The first-in-human phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001 in patients with recurrent or progressive IDH1-mutant gliomas

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Conflict of Interest

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Abstract

Background: Approximately 70% of lower-grade gliomas harbor isocitrate dehydrogenase 1 (IDH1) mutations, resulting in accumulation of oncometabolite D-2-hydroxyglutarate (D-2-HG); this leads to epigenetic dysregulation, oncogenesis, and subsequent clonal expansion. DS-1001 is an oral brain-penetrant mutant IDH1 selective inhibitor. This first-in-human study investigated the safety, pharmacokinetics, pharmacodynamics, and efficacy of DS-1001.

Methods: This was a multicenter, open-label, dose-escalation, phase I study of DS-1001 for recurrent/progressive IDH1-mutant (R132) glioma (N = 47) (NCT03030066). DS-1001 was administered orally at 125–1400 mg twice daily. Dose escalation used a modified continual reassessment method.

Results: The maximum tolerated dose was not reached. Eight patients were continuing treatment at the data cut-off. Most adverse events (AEs) were grade 1–2. Twenty patients (42.6%) experienced at least one grade 3 AE. No grade 4 or 5 AEs or serious drug-related AEs were reported. Common AEs (>20%) were skin hyperpigmentation, diarrhea, pruritus, alopecia, arthralgia, nausea, headache, rash, and dry skin. The objective response rates were 17.1% for enhancing tumors and 33.3% for non-enhancing tumors. Median progression-free survival was 10.4 months (95% confidence interval [CI], 6.1 to 17.7 months) and not reached (95% CI, 24.1 to not reached) for the enhancing and non-enhancing glioma cohorts, respectively. Seven on-treatment brain tumor samples showed a significantly lower amount of D-2-HG compared with pre-study archived samples.

Conclusions: DS-1001 was well-tolerated with a favorable brain distribution. Recurrent/progressive IDH1-mutant glioma patients responded to treatment. A study of DS-1001 in patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 glioma is ongoing (NCT04458272).

Keywords: DS-1001, brain-penetrant selective IDH1 inhibitor, D-2-HG, IDH1-mutant gliomas, lower-grade glioma

Key points

- DS-1001 is an oral brain-penetrant selective inhibitor of mutant IDH1
- IDH1-mutant glioma patients responded to DS-1001, which was well-tolerated
- This is the first report demonstrating responses including CR with an IDH inhibitor

Importance of the Study

Mutations of the isocitrate dehydrogenase (*IDH*) gene, the majority of which are *IDH1* R132H mutations, are the hallmark of lower-grade gliomas. Mutant IDH1 harbors a neomorphic activity resulting in accumulation of the oncometabolite D-2-hydroxyglutarate (D-2-HG). In preclinical studies, DS-1001 has been shown to inhibit mutant IDH1, reducing D-2-HG levels and tumor size. This multicenter, open-label, dose-escalation, phase I study investigated the tolerability of DS-1001 administered orally at 125–1400 mg twice daily for recurrent/progressive IDH1 mutant glioma (N = 47, of which 27.7% were 1p/19q codeleted). The objective response rates were 17.1% for enhancing tumors and 33.3% for non-enhancing tumors. The status of 1p/19q was not associated with outcome. DS-1001 was well-tolerated with favorable brain distribution and produced a reduction in tumor D-2-HG levels.

Introduction

According to the latest World Health Organization (WHO) Classification of Tumours of the Central Nervous System (WHO CNS5), adult-type diffuse gliomas are classified based on the isocitrate dehydrogenase 1/2 (IDH1/2) mutations and 1p/19q codeletion statuses.[1–4] Oligodendrogliomas are defined by the presence of IDH1/2 mutations and 1p/19q codeletion, whereas astrocytomas are diagnosed when IDH1/2 mutations but not 1p/19q codeletion are present. Thus, the presence of IDH mutation represents a fundamental characteristic of lower-grade gliomas. The most frequent mutation (83%–90%) of IDH1/2 in lower-grade gliomas is a substitution of the amino acid residue 132 from arginine to histidine (R132H) in IDH1.[5–8] While wild-type IDH1 catalyzes the oxidative decarboxylation of isocitrate and produces alpha-ketoglutarate in the tricarboxylic acid cycle,[9] mutant IDH1 produces the oncometabolite D-2-hydroxyglutarate (D-2-HG). D-2-HG competitively inhibits alpha-ketoglutarate–dependent dioxygenases, including epigenetic regulators.[10–14] It has been suggested that the accumulation of D-2-HG leads to early gliomagenesis, followed by clonal expansion through epigenetic dysregulation.[15,16] Complete surgical removal of IDH-mutated gliomas cannot be achieved because of their infiltrative nature, resulting in recurrence, malignant progression, and eventual fatality.[2] Current treatment strategies are

radiotherapy and chemotherapy. However, radiotherapy can induce sequelae such as neurocognitive and neuroendocrine dysfunction,[3,17–21] and chemotherapeutic strategies are often only transiently effective, highlighting the need for novel therapeutic strategies to treat gliomas. Therefore, the neomorphic enzymatic activity of mutant IDH1 serves as a potential therapeutic target for IDH1-mutant tumors.

DS-1001 is an orally available, small molecule selective mutant IDH1-R132 inhibitor with high permeability through the blood–brain barrier. In preclinical studies, DS-1001 showed good distribution to the brain in mice.[22] Tumor growth inhibition and D-2-HG reduction were also observed in an orthotopic patient-derived xenograft model by continuous administration of DS-1001. Given these findings, inhibition of mutant IDH1 by DS-1001 could provide a novel therapeutic approach in patients with IDH1-mutant gliomas.

Here, we report the results of a first-in-human study of DS-1001, which aimed to investigate the maximum tolerated dose (MTD), recommended phase II dose (RP2D), tolerability and safety profiles, pharmacokinetics (PK), pharmacodynamics (PDy), and efficacy of DS-1001 in patients with IDH1-mutated gliomas.

Patients and Methods

Study Design

This was a multicenter, phase I, open-label study (NCT03030066). We present the results up to the data cut-off (January 31, 2021). The institutional review board of each participating center approved the trial. The study was performed according to the Declaration of Helsinki (1996 revision), under the principles of good clinical practice. All participants provided written informed consent before screening and enrollment.

Patients

For inclusion in the study, patients (≥ 20 years old) had to meet all of the following criteria: histologically confirmed glioma (grades 2–4) with an IDH1-R132 mutation; recurrent or progressive disease (PD) following standard treatment including radiotherapy; measurable lesion(s) as per Response Assessment in Neuro-Oncology (RANO)[23] and RANO-low-grade glioma (RANO-LGG)[24] criteria; an expected survival of ≥ 3 months; Eastern Cooperative Oncology Group performance status of 0 to 2; adequate hematological function (absolute neutrophil count ≥ 1200/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 9.0 g/dL); hepatic function (total bilirubin ≤ 1.5

mg/dL, and aspartate transaminase and alanine aminotransferase ≤ 100 IU/L) and renal function (serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min). Patients underwent baseline screening evaluations within 14 days before study Day 1. Background data were collected from patients' health records; previous MRI and pathology material were also evaluated.

Treatment Regimen, Drug Administration, and Dose Escalation

DS-1001 (supplied by Daiichi Sankyo Co., Ltd.) was administered orally twice daily (bid) in 21-day cycles until disease progression or intolerable toxicity occurred. The dose escalation was guided by the modified continual reassessment method (mCRM) according to a Bayesian logistic regression model,[25] and governed by the escalation with overdose control principle.[26] Cohorts of three to six patients were enrolled and assessed for dose-limiting toxicity (DLT) before escalation to a new higher dose. Six dose levels (125–1400 mg bid) were tested (**Table S1**).

Safety Evaluation

Safety assessments included adverse events (AEs), serious AEs (SAEs), treatment-emergent AEs (TEAEs), physical examination findings, Karnofsky Performance Status, and laboratory parameters (hematology and serum chemistry). TEAEs were documented at each study visit and were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). DLTs are those not associated with the underlying disease or its progression, complications, or concomitant drugs and are detected during the 21-day treatment cycle. Cardiac toxicity was monitored by left ventricular ejection fraction assessments using echocardiography or multiple gated acquisition.

Pharmacokinetics

Blood samples were collected for PK analysis for DS-1001 at protocol-defined time points. Each patient underwent serial blood sample collection by venipuncture at DS-1001 pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 h after morning dose on Days 1 and 8 in Cycle 1. Additionally, a single pre-dose blood sample was collected on Days 4, 6, and 15 of Cycle 1 and Day 1 of Cycle 2. Plasma PK parameters for DS-1001, including the maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the area under the

plasma concentration–time curve up to 8 h post-dose ($AUC_{0–8h}$), were calculated by non-compartmental methods using Phoenix™ WinNonlin® Version 8.1 (Certara, Princeton, NJ, USA). For exploratory purpose, cerebrospinal fluid (CSF) samples were collected at screening and on Day 15 of Cycle 1 (±3 days). Patients in the exploratory study received DS-1001 treatment until surgery, and plasma and tumor samples were obtained prior to salvage surgical resection. DS-1001 concentrations in plasma, CSF, and resected tumor tissue samples were measured by liquid chromatography tandem-mass spectrometry (LC-MS/MS).

Efficacy Measurements

Malignant transformation of Grade 2 gliomas is often associated with tumor contrast enhancement on T1-weighted brain MRI. Therefore, patients were divided into enhancing and non-enhancing groups based on the presence or absence of tumor contrast enhancement judged by each investigator at the time of enrollment to estimate the grade at the time of drug administration.

Using MRI, investigators assessed treatment efficacy every 6 weeks. Tumor response was assessed by RANO for enhancing tumors and RANO-LGG for non-

enhancing tumors. Briefly, the area of the longest diameter of the lesion and the largest size orthogonal to the longest diameter (as the shorter diameter) were measured in the largest slice of the flare high or T2 images, as described previously.[27] A second scan confirmed the best overall response at 4 weeks or more after the initial assessment. Endpoints included best overall response and objective response rate (ORR) (defined as proportion of patients with a confirmed best overall response of complete response [CR], partial response [PR], or minor response [MR]). Progression-free survival (PFS) was defined as the interval from the first dose to disease progression or death from any cause, whichever occurred first.

We also performed an exploratory analysis in patients who planned to undergo salvage surgery after developing PD, had provided informed consent, and received DS-1001 treatment until surgery. Tumor samples were obtained from those patients to measure the free form of DS-1001 and D-2-HG levels for PK and PDy analyses.

Pharmacodynamic D-2-HG Assessment

Patients who planned to undergo salvage surgery after developing PD and provided informed consent received DS-1001 treatment until surgery. Tumor samples and corresponding plasma samples were provided on the day of the surgery. DS-1001

concentrations in the resected tumor samples and corresponding plasma samples were measured using validated LC-MS/MS methods. Tumor tissues were homogenized in 0.1 w/v% bovine serum albumin solution. Then, D-2-HG concentrations in the tissues were measured by LC-MS/MS after derivatization with diacetyl-L-tartaric anhydride.[28] Commercially available D-2-HG (Sigma-Aldrich Co. LLC., Tokyo, Japan) was used as a reference standard. This analysis was conducted at Shin Nippon Biomedical Laboratories, Ltd. (Wakayama, Japan).

1p/19q Detection

Multiplex ligation-dependent probe amplification analysis of initial tumor biopsy samples was implemented to determine the 1p/19q status for the diagnosis of oligodendroglioma. The analysis to determine the 1p/19q status for the diagnosis of oligodendroglioma was performed using the SALSA MLPA Probemix P088 kit and Coffalyser.Net software (MRC Holland, Amsterdam, the Netherlands) according to the manufacturer's recommendation.[29]

Statistical Analysis

The minimum number of patients necessary to accurately select the MTD and/or RP2D using the mCRM was set at 18. The maximum number of patients was set at 60 considering potential drop-outs and evaluating safety, tolerability, PK, PDy, and preliminary antitumor effect.

All patients who received at least one dose of DS-1001 were included in the safety analyses, with the MTD analysis only including patients who met predefined adequate exposure criteria. Efficacy analyses included patients who had at least one available efficacy measurement after the start of study treatment. PK analyses included patients who had at least one PK sample obtained, analyzed, and measured. Analyses of AEs included TEAEs (i.e., those who started or worsened in severity on or after initiating treatment until 28 days after the last dose of DS-1001). AEs were counted once per patient using coded preferred terms at the worst severity and strongest causality. Medical coding of AEs was based on the Medical Dictionary for Regulatory Activities version 23.1, and AEs and laboratory test results were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Demographics, safety, efficacy, and PK data were summarized descriptively. We used SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) for statistical analyses.

Results

Patient Characteristics

Between January 2017 and January 2021, 47 patients were enrolled in the study. Patient characteristics are shown in **Table 1**. Four of the 47 patients had oligodendroglioma (IDH-mutant, grade 2) and 11 had oligodendroglioma (IDH-mutant, grade 3). Twelve had astrocytoma (IDH-mutant, grade 2), 11 had astrocytoma (IDH-mutant, grade 3), and 7 had astrocytoma (IDH-mutant, grade 4). Thirty-five patients had enhancing tumors, and 12 had non-enhancing tumors. The presence of IDH1 mutations was determined by the local investigators at each site. All patients received radiotherapy prior to enrollment in the study; 30 of 35 patients (85.7%) with enhancing tumors, and eight of 12 patients (66.7%) with non-enhancing tumors received chemotherapy prior to enrollment in the study. The median times since the end of the last systemic therapy and radiotherapy were 2.8 months and 35.7 months, respectively.

A total of 39 patients discontinued the study: 30 discontinued due to PD, one discontinued due to an AE of alanine aminotransferase increased, seven withdrew consent, and one discontinued for a reason unrelated to the treatment. At the time of the

data cut-off (January 31, 2021), eight patients were receiving ongoing treatment in this study.

Safety

All 47 patients were evaluable for safety. The MTD was not reached, even at the highest dose level of 1400 mg bid. One DLT, grade 3 white blood cell count decreased, occurred at a dose of 1000 mg bid. Most patients (45 of 47 [95.7%]) experienced at least one AE of any grade or causality. The most common AEs (≥ 20%) were skin hyperpigmentation (53.2%), diarrhea (46.8%), pruritus (29.8%), alopecia (27.7%), arthralgia (27.7%), nausea (25.5%), headache (23.4%), rash (23.4%), back pain (21.3%), and dry skin (21.3%) (**Table 2**). Most AEs were grade 1–2. No grade 4 or 5 AEs or serious drug-related AEs were reported. Twenty (42.6%) subjects experienced at least 1 Grade 3 TEAE, Grade 3 events that were reported in more than 1 subject were neutrophil count decreased (12.8%), alanine aminotransferase increased (6.4%), white blood cell count decreased (6.4%), aspartate aminotransferase increased (4.3%), diarrhea (4.3%), and hypophosphatemia (4.3%)

Twenty-seven (57.4%) subjects had at least 1 dose interruption due to TEAEs. Most frequently reported TEAEs (≥ 10%) leading to dose interruption included neutrophil count decreased (6 [12.8%]) and arthralgia (5 [10.6%]). TEAEs associated with dose reduction were reported in 13 patients (27.7%), most of which were pain-related events (arthralgia [10.6%], back pain [6.4%], and neck pain [2.1%]) or laboratory test-related events (neutrophil count decreased [6.4%], alanine aminotransferase increased [4.3%], and white blood cell count decreased [4.3%]). These pain-related TEAEs were characterized as late onset, mostly grade 1 or 2, and reversible, and they persisted for a long time while the study drug was being administered in some of the patients. Overall, DS-1001 had a favorable safety profile.

Pharmacokinetics

Following oral administration of DS-1001, the median T_{max} was observed at 2–6 hours on Day 1 of Cycle 1 and 2–4 hours on Day 8 of Cycle 1 across the dose range of 125–1400 mg bid (**Table S2**). Mean plasma trough concentration reached a plateau after the pre-dose at Day 4, except for the 1400-mg bid dose, suggesting that the steady-state levels were achieved by Day 4 of DS-1001 dosing at most dose levels (data not shown).

On Day 1 and Day 8 of Cycle 1, the increase in C_{max} and $AUC_{0–8h}$ was approximately dose-proportional from 125 to 700 mg bid and was less than dose-proportional from 700 to 1400 mg bid (**Table S2** and **Figure S1**). DS-1001 also appeared in CSF on Day 15 of Cycle 1, which demonstrated the distribution of DS-1001 in the CNS (**Figure S2**).

Efficacy

All 47 patients were evaluable for efficacy. In the 35 enhancing tumors assessed by RANO, we observed two CRs and four PRs. In the 12 non-enhancing tumors assessed by RANO-LGG, we found one PR and three MRs. The ORRs were 17.1% for enhancing tumors and 33.3% for non-enhancing tumors (**Table 3**). The waterfall plot shows the best percentage change in target tumor size (**Figure 1A, B**). In patients with measurable disease at baseline, tumor measurements decreased from baseline in 15 of 35 patients with enhancing tumors (42.9%) and 11 of 12 patients with non-enhancing tumors (91.7%; **Figure 1A, B**). Notably, among the 35 patients with enhancing tumors, two patients showed CR. The patient with astrocytoma (IDH-mutant, grade 4) has experienced CR for approximately 174 weeks and is still on treatment. The other patient

with IDH1-mutant anaplastic oligodendroglioma has experienced CR for approximately 95 weeks and is still on treatment. Furthermore, three patients with enhancing tumors showed significant tumor shrinkage, approaching CR. MRI scans of a patient who showed CR and a patient who showed MR are shown in **Figure S3**. Five of the 10 responders have had a continuous response and remain on treatment. The treatment duration was from 123 weeks to 207 weeks. The median response duration has not been reached for both lesion types.

The 1p/19q codeletion was detected in 10 of 35 patients with enhancing tumors (28.6%) and three of 12 patients with non-enhancing tumors (25.0%; **Table 1**). Measurable response was observed in both 1p/19q codeleted and non-codeleted cases (**Figure S4**).

At the time of the data cut-off (January 31, 2021), eight patients (17.0%) remained on treatment, and 39 patients (83.0%) discontinued treatment, mainly due to disease progression. Patients with enhancing gliomas had a median treatment duration of 7.3 (range, 0–190) weeks, and three patients (8.6%) remain on treatment. In patients with non-enhancing gliomas, the median treatment duration was 91.2 (range, 15–207) weeks, and five of 12 patients (41.7%) remain on treatment (**Table S3**). The swimmers plot showed that the duration of the response was remarkably long once the tumor

responded in both enhancing and non-enhancing tumors (**Figure 1C, D**). The median PFS were 10.4 weeks (95% confidence interval [CI], 6.1 to 17.7 weeks) for the enhancing glioma cohorts, and not reached (95% CI, 24.1 to not reached) for the non-enhancing glioma cohorts, across all doses (**Figure S5**).

Pharmacodynamic Analysis

To examine whether the drug penetrated into the brain and inhibited the production of D-2-HG in the tumor tissue, we conducted an additional exploratory study in patients with PD who underwent salvage surgery (**Figure S6**). These patients continued the treatment until surgery, and the concentrations of DS-1001 and D-2-HG were measured in resected tumor tissues (**Table 4**). Even though the dose of DS-1001 and sampling time from the last dose varied among the patients, a high drug concentration was detected in all resected tumor samples, indicating the highly efficient brain penetration of the drug. The D-2-HG levels were also measured in the matched archived frozen tumor tissues collected at the previous surgery when available. The D-2-HG levels in the plasma were not elevated above normal levels in patients with glioma; however, the D-2-HG levels in on-treatment tumor tissues were extremely low compared with

matched archived samples (**Figure 2**). The D-2-HG levels in archived and post-treatment tumor tissues of each patient are shown in **Table S4**. The amount of D-2-HG was considerably lower after treatment than before with DS-1001. D-2-HG levels in CSF were not evaluable as a PDy marker due to being below the measurement limit (data not shown).

Discussion

The rationale for targeting mutant IDH in diseases such as acute myeloid leukemia has been proven to be well founded.[30,31] However, substantial clinical benefits following IDH inhibitor treatment remain to be confirmed. Nonetheless, the mutant IDH is an attractive molecular target for glioma therapy, with mutant IDH inhibitors including ivosidenib (AG-120),[32,33] vorasidenib (AG-881),[34,35] olutasidenib (FT-2102),[36] and BAY1436032[37] currently being evaluated in clinical trials involving patients with gliomas. Our present study shows that twice-daily oral administration of DS-1001 resulted in antitumor activity in patients with recurrent/progressive IDH1-mutated gliomas.

The most common AE in the present study was grade 1/2 hyperpigmentation, which resembled sunburn and was observed only on the face and forearms. The mechanism of this symptom is still unknown; however, it was reversible and manageable. While most AEs were grade 1/2, at doses ≥ 500 mg bid, most patients who received long-term administration of DS-1001 required dose modifications due to episodes of pain. On the other hand, at doses ≤ 250 mg BID, there was no dose modification due to pain. Therefore, we considered < 500 mg bid to be more appropriate doses for future clinical trials for diseases requiring long-term administration of DS-1001, such as chemotherapy- and radiotherapy-naïve *IDH1*-mutated WHO grade 2 gliomas. Although the data are limited, responses were observed at doses ≥ 125 mg bid. Furthermore, 125 mg bid of DS-1001-treated brain tumor samples showed significantly lower levels of D-2-HG compared with the pre-treatment samples. Considering the *in vitro* half maximal inhibitory concentration data, the concentration of DS-1001 in the brain tumor was sufficient to account for this effect.[22] From the PK/PDy data, the safety profile and preliminary clinical responses, ≤ 250 mg bid was selected as the RP2D. DS-1001 was well-tolerated and had a favorable safety profile, indicating that this agent can be administered for long-term treatment.

Among the 47 patients, 10 showed tumor regression, including two CRs, five PRs, and three MRs after DS-1001 treatment. We observed a 17.1% ORR for patients with contrast-enhancing gliomas: two CRs, four PRs, and the duration of response was sustainable. To the best of our knowledge, the ORRs reported here are the highest in this class of agents.[38,39] Moreover, DS-1001 treatment showed similar response in both 1p/19q codeleted and non-codeleted populations (**Table S5 and Figure S4**). While the mutation of IDH1 is considered to occur early on during gliomagenesis,[2] our findings suggest that some enhancing (malignant transformed) tumors and even recurrent malignant gliomas are still dependent on mutated IDH1 or D-2-HG production. Two patients achieved CR and showed long-term efficacy, suggesting that DS-1001 may be a promising option for such patients. As expected, the ORR was even higher at 33.3% in less aggressive non-enhancing gliomas, and many enhancing gliomas were refractory to the mutated IDH1 inhibitor. Notably, the resected tumors on treatment beyond PD displayed a significantly low amount of D-2-HG even after PD, suggesting that such refractory tumors developed mutations in other driver genes rather than acquired resistance to DS-1001 through trans/cis dimer interface mutation within IDH1/2.[40]

DS-1001 is the first IDH inhibitor showing responses, including CR, in patients with recurrent/progressive IDH1-mutated glioma. On-treatment tumor samples showed

favorable brain distribution of DS-1001 and significantly low levels of D-2-HG in brain tumors with DS-1001. Data from this first-in-human phase I study suggest that DS-1001 was well-tolerated and had a favorable safety profile. Further follow-up and additional clinical studies are clearly warranted for this agent. A phase II study of DS-1001 in patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas is ongoing to verify the efficacy of DS-1001 as a single agent (NCT04458272). And, another phase II study is planned outside Japan to evaluate the efficacy of DS-1001 (by AnHeart Therapeutics under the name AB-218), in patients with recurrent/progressive IDH1 mutated WHO Grade 2/3 gliomas after receiving maximum 2 prior therapies for disease recurrence/progression (NCT05303519).

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Data sharing statement

De-identified individual participant data and applicable supporting clinical trial documents may be available upon request at https://vivli.org/. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web https://vivli.org/ourmember/daiichi-sankyo/.

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Figure Legends

Figure 1. Efficacy of DS-1001: waterfall plot of best percentage change in target tumor size in patients with (A) enhancing tumors and (B) non-enhancing tumors, and swimmers plot of the duration of response in patients with (C) enhancing and (D) non-enhancing tumors

Patients with enhancing tumors are shown in panel (A) and non-enhancing tumors in panel (B). In two patients, change in tumor size could not be assessed because they had no target lesion or observed tumor hemorrhage, and thus, these patients were excluded from this analysis. Two patients (denoted by *1–2) showed a change over 100%.

Patients with enhancing tumors are shown in panel (C) and non-enhancing tumors in panel (D). Bar colors represent glioma type (astrocytoma or oligodendroglioma) and bar symbols represent the type of response. Arrows at the end of the bars indicate patients who remained on DS-1001. The length of the bars represents the duration of therapy. In general, long response duration was observed in those who responded to treatment regardless of whether a patient had enhancing or non-enhancing tumors.

Abbreviations: CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Comparison of D-2-HG levels in archived tumor samples versus on-treatment tumor tissues according to DS-1001 dose

Circles represent individual patients, and lines represent the median average D-2-HG concentration at each DS-1001 dose or in archived samples. Tumor D-2-HG concentration at four DS-1001 dose levels (125–700 mg bid) is lower than archived samples.

Abbreviations: bid, twice daily; D-2-HG, D-2-hydroxyglutarate.

TABLES

Table 1. Patient characteristics

Characteristic	Enhancing (n = 35)	Non-enhancing (n = 12)	Total (N = 47)
Median age, years (min, max)	46.0 (29, 77)	38.5 (28, 49)	44.0 (28, 77)
Female, n (%)	14 (40.0)	4 (33.3)	18 (38.3)
ECOG PS, n (%)			
0	19 (54.3)	8 (66.7)	27 (57.4)
1	13 (37.1)	4 (33.3)	17 (36.2)
2	3 (8.6)	0 (0.0)	3 (6.4)
IDH1 mutation, n (%)			
R132H	34 (97.1)	12 (100.0)	46 (97.9)
R132L	1 (2.9)	0 (0.0)	1 (2.1)
Most recent diagnosis, n (%)			
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2	2 (5.7)	2 (16.7)	4 (8.5)
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3	10 (28.6)[a]	1 (8.3)	11 (23.4)
Oligodendroglioma, grade 3, NOS	1 (2.9)	0 (0.0)	1 (2.1)
Astrocytoma, IDH-mutant,	6 (17.1)	6 (50.0)	12 (25.5)

grade 2			
Astrocytoma, IDH-mutant, grade 2, NOS	0 (0.0)	1 (8.3)	1 (2.1)
Astrocytoma, IDH-mutant, grade 3	9 (25.7)	2 (16.7)	11 (23.4)
Astrocytoma, IDH-mutant, grade 4	7 (20.0)	0 (0.0)	7 (14.9)
1p19q status[b], n (%)			
Non-codeleted	22 (62.8)	8 (66.7)	30 (63.8)
Codeleted	10 (28.6)	3 (25.0)	13 (27.7)
Not evaluated	3 (8.6)	1 (8.3)	4 (8.5)
Number of prior recurrences, n (%)			
1	13 (37.1)	7 (58.3)	20 (42.6)
2	11 (31.4)	5 (41.7)	16 (34.0)
≥3	11 (31.4)	0 (0.0)	11 (23.4)
Median duration from initial diagnosis, years (min, max)	4.9 (0.5, 15.3)	5.8 (2.4, 12.6)	5.2 (0.5, 15.3)
Prior radiation therapy, n (%)	35 (100.0)	12 (100.0)	47 (100.0)
Prior chemotherapy, n (%)	30 (85.7)	8 (66.7)	38 (80.9)
Temozolomide	30 (85.7)	5 (41.7)	35 (74.5)
Nimusutine	8 (22.9)	6 (50.0)	14 (29.8)
Bevacizumab	7 (20.0)	0 (0.0)	7 (14.9)

Median time since last radiation therapy, months (range)	29.9 (3.8, 175.9)	64.9 (3.5, 125.8)	35.7 (3.5, 175.9)
Median time since last chemotherapy, months (range)	2.1 (1.1, 103.8)	33.1 (2.6, 81.9)	2.8 (1.1, 103.8)

[a]Two of 10 patients were presumed to have oligodendroglioma based on the telomerase reverse transcriptase promoter and *IDH1* mutations.

[b]The evaluation was performed collectively and centrally, not by local judgment at each facility.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IDH1, isocitrate dehydrogenase 1; NOS, not-otherwise-specified.

Table 2. Safety

AE	All grades (N = 47)	Grade 3 (N = 47)
All AEs, n (%)	45 (95.7)	20 (42.6)
Preferred term, n (%)[a]		
Skin hyperpigmentation	25 (53.2)	0
Diarrhea	22 (46.8)	2 (4.3)
Pruritus	14 (29.8)	0
Alopecia	13 (27.7)	0
Arthralgia	13 (27.7)	1 (2.1)
Nausea	12 (25.5)	0
Headache	11 (23.4)	1 (2.1)
Rash	11 (23.4)	0
Back pain	10 (21.3)	0
Dry skin	10 (21.3)	0
Vomiting	9 (19.1)	0
Neutrophil count decreased	7 (14.9)	6 (12.8)
Nasopharyngitis	7 (14.9)	0
Feces soft	6 (12.8)	0
Decreased appetite	5 (10.6)	0

Alanine aminotransferase increased	4 (8.5)	3(6.4)
Aspartate aminotransferase increased	3 (6.4)	2 (4.3)
White blood cell count decreased	3 (6.4)	3(6.4)
Hypophosphatemia	2 (4.3)	2 (4.3)

[a]Patients were only counted once even if the same AE was reported more than once.

Abbreviation: AE, adverse event.

Table 3. Best overall response

Response	Enhancing (n = 35)	Non-enhancing (n = 12)
Confirmed best overall response, n (%)		
Complete response	2 (5.7)	0 (0.0)
Partial response	4 (11.4)	1 (8.3)
Minor response[a]	NA	3 (25.0)
Stable disease	11 (31.4)	8 (66.7)
Progressive disease	17 (48.6)	0 (0.0)
Not evaluated	1 (2.9)[b]	0 (0.0)
Objective response rate, n (%)	6 (17.1)	4 (33.3)

[a]Category of minor response is applied to patients meeting the Response Assessment in Neuro-Oncology-Low-grade glioma criteria only.

[b]Study treatment was discontinued before the first response assessment.

Abbreviation: NA, not applicable.

Table 4. Drug concentration in resected tumor samples

Measure	Patient #001	Patient #002	Patient #003	Patient #004	Patient #005	Patient #006	Patient #007
Dose	125 mg bid	250 mg bid	500 mg bid	500 mg bid	500 mg bid	700 mg bid	500 mg bid
Sampling time after last dose, h	6.0, 6.3[b]	5.5, 7.2[b]	16.9	4.1, 4.2[b]	4.4	7.2	5.0, 5.2[b]
DS-1001 concentration[a] in resected tumor tissue, ng/g tissue	555, 999[b]	2770, 4310[b]	5720	4250, 4270[b]	1020, 2430[b]	6130	2460, 3690[b]
Brain/plasma concentration ratio	0.10, 0.18[b]	0.35, 0.54[b]	0.77	0.19	NC[c]	0.58	0.20, 0.30[b]

[a]Drug concentration was expressed as a free form of DS-1001.

[b]Data represent the range (min, max) of values as multiple samples were taken per patient.

[c]Brain/plasma ratio was NC as the corresponding plasma sample was taken approximately 3 h earlier.

Abbreviations: bid, twice daily; NC, not calculated.

Figure 1A

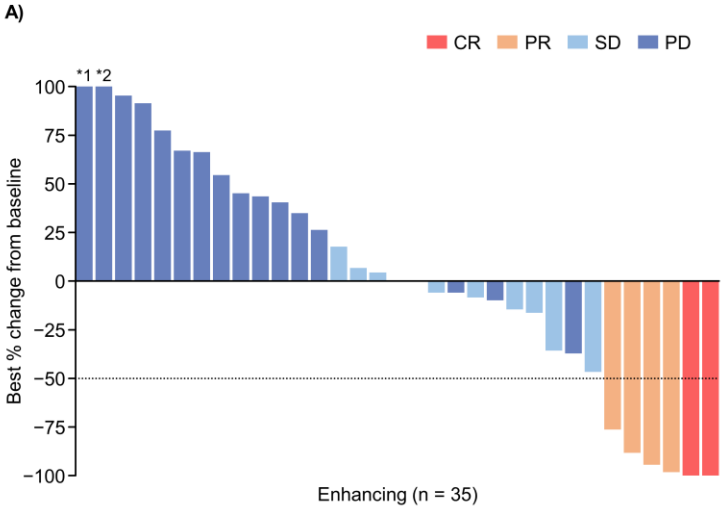

Figure 1B

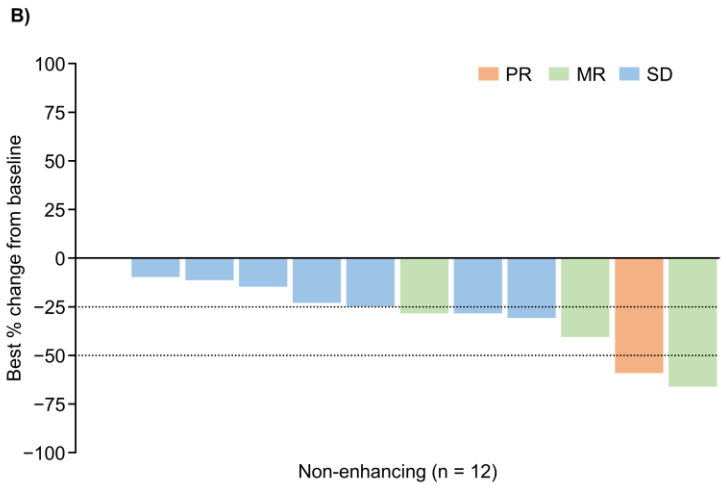

Figure 1C-D

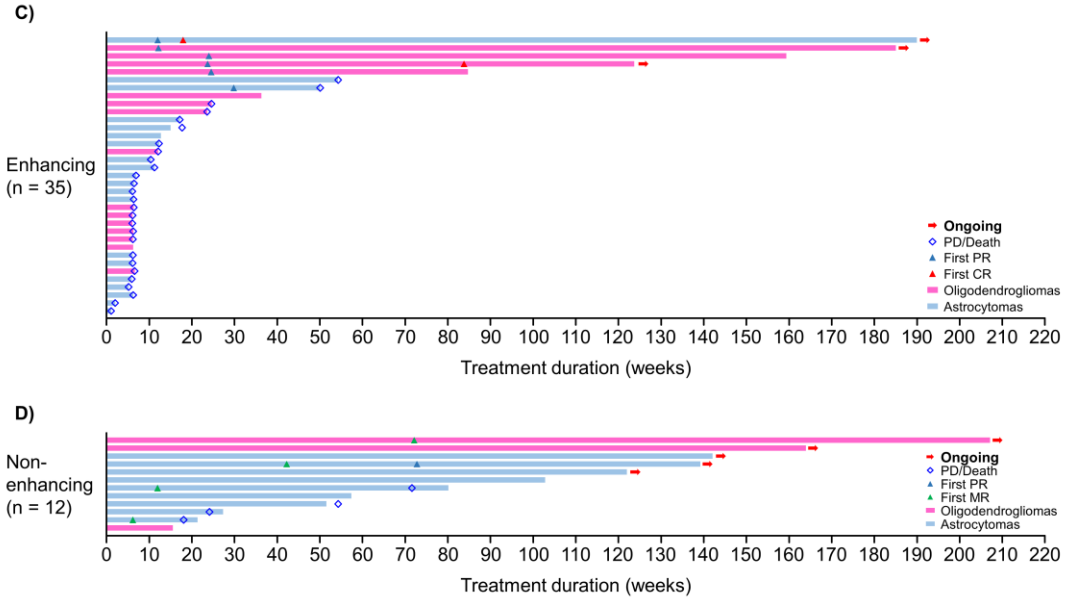

Figure 2