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ARTICLE

Acute myeloid leukemia

Safety and efficacy of BAY1436032 in IDH1-mutant AML: phase I study results

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Abstract

The mutant IDH1 (mIDH1) inhibitor BAY1436032 demonstrated robust activity in preclinical AML models, supporting clinical evaluation. In the current dose-escalation study, BAY1436032 was orally administered to 27 mIDH1 AML subjects across 4 doses ranging from 300 to 1500 mg twice-daily. BAY1436032 exhibited a relatively short half-life and apparent non-linear pharmacokinetics after continuous dosing. Most subjects experienced only partial target inhibition as indicated by plasma R-2HG levels. BAY1436032 was safe and a maximum tolerated dose was not identified. The median treatment duration for all subjects was 3.0 months (0.49–8.5). The overall response rate was 15% (4/27; 1 CRp, 1 PR, 2 MLFS), with responding subjects experiencing a median treatment duration of 6.0 months (3.9–8.5) and robust R-2HG decreases. Thirty percent (8/27) achieved SD, with a median treatment duration of 5.5 months (3.1–7.0). Degree of R-2HG inhibition and clinical benefit did not correlate with dose. Although BAY1436032 was safe and modestly effective as monotherapy, the low overall response rate and incomplete target inhibition achieved at even the highest dose tested do not support further clinical development of this investigational agent in AML.

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Introduction

Somatic hotspot mutations in isocitrate dehydrogenase 1 (*IDH1*) have been identified in a variety of cancers, with a frequency of ~7% in acute myeloid leukemia (AML) [1–6]. Tumor-associated *IDH1* mutations (*mIDH1*) change the conserved arginine at codon 132 in the enzymatic active site to a variety of alternative amino acids (R132X), 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-hydroxyglutarate (R-2HG). Subjects with *mIDH1* AML show elevated R-2HG levels, which inhibits α-KG-dependent enzymes, thereby leading to epigenetic alterations and ultimately impaired hematopoietic differentiation [7–14].

BAY1436032 is an oral small-molecule inhibitor of mIDH1 that is active in preclinical models of *mIDH1* cancer [15–17]. Most mIDH1 inhibitors, including BAY1436032, reportedly interact with an allosteric site on the mutant enzyme, although an inhibitor which interacts directly with the active site was recently described [18]. Preclinical experiments focusing on *mIDH1* AML found that BAY1436032 inhibits R-2HG production and colony growth *in vitro*, while promoting leukemic blast clearance, myeloid differentiation, and survival in animal models [16]. Supported by these encouraging preclinical findings, BAY1436032 was evaluated in a phase I clinical study in subjects with *mIDH1* AML (NCT03127735), the results of which are presented herein. Objectives of the study include determination of the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D), and evaluation of the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and clinical activity of BAY1436032.

Materials and methods

Study design

This study was an open-label, nonrandomized, multicenter phase I trial. Subjects were screened at 13 hospital sites in 2 countries (USA and Germany). The study was to consist of dose-escalation followed by dose-expansion. The MTD identified in dose-escalation was to be used in the dose-expansion. If MTD was not reached in dose-escalation, a dose for the expansion would be selected based on available PK, pharmacodynamic, safety, and efficacy data. BAY1436032 was administered twice-daily (BID) in continuous 28-day cycles. In dose-escalation, up to 9 evaluable subjects could be enrolled per cohort, with a minimum of 3 dose-limiting toxicity (DLT)-free evaluable subjects required prior to escalating to the next highest dose. Bayesian dose-DLT modeling was performed to help guide dosing decisions [19]. MTD was defined as the highest dose of BAY1436032 that could be given such that ≤25% of subjects were predicted to experience a DLT.

DLTs were differentially defined for nonhematopoietic versus hematopoietic toxicities. Nonhematopoietic toxicities of ≥grade 3 occurring during the first cycle of treatment were to be considered DLTs with the following exceptions: (1) Alopecia and nausea controlled by medical management; (2) Tumor lysis syndrome if successfully managed clinically and resolved within 7 days without any end-organ damage; (3) Differentiation syndrome (DS) if successfully managed clinically and resolved within 7 days without any end-organ damage; (4) Asymptomatic ≥grade 3 electrolyte abnormalities not considered clinically significant by the investigator. Missing >20% of doses of study drug due to any drug-related toxicity, or delay in the start of cycle 2 by more than 14 days due to any drug-related toxicity, were also considered DLTs. For certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and the sponsor determined whether the adverse event (AE) should be assessed as a DLT.

For hematological toxicities, thrombocytopenia of ≥grade 3 with clinically significant bleeding, or grade 4 neutropenia persisting 42 days after the start of treatment in the absence of active AML, were considered DLTs.

DLTs identified during the first cycle of treatment were used to guide dose-escalation decisions and to determine the MTD, and if safety issues appeared in subsequent cycles they were also to be considered. Hydroxyurea was permitted during the first cycle if white blood cell (WBC) exceeded 20×10^9/L and was also permitted for treatment of DS.

The study protocol was approved by the institutional review board of 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. Data were entered into clinical research forms by the study investigators and their staff. The study was sponsored by Bayer AG.

Subjects

Male and female subjects of ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and advanced AML were eligible. Information regarding ELN 2010 risk classification was collected during screening [20]. Subjects were required to harbor a missense mutation in *IDH1-R132X* based on local testing reported by study investigators, with sponsor review of test results prior to enrollment. *IDH1* mutational status from a bone marrow

sample collected during screening was retrospectively evaluated at Foundation Medicine. Subjects were to be relapsed or refractory to at least 1 previous line of therapy, or intolerable to or unable to receive established therapies, and could have received any number and type of prior therapies prior to enrollment, except those targeting mIDH1. A cohort sample size of 3 to 9 DLT-evaluable subjects in dose-escalation was chosen based on experience and simulation results from 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. Dose-expansion was not conducted in this study.

Study assessments

The primary objectives of the study were to determine the safety, tolerability, MTD, and/or RP2D dose of BAY1436032 administered in a twice-daily dosing schedule in subjects with *mIDH1* advanced AML. Secondary objectives were to evaluate PK and to assess pharmacodynamic effects and evidence of clinical efficacy.

Safety

Safety and tolerability were evaluated by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and various laboratory assessments. For safety monitoring, subjects were scheduled for clinic visits every week for the initial three cycles of treatment, after which time visits could be reduced to every-other-week with investigator and sponsor agreement. Cardiac function was assessed with triplicate 12-lead electrocardiograms (ECG) at screening, C1-D1, C1-D2, C1-D15, D1 of every subsequent cycle, and at treatment end. Severity of adverse events and toxicities were graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. AEs are presented by the Medical Dictionary for Regulatory Activities (MedDRA) v21.1.

Efficacy

Disease assessments and response evaluations from bone marrow aspirate or biopsy were scheduled at screening, C2-D1, C3-D1, D1 of every second cycle thereafter, and at treatment end (if not done on D1 of the last cycle). Peripheral blood was analyzed at each of these time points and at additional times between bone marrow assessments. Clinical efficacy was assessed by investigators using the modified 2003 International Working Group response criteria for AML [21] with some changes based on 2017 European Leukemia Net recommendations [22]. Response categories included: complete remission (CR), morphologic CR with incomplete hematological recovery (CRh), morphologic CR with incomplete platelet recovery (CRp), morphologic leukemia-free state (MLFS), partial remission (PR), stable disease (SD), and progressive disease (PD). Overall response rate included CR, CRh, CRp, MLFS, and PR. Following study completion, investigators provided survival information.

Pharmacokinetics

Plasma samples were collected at various times on C1-D1, C1-D2, C1-D8, and C1-D15 and stored frozen for PK assessments. Collection times on these days are indicated on Supplementary Fig. S1 (C1-D8 PK results are not shown). The evening dose of BAY1436032 was withheld on C1-D1 to facilitate assessment of the 24-h single-dose time point on C1-D2. Quantitative analysis of BAY1436032 (free acid) in plasma was performed as described in Supplementary Methods.

Pharmacodynamics

For quantification of R-2HG, plasma samples were collected at the following time points and stored frozen: screening, C1-D1 (pre-dose and post-dose), C1-D8 (pre-dose), C1-D15 (pre-dose and post-dose), C1-D22 (pre-dose), pre-dose on D1 and D15 of each cycle thereafter, and at treatment end. Plasma R-2HG concentrations were measured by Eurofins as described in Supplementary Methods.

Retrospective mutational analysis

Mutational analysis was performed on bone marrow aspirates or biopsies collected during screening and on a subset of samples collected during BAY1436032 treatment. Testing was performed by Foundation Medicine using the FoundationOne Heme panel which detects alterations in >400 tumor-associated genes via next-generation sequencing. Information provided by Foundation Medicine included the allelic frequency and the likely pathogenic nature of each alteration identified.

Results

Subjects

Thirty-three *mIDH1* AML subjects signed informed consent, 27 received BAY1436032 treatment and 6 failed

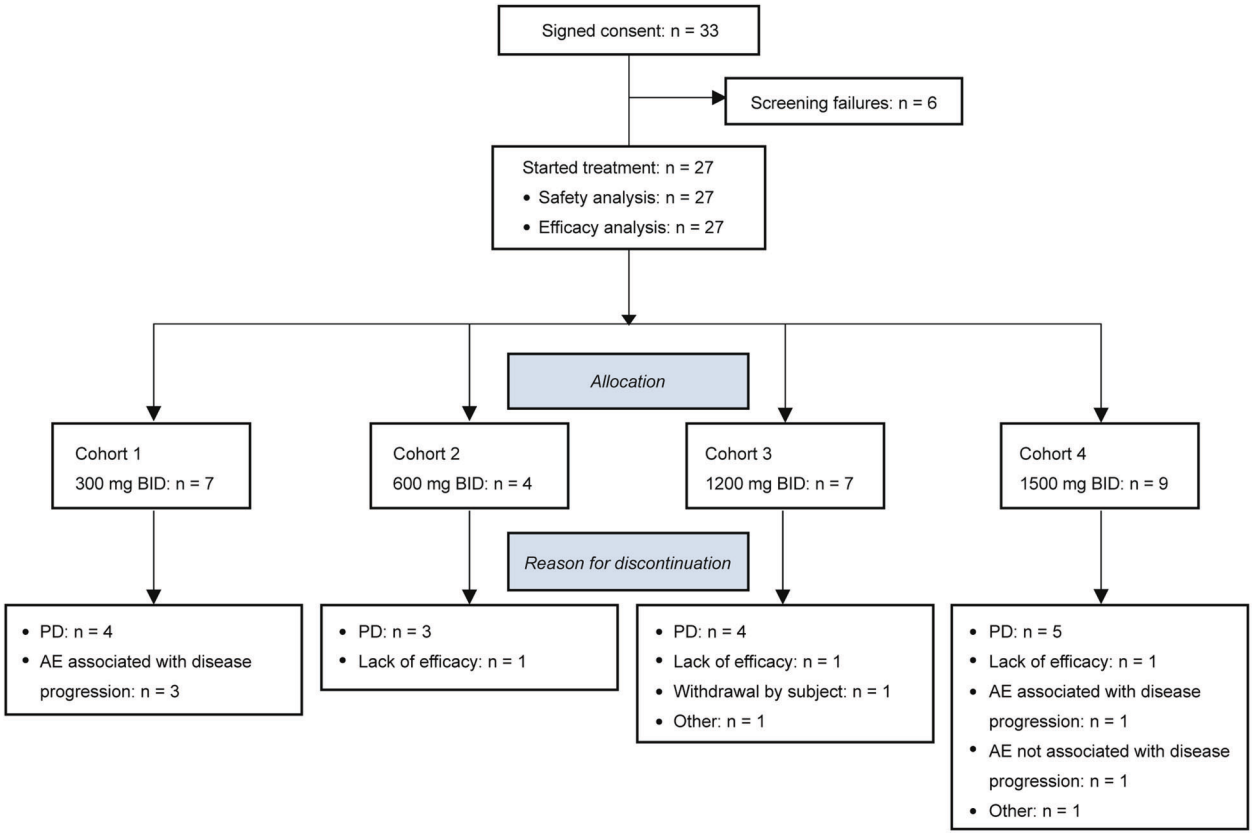

Fig. 1 Subject disposition. The chart shows an overview of subjects who signed consent to participate in the study, their allocation into dose-escalation treatment cohorts, and reasons for their discontinuation from the study.

screening for various reasons (e.g., presence of an uncontrolled infection). The first subject started treatment on June 28, 2017 and the last study visit was on December 5, 2018. All subjects were treated within dose-escalation, and a planned dose-expansion was not pursued. BAY1436032 tablets were orally administered BID, with the evening dose withheld on the first day of treatment to facilitate PK analysis. Administration was continuous and each treatment cycle was 28 days. Subjects were treated across 4 dosing cohorts: cohort 1 (300 mg BID; $n = 7$); cohort 2 (600 mg BID; $n = 4$); cohort 3 (1200 mg BID; $n = 7$) and cohort 4 (1500 mg BID; $n = 9$) (Fig. 1). The dosing schedule and starting dose were selected based on preclinical PK modeling and safety data, and on the results of the ongoing first-in-human phase I trial of BAY1436032 in subjects with *mIDH1* solid tumors (NCT02746081; [23]). Baseline demographics and disease characteristics are provided in Table 1. Subjects had received a median of 2 (0–8) prior systemic therapies for AML and 4 had received no prior systemic therapies. The prevalence of individual *IDH1-R132X* mutations across the 27 treated subjects based on investigator-reported information was as follows: R132C ($n = 15$), R132H ($n = 5$), R132G ($n = 3$), R132L and R132S ($n = 2$ each). Consistent with previous reports [4, 24], R132C and R132H were the most prevalent *IDH1* mutations identified.

Pharmacokinetics and Pharmacodynamics

PK analysis was performed on C1-D1 after single-dose oral administration and on C1-D15 following continuous BID dosing. Following single oral administration, BAY1436032 plasma concentrations were detectable 30 min after administration. Maximum plasma concentrations were observed ~3 to 4 h after single-dose and continuous BID administration (Supplementary Fig. S1). In the evaluated dose range, BAY1436032 exposure after single-dose administration generally increased in a dose-proportional manner (1.6–2.0-fold); however, dose-proportionality was not apparent after continuous BID administration. Minimal accumulation was evident at C1-D15 and inter-subject variability was high in all cohorts for the main PK parameters evaluated (Supplementary Fig. S1 and Table S1).

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 time points during

Table 1 Baseline demographic and disease characteristics[a].

	Cohort 1: 300 mg BID $n = 7$	Cohort 2: 600 mg BID $n = 4$	Cohort 3: 1200 mg BID $n = 7$	Cohort 4: 1500 mg BID $n = 9$	Total $n = 27$
Age [median (range), in years]	67 (37–86)	72 (51–76)	70 (42–83)	68 (27–79)	69 (27–86)
Sex, *n* (%)					
Male	4 (57)	2 (50)	3 (43)	3 (33)	12 (44)
Female	3 (43)	2 (50)	4 (57)	6 (67)	15 (56)
AML classification, *n* (%)					
De novo AML	5 (71)	3 (75)	4 (51)	7 (78)	19 (70)
Secondary AML	2 (29)	1 (25)	3 (43)	2 (22)	8 (30)
ECOG performance status, *n* (%)					
0	1 (14)	1 (25)	1 (14)	1 (11)	4 (15)
1	4 (57)	2 (50)	6 (86)	7 (78)	19 (70)
2	2 (29)	1 (25)	0	1 (11)	4 (15)
Time from initial diagnosis to 1st dose of study drug [median (range), in months][b]	9 (1–32)	10 (2–19)	9 (1–25)	15 (5–44)	11 (1–44)
ELN risk classification, *n* (%)[c]					
Favorable	0	0	1 (14)	2 (22)	3 (11)
Intermediate	1 (14)	1 (25)	3 (43)	2 (22)	7 (26)
Adverse	4 (57)	2 (50)	2 (29)	5 (56)	13 (48)
Missing	2 (29)	1 (25)	1 (14)	0	4 (15)
mIDH1 identified, *n* (%)[d]					
R132C	3 (43)	2 (50)	5 (71)	5 (56)	15 (56)
R132H	3 (43)	0	0	2 (22)	5 (19)
R132G	1 (14)	2 (50)	0	0	3 (11)
R132L	0	0	2 (29)	0	2 (7)
R132S	0	0	0	2 (22)	2 (7)
Number of prior systemic antileukemic lines of therapies for AML, [median (range)]	1 (0–4)	1 (1–3)	2 (0–4)	3 (1–8)	2 (0–8)
Subjects having received at least 1 prior systemic antileukemic therapy for AML, *n* (%)	5 (71)	4 (100)	5 (71)	9 (100)	23 (85)
Prior allogeneic transplantation					
No	6 (86)	4 (100)	7 (100)	7 (78)	24 (89)
Yes	1 (14)	0	0	2 (22)	3 (11)

BID twice-daily, *ECOG* Eastern Cooperative Oncology Group, *ELN* European LeukemiaNet, *n* number of subjects.

[a]Percentages are calculated including missing values.

[b]For the calculation of time from initial diagnosis, only subjects with complete date information (year, month, day) are included.

[c]ELN classification as per 2010 recommendations [20].

[d]Investigator-reported *mIDH1* results used for subject enrollment are shown. Retrospective evaluation of baseline leukemic samples at a central laboratory via next-generation sequencing confirmed investigator-reported results in all evaluable cases.

treatment. Baseline R-2HG levels were highly variable, with a median concentration of 1755 ng/mL (78–14,749) (Supplementary Table S2). Of the 27 subjects treated, 26 had baseline R-2HG levels above those seen in *wtIDH1* cancers (61 ng/mL) and above the 97th percentile upper reference limit found in healthy individuals (138 ng/mL) [25, 26].

All subjects achieved a lowering of baseline R-2HG levels during BAY1436032 treatment, with a median maximal decrease across all subjects of 66% (16–99) (Supplementary Table S2). However, only 5/26 subjects with an elevated baseline R-2HG level experienced a reduction to a normal level of ≤138 ng/mL. Maximal R-2HG decreases did not show a clear relationship with

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