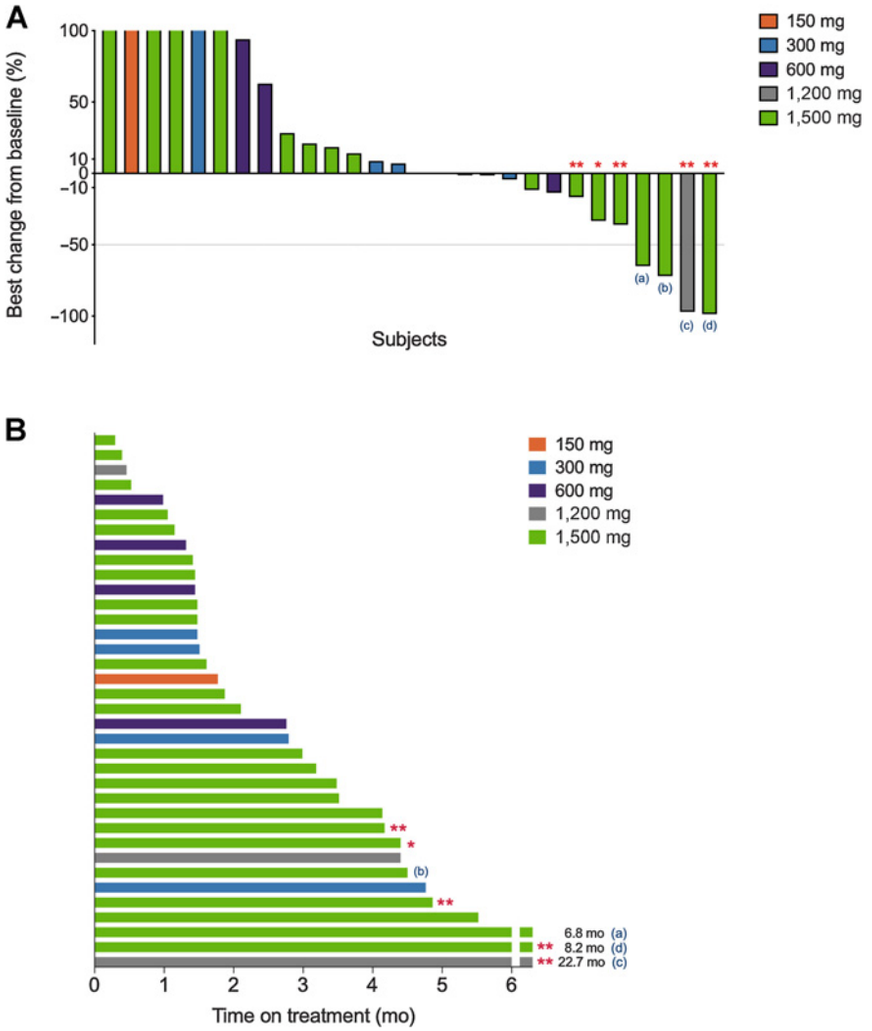

Figure 3.

LGG: maximum change from baseline in the sum of target lesions and duration of treatment. LGG subjects treated in dose escalation and dose expansion were included in the analysis. BAY1436032 was administered twice daily at the doses indicated. Subjects who experienced an objective response are indicated with a–d: (a) anaplastic oligodendroglioma, best response of PR, PFS of 6.5 months (mo); (b) anaplastic oligodendroglioma, best response of PR, PFS of 2.8 months; (c) anaplastic astrocytoma, best response of CR, PFS censored at 22 months (ongoing at the time of data cutoff and still on treatment as of August 2020); and (d) anaplastic astrocytoma, best response of PR, PFS censored at 6.8 months (ongoing at the time of data cutoff and still on treatment as of August 2020). Subjects who were still ongoing at the time of data cutoff (November 2018), but off study as of August 2020, are depicted with a single asterisk, while those still ongoing as of August 2020 (and on treatment for >2 years) are depicted with a double asterisk. **A,** Maximum change from baseline in the sum of target lesions in subjects with valid baseline and during treatment tumor measurements. Measurements are as of the data cutoff date of November 2018. Subjects depicted as having an increase of 100% from baseline had actual increases >100%. **B,** Time on treatment as of the data cutoff date. The actual duration of treatment (in months) at the time of data cutoff is indicated for subjects who had a duration of treatment >6 months by that time.

Pharmacokinetics and pharmacodynamics

A potential association between exposure and clinical outcome was evaluated for a subset of subjects with LGG treated at the two doses at which objective responses were observed (i.e., 1,200 and 1,500 mg twice daily). Pharmacokinetics (C_{max} on C1-D1) and best response data available for 21 such subjects are depicted in Supplementary Fig. S4. This analysis showed no clear relationship between exposure and therapeutic activity. On the basis of the results of this exploratory analysis, additional exposure/response analyses were not performed.

A potential correlation between R-2HG suppression and clinical outcome was evaluated for subjects with intrahepatic cholangiocarcinoma because most had an elevated baseline plasma R-2HG level and had been treated with the highest dose of BAY1436032 tested (1,500 mg twice daily; **Fig. 2**; Supplementary Table S3). Because none of these subjects achieved an OR, PFS and SD were used as measures of potential clinical benefit. While a clear correlation between the level of R-2HG suppression and clinical outcome was not evident, the subject who achieved the longest PFS (censored at 9.7 months because the subject was still in treatment at the time of data cutoff) showed a rapid and robust R-2HG decrease to a level associated with healthy individuals, which was maintained throughout 16 treatment cycles.

Mutational analysis

The frequency of specific *IDH1* mutations detected in each tumor type was consistent with literature reports (3–6, 20), with 93% (50/54) of evaluable subjects with glioma harboring a R132**H** mutation (Supplementary Tables S5 and S8), and the majority of subjects with intrahepatic cholangiocarcinoma (69%; 11/16; Supplementary Table S7) and chondrosarcoma (71%; 5/7; Supplementary Table S6) harboring a R132**C** mutation. Details of the analysis of *IDH1* and other tumor-associated mutations are described in the Supplementary Results.

Discussion

In this study, the mIDH1 inhibitor, BAY1436032, was evaluated at five different dose levels (150–1,500 mg twice daily) in 29 subjects in dose escalation and at 1,500 mg twice daily in 52 subjects in dose expansion. Subjects harbored a mutation which altered the residue at position R132 of IDH1 to any one of a number of different amino acids, each of which is known to generate the R-2HG oncometabolite and to be inhibited by BAY1436032 (11, 15). The decision to use the 1,500 mg twice daily for dose expansion, rather than evaluating additional higher doses was largely based on a comparison of pharmacokinetics

from the 1,200 and 1,500 mg doses, in addition to the findings that the 1,200 mg dose demonstrated near complete suppression of R-2HG and a durable and ongoing CR in a subject with LGG.

BAY1436032 was found to be generally well tolerated. In dose escalation, an MTD was not identified as there were no DLTs or TESAEs, and all drug-related TEAEs were grade ≤2. In dose expansion, there was one drug-related TEAE grade >3 (grade 4 lipase increase), and one subject in Japan experienced an AE of grade 3 maculopapular rash that was assessed as drug related and a DLT, in addition to a drug-related TESAE (grade 3 hypersensitivity), which resolved following discontinuation of study drug. The favorable safety profile of BAY1436032 was consistent with preclinical studies, demonstrating that BAY1436032 is a highly specific inhibitor of mIDH1, which exhibits little activity against wtIDH1 or wtIDH2 (11, 15), and with prior clinical experience with BAY1436032 in subjects with AML (21).

Although overall clinical activity was modest, a subset of subjects with LGG showed clinical benefit, with an ORR of 11% (one CR and three PRs), a best response of SD in 43%, and a 3-month PFS rate of 0.31 (0.15–0.46). Four of these subjects (one CR, one PR, and two SDs) have been on treatment for >2 years and were still ongoing as of August 2020. Each of the subjects with LGG who experienced an OR harbored an anaplastic tumor. The observed clinical activity of BAY1436032 in subjects with LGG was consistent with preclinical experiments (11, 16). None of the subjects with tumor types other than LGG showed an OR or were still on treatment as of August 2020.

The mIDH1 inhibitors, ivosidenib and vorasidenib, were evaluated previously in subjects with glioma (22–26). In a phase I study of ivosidenib in advanced glioma, subjects with nonenhancing glioma showed an ORR of 3% and SD in 86%, while those with enhancing glioma showed no OR and SD in 45% (24). A phase I study of vorasidenib in nonenhancing LGG showed an ORR of 18% (one PR and two minor responses) and SD in 73% (26). While the ORR appears to be at least as good for BAY1436032 as for ivosidenib or vorasidenib, additional measures of clinical activity, such as percentage SD and 3-month PFS rate, appear to be lower for BAY1436032. However, in this study, at least 75% of subjects with LGG had anaplastic tumors, and only enhancing target lesions were considered measurable. Overall, 33 of the 35 evaluable subjects with LGG had contrast-enhancing lesions, as this was an eligibility requirement for subjects enrolled in the dose expansion. In addition, the subjects with LGG in this study who were evaluable for efficacy were heavily pretreated, with each subject having received prior radiotherapy and at least one, and often multiple, prior systemic anticancer therapies. In contrast, in the vorasidenib glioma study, all subjects had nonenhancing tumors, which were mostly grade 2 (26), and in the ivosidenib glioma study, subjects with nonenhancing tumors showed a better clinical outcome than those with enhancing tumors (24). The clinical data from vorasidenib and ivosidenib indicate that BAY1436032 would be anticipated to exhibit better clinical activity in subjects with less advanced, nonenhancing tumors than what was observed in the LGG population treated in this study. It has been hypothesized that more advanced m*IDH1* LGG is less susceptible to m*IDH1* inhibition compared with less advanced LGG, due to their acquisition of additional driver mutations or to their reduced susceptibility to therapeutic reversion of epigenetic changes induced by m*IDH1* (2, 3).

In addition to glioma, ivosidenib was also clinically evaluated in OTT. In a phase III study of ivosidenib in cholangiocarcinoma, the ORR was 2% (three PRs), SD was seen in 51%, and the 6-month PFS was 32% (27), and in a phase I study in chondrosarcoma, there were no OR, SD in 52%, and 3-month PFS in 62% (28). The low ORR observed in this investigation (11% in LGG; no OR in nonglioma tumors) is thus consistent with results obtained for other m*IDH1* inhibitors in subjects with solid tumors, and is in contrast to the relatively high response rate reported for ivosidenib in m*IDH1* AML (29). Because evidence suggests that m*IDH1* inhibition facilitates the differentiation and growth arrest of malignant cells, rather than inducing overt cytotoxicity in these cells (9, 11, 13), the differential clinical activity of these agents in AML versus solid tumors in terms of objective responses is not unexpected.

BAY1436032 showed rapid and robust target engagement as indicated by a decrease in plasma R-2HG to levels associated with healthy individuals in many of the intrahepatic cholangiocarcinoma subjects evaluated, with a median maximal reduction of 76% (0–98). Robust R-2HG suppression was also reported for ivosidenib and vorasidenib (22, 27, 28, 30). Because many subjects with solid tumor treated with m*IDH1* inhibitors showed rapid and sustained suppression of R-2HG without apparent clinical benefit, ancillary factors that may influence response remain to be discovered.

Some limitations of this study include the treatment of only a small number of nonglioma subjects at doses <1,500 mg twice daily ($n = 4$), thereby precluding the conduct of a meaningful dose/pharmacodynamics response analysis based on R-2HG decreases. In addition, the treatment of a small number of subjects with LGG treated at doses <1,500 mg twice daily ($n = 12$ treated across four different doses) makes it difficult to evaluate a potential dose/clinical outcome relationship. Nonetheless, an exploratory analysis showed no clear relationship between exposure and therapeutic activity among subjects with LGG treated at the two doses at which objective responses were observed (i.e., 1,200 and 1,500 mg twice daily). Additional limitations of this study for determining potential maximal efficacy of BAY1436032 in the LGG population include the focus on treating subjects with enhancing versus nonenhancing tumors, and the enrollment of predominantly heavily pretreated/refractory subjects. Finally, fresh baseline biopsies were not required for IDH1 testing, and on-treatment tumor biopsies that could have been used to evaluate potential changes in differentiation-associated genes (11, 16) were not obtained in this study.

In addition to m*IDH1* solid tumors, BAY1436032 was also evaluated in subjects with m*IDH1* advanced AML (NCT03127735; ref. 21). In that study, the objective response rate was 15% (median treatment duration of 6 months for responding subjects), and a best response of SD was achieved by 30% (median treatment duration of 5.5 months). The median maximal R-2HG decrease induced by BAY1436032 was 66% and most subjects did not experience a decrease to a level associated with healthy individuals. Although baseline R-2HG levels were substantially higher in AML (median of 1,755 ng/mL; ref. 21) than in intrahepatic cholangiocarcinoma (452 ng/mL; current study), the level of maximum R-2HG decrease mediated by BAY1436032 does not appear to be influenced by baseline R-2HG levels.

In summary, BAY1436032 was generally well tolerated by subjects harboring various types of m*IDH1* solid tumors, demonstrated target inhibition in most evaluable subjects, and exhibited clinical activity in a subset of subjects with LGG as indicated by durable objective responses and SD. Bayer is not pursuing further clinical development of BAY1436032. BAY1436032 was developed as a collaboration between Bayer and the German Research Cancer Center (DKFZ), which now holds development rights for this investigational agent.

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