Phase II study of safusidenib erbumine in patients with chemotherapy- and radiotherapy-naïve isocitrate dehydrogenase 1-mutated WHO grade 2 gliomas

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Phase II of safusidenib erbumine in glioma

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Abstract

Background: Gliomas are primary brain tumors arising from glial cells. WHO grade 2 gliomas are initially managed with surgery for diagnosis and tumor reduction. However, complete resection is difficult due to their infiltrative growth into the normal brain and the need to preserve brain function. Current treatment options for WHO grade 2 gliomas are limited. Isocitrate dehydrogenase 1 (IDH1) mutations are frequently observed in WHO grade 2 gliomas. Safusidenib erbumine is a selective inhibitor of mutant IDH1 with substantial blood-brain barrier penetration. This study aimed to investigate the efficacy and safety of safusidenib erbumine in patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas.

Methods: This phase II study implemented a multicenter, open-label, single-arm design and evaluated the efficacy and safety of safusidenib erbumine in 27 patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas (NCT04458272).

Results: The confirmed objective response rate according to the Response Assessment in Neuro-Oncology criteria for WHO grade 2 gliomas was 44.4%. Median progression-free survival was not reached, with an event-free probability of 87.9% at 24 months. The frequently reported treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities Preferred Terms (reported in ≥40%) were alopecia (59.3%), arthralgia (55.6%), skin hyperpigmentation (48.1%), and alanine aminotransferase increased (40.7%). TEAEs were characterized as mostly grade 1 or 2. The incidence of treatment-related grade ≥3 TEAEs was 18.5%.

Conclusions: Safusidenib erbumine is a potential treatment option for patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas.

Keywords

safusidenib erbumine, grade 2 gliomas, IDH1 inhibitor, chemotherapy- and radiotherapy-naïve, delayed recurrence and progression

Key Points

- The confirmed ORR and CBR per the RANO-LGG criteria were 44.4% and 81.5%.
- Median PFS was not reached. Event-free probability at 24 months was 87.9%.
- The safety profile was manageable with mostly mild to moderate adverse events.

Importance of the Study

This study addresses a critical unmet need in the treatment of WHO grade 2 gliomas, which are challenging to manage due to their infiltrative growth and the necessity of preserving brain function. Mutations in isocitrate dehydrogenase 1 (IDH1) are common in these tumors. The current treatment options for WHO grade 2 gliomas are limited. Safusidenib erbumine, a selective inhibitor targeting mutant IDH1 with strong blood-brain barrier penetration, offers a promising therapeutic approach. The phase II trial demonstrated a notable objective response rate of 44.4% in this patient group, suggesting meaningful antitumor activity. Additionally, the safety profile was manageable, with mostly mild to moderate adverse events, supporting its tolerability. This study provides important clinical evidence supporting safusidenib erbumine as a potential new treatment, offering hope for improved disease control and patient outcomes in chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas.

Introduction

Gliomas are primary tumors of the central nervous system (CNS) that arise from glial cells, the supporting cells of the nervous system. In the 2021 WHO CNS classification, the common

diffuse gliomas of adults were divided into three types based on a combination of histologic and molecular features: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype. The presence or absence of IDH gene mutations is considered essential for the diagnosis of gliomas. Astrocytomas are classified as WHO grade 2, 3, or 4, whereas oligodendrogliomas are classified as WHO grade 2 or 3.[1] The initial treatment for WHO grade 2 gliomas is surgery for histological diagnosis and reduction of tumor burden. However, complete resection of tumors is difficult because they infiltrate normal brain tissue, and preservation of brain function is required. According to the European Association of Neuro-oncology (EANO) 2021 guidelines, the management of WHO grade 2 gliomas is determined by histologic and molecular subtype, patient age and clinical status, and the extent of resection. In younger patients (approximately <40–45 years) with IDH-mutant astrocytomas or oligodendrogliomas who undergo gross total resection, these tumors may be managed with a watch-and-wait strategy. In contrast, patients aged 40 years or older, or those with incomplete resection, are recommended to receive adjuvant radiotherapy followed by procarbazine, lomustine, and vincristine (PCV) chemotherapy.[2] Although this approach improves survival, it is associated with substantial toxicity, including hematologic and neurologic adverse events as well as cognitive decline. No standard therapy has been established for recurrent WHO grade 2 gliomas after radiation therapy and chemotherapy. Currently, there are limited treatment options for WHO grade 2 gliomas (diffuse astrocytic and oligodendroglial tumors). Therefore, a novel treatment option that delays tumor recurrence or progression, thereby delaying time to radiation and chemotherapy and their associated toxicities, and improves outcomes is desired.

Vorasidenib, an oral dual inhibitor of mutant IDH1/2, demonstrated significant clinical benefit in the Phase III INDIGO trial for patients with IDH-mutant grade 2 glioma.[3] In the trial, vorasidenib improved progression-free survival (PFS), with a median of 27.7 months compared

to 11.1 months for placebo. Based on these results, the FDA approved vorasidenib in 2024 for patients aged ≥12 years with IDH1/2-mutant grade 2 astrocytoma or oligodendroglioma following surgery, demonstrating the effectiveness of IDH inhibition in this setting. This approval established a precedent for targeting IDH mutations as a therapeutic approach for IDH-mutant gliomas.

Safusidenib erbumine (hereafter referred to as safusidenib) is a selective inhibitor of mutant IDH1 and demonstrates significant blood–brain barrier penetration.[4] In the DS1001-A-J101 study, in which safusidenib was evaluated in recurrent/progressive IDH1-mutant glioma, a high objective response rate (ORR) was observed in patients with both enhancing and non-enhancing gliomas.[5] Recent molecular genetic analyses have revealed that, in these IDH-mutant gliomas, the IDH1 mutation is a genetic aberration that occurs at the earliest stage of glioma development, followed by the gradual acquisition of additional aberrations.[6-9] Gliomas at an earlier stage of tumor development are therefore considered to retain a more mutant IDH1-dependent state and may represent a more appropriate target for safusidenib from a tumor biology perspective. Therefore, the therapeutic efficacy of safusidenib can be expected with early intervention in patients with IDH1-mutated gliomas before radiotherapy and chemotherapy as the first postoperative treatment. In the phase I study of safusidenib, doses ranging from 125 to 1,400 mg twice daily demonstrated approximately dose-proportional pharmacokinetics and an overall favorable safety profile. However, long-lasting, delayed pain events (e.g., arthralgia and back pain) occurred in 40.4% of patients, and 22% required dose modifications at doses ≥500 mg twice daily, with modeling predicting that approximately 40% would require adjustments with long-term administration. In contrast, no dose modifications due to pain occurred at doses ≤250 mg twice daily. Preliminary efficacy signals were observed at doses ≥125 mg, including reductions in intratumoral D-2-hydroxyglutarate concentrations. Based on these findings, 250 mg twice daily was selected as the recommended phase II dose,

147 providing a balance between tolerability and biological activity.

148 Accordingly, this study investigated the efficacy and safety of safusidenib in chemotherapy-
149 and radiotherapy-naïve patients with IDH1-mutated WHO grade 2 gliomas.

150

151 **Materials and Methods**

152 ***Study design and patients***

153 This phase II study was a multicenter, open-label, single-arm trial conducted in Japan and
154 evaluated the efficacy and safety of safusidenib in patients with chemotherapy- and
155 radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas (NCT04458272). The study was
156 approved by the institutional review board of each study site. Written informed consent was
157 obtained from all patients prior to their participation in the study.

158 Two types of central eligibility judgments were made before patient enrollment. The first
159 assessment involved the IDH1 mutation status, assessed by the central laboratory for IDH
160 mutation analysis; the second assessment involved eligibility based on imaging data, including
161 the presence or absence of measurable non-enhancing lesions, assessed by the Independent
162 Efficacy Review Committee (IERC).

163 Patients with WHO grade 2 gliomas, classified according to the 2016 WHO classification,
164 as prespecified in the study protocol (Trial Initiation: 2020), were included if they met the
165 inclusion criteria, which required at least one measurable, non-enhancing lesion as defined by
166 the RANO-LGG criteria, and did not meet any of the exclusion criteria. Patients with residual
167 tumors after surgery were eligible, and those with evidence of progressive tumors at baseline
168 were also permitted to enroll. A comprehensive list of inclusion and exclusion criteria is
169 presented in **Supplementary Table S1**. The duration of each patient's participation in the study
170 was from the consent date to the end of the follow-up.

171 ***Drug administration***

The dose of safusidenib was 250 mg twice daily (bid) (500 mg/day). One cycle lasted 28 days, and oral administration of safusidenib was continued twice daily until the patient met any criteria for treatment discontinuation.

Efficacy measurements

The IERC reported the results of the two-dimensional assessment by blinded central review, per the Response Assessment in Neuro-Oncology (RANO). The results of the assessment recorded from the initiation of the study treatment until the first documented disease progression or the start of any anticancer therapy, whichever occurred earlier, were used for all efficacy analyses.

The primary efficacy endpoint was confirmed ORR according to RANO criteria for low-grade glioma (RANO-LGG criteria).[10] ORR was defined as the proportion of patients whose best overall response was complete response (CR), partial response (PR), or minor response (MR) confirmed during the study period after treatment initiation.

The secondary efficacy endpoints included ORR after 12 and 24 months from the initiation of the study treatment, clinical benefit rate (CBR) per the RANO-LGG criteria (two-dimensional assessment), CBR after 12 and 24 months from the initiation of the study treatment, percent change in tumor size, time to response (TTR), duration of response (DoR), and progression-free survival (PFS). In this study, stable disease (SD) contributing to CBR was prespecified as SD with <0% change from baseline to emphasize sustained, nontrivial tumor shrinkage and to demonstrate the clinical significance of not increasing tumor size; therefore, SD with slight increases (0–<25%) was not counted toward CBR. The percent change in tumor size was defined as the percentage change from baseline in the sum of the products of perpendicular diameters (SPD) (two-dimensional assessment) of all target lesions. TTR was defined as the time from the initiation of study treatment to the first overall response of CR, PR, or MR. DoR was defined as the duration from the date of the first overall response of CR,

PR, or MR to the date of disease progression (first documented progressive disease [PD]) or death from any cause, whichever occurred first. PFS was defined as the time from the study treatment start date to the date of the first PD or death due to any cause, whichever occurs first.

All radiologic assessments of response and progression were performed by the IERC. Imaging data were submitted directly from each participating site to this committee without involvement of the sponsor. The committee reviewed all images independently, and the sponsor had no role in or influence over the determination of response or progression.

Safety evaluation

The safety endpoints included dosing, extent of exposure, treatment-emergent adverse events (TEAEs), pain-related TEAEs, and TEAEs associated with dose modification. TEAEs were defined as those adverse events that newly occurred or worsened relative to the pre-treatment state after the first dose of the study drug and were assessed through 30 days after the last dose. Pain-related adverse events were defined as preferred terms (PTs) within Medical Dictionary for Regulatory Activities (MedDRA) HLTs "Muscle pains," "Musculoskeletal and connective tissue pain and discomfort," "Joint related disorders NEC," and MedDRA PT "Arthralgia." The TEAEs were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).

It should be noted that a Good Clinical Practice (GCP) noncompliance issue regarding the collection of adverse events was identified during the study. Therefore, all safety data presented in this manuscript are based on a subsequent re-investigation and re-collection of adverse events performed in strict accordance with the study protocol to ensure data integrity. This process was conducted by a contract research organization (CRO) fully independent of the sponsor.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

All patients treated with ≥1 dose of safusidenib were included in both the efficacy and safety analyses. For the ORR as evaluated by the assessment results following the IERC per RANO-LGG criteria (two-dimensional assessment), a binomial test was conducted under the null hypothesis that the ORR was ≤5%, using a one-sided significance level of 5%. Frequency tables were prepared for the best response, ORR, and CBR, and the two-sided 95% confidence intervals (CIs) for the proportions of each response were calculated. Time-to-event variables, including PFS and DoR, were estimated descriptively using the Kaplan–Meier method; PFS results were presented with the Kaplan-Meier curve, median, and 95% CI, whereas DoR was summarized by the median with 95% CI. The 95% CIs for all median survival times were calculated with the Brookmeyer–Crowley method based on log–log transformation. Patients who had not experienced PD or had not died (regardless of cause) by the data cutoff date were censored on the day of the last available tumor response assessment. To determine the best percent change in tumor size (SPD) of target lesions from baseline, waterfall and spider plots were prepared. Only patients with measurable disease at baseline were included in the waterfall and spider plots. A swimmer plot depicting the treatment duration (months) for individual patients was generated, showing the time of the first MR, PR, CR, and PFS events and an indication of whether treatment was ongoing at the time of the data cutoff. For all new or aggravated adverse events occurring after the start of the study drug, frequency tables were prepared by type of event, causality with the study drug, and grade according to the NCI CTCAE Version 5.0.

Sample size

The threshold ORR was set to 5%, primarily because no established treatment existed at the time of study initiation for the target patients. The expected ORR was set at 30%, based primarily on the opinions of clinical experts and Phase I efficacy data. The target sample size was set at 25 patients to achieve ≥90% statistical power.

Results

Patient disposition, demographics, and baseline characteristics

The first patient provided informed consent on July 8, 2020. The patient disposition is presented in **Supplementary Table S2**. Overall, 27 patients were enrolled and received safusidenib treatment. All patients had measurable non-enhancing disease at baseline. As of the data cutoff (March 10, 2023), the median follow-up was 28.0 months, and 19 patients (70.4%) remained on treatment. All 27 patients were included in the safety and efficacy analyses. Patient demographic and baseline characteristics are shown in **Table 1.** The median age at enrollment was 41.0 years (range, 24 to 58). Sex distribution was almost equal (14 male and 13 female patients). All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, except for one patient with an ECOG PS of 1. All patients had a Karnofsky performance status score of 90 or higher, except for one patient with a score of 80. The median SPD of target lesions at baseline was 1011.5 mm^2 (range, 130.11 to 3866.82). Regarding cancer types based on local judgment (latest diagnosis), 17 patients had oligodendroglioma, and 10 patients exhibited diffuse astrocytoma. All patients had gliomas with IDH1-R132H mutation, except for one patient with an IDH1-R132C mutation as determined by central assessments. Furthermore, the 1p/19q codeletion status based on local judgment was non-codeletion in 7 patients, codeletion in 12 patients, and missing in eight patients. The cancer types and 1p/19q codeletion status were retrospectively analyzed by central assessment and are presented in **Supplementary Table S3.**

Efficacy

Primary efficacy analysis was performed on the confirmed ORR according to the RANO-LGG criteria, and the results are summarized in **Table 2**. The study met its primary endpoint, with the confirmed ORR of 44.4% (P<0.0001; 12/27 patients; 95% CI: 25.5%–64.7%) per the

RANO-LGG criteria, including four (14.8%) PRs and eight (29.6%) MRs. The confirmed CBR per the RANO-LGG criteria was 81.5% (95% CI: 61.9%–93.7%) (**Table 2**). Twelve months after the initiation of the study treatment, the confirmed ORR per the RANO-LGG criteria was 44.4% (95% CI: 25.5%–64.7%) with 12 responders, including PR and MR. The confirmed CBR per the RANO-LGG criteria was 70.4% (95% CI: 49.8%–86.2%) (**Supplementary Table S4**). Twenty-four months after the initiation of the study treatment, the confirmed ORR per the RANO-LGG criteria was 33.3% (95% CI: 16.5%–54.0%) with nine responders, including PR or MR. The confirmed CBR per the RANO-LGG criteria was 55.6% (95% CI: 35.3%–74.5%) (**Supplementary Table S4**). Analyses by histologic subtype, based on both site pathology assessments and central pathology review, did not reveal differential responses or progression patterns between astrocytoma and oligodendroglioma (**Supplementary Table S5**).

Of the 27 patients, the median best percent change in the SPD of the target lesions was −27.22% (range, −82.5 to 30.2) (**Supplementary Table S6**). The waterfall (A) and spider plots (B) of the percent change in the SPD of the target lesions are shown in **Figure 1.** In most patients, the tumor size was reduced or maintained. A swimmer's plot of treatment duration is shown in **Figure 2**. Representative MRI scans of a patient who achieved PR, assessed by SPD, are shown in **Supplementary Figure S1**.

Among the 27 patients, the median TTR for confirmed responders was 12.70 months (range, 5.6 to 21.2), with 12 responders at the time of the data cutoff. Median DoR could not be estimated because no progression events had occurred (**Supplementary Table S7**).

The PFS data are summarized in **Supplementary Table S8.** The Kaplan-Meier plot of PFS is shown in **Figure 3**. As of the data cutoff date, 24 of the 27 patients (88.9%) were censored. Of those 24 patients, 21 (77.8%) were still followed up without events, and the

median PFS could not be estimated. The event-free probability at 24 months was 87.9% (95% CI: 67.0%–96.0%).

Safety

The dose and extent of exposure are summarized in **Supplementary Table S9**. The median treatment duration was 27.4 months (range, 3 to 31). The incidences of TEAEs in the safety analysis set are summarized in **Supplementary Table S10.** Of the 27 patients in the safety analysis set, 26 (96.3%) experienced TEAEs and treatment-related TEAEs. A total of 10 patients (37.0%) experienced grade ≥3 TEAEs, of which 5 patients (18.5%) experienced treatment-related grade ≥3 TEAEs. One patient had a grade 4 event of increased blood creatine phosphokinase, and no grade 5 events were reported. Four (14.8%) patients experienced serious grade 3 TEAEs, including "hepatic function abnormal" in two patients, amnesia in one patient, and headache in one patient. Among them, three (11.1%) patients had TEAEs that led to study treatment discontinuation. The events of "hepatic function abnormal" reported in two patients were considered related to the study drug by the investigators. These events were resolved with study treatment dose interruption and/or appropriate medical management. The remaining patient who discontinued treatment had amnesia, which was not considered related to the study drug.

The number and percentage of patients with TEAEs, regardless of causality, that occurred in at least 10% of the total patients are presented as PT in **Supplementary Table S11.** The frequently reported TEAEs by PT (reported in ≥40% of the total patients) were alopecia, arthralgia, skin hyperpigmentation, and "alanine aminotransferase increased." The median time to onset was 141 days for alopecia, 30 days for skin hyperpigmentation, and 169 days for arthralgia (**Supplementary Table S12**). These events were generally persistent during treatment, and most improved or resolved after dose interruption or discontinuation; however, in some patients, the events had not resolved by the end of study observation because safety

follow-up was concluded once clinical stability was achieved, as prespecified in the study protocol.

Alopecia led to a dose reduction in 1 patient (3.7%) and a dose interruption in 1 patient (3.7%). Arthralgia led to dose reductions in 3 patients (11.1%) and dose interruptions in 9 patients (33.3%). Skin hyperpigmentation did not result in any dose reductions or interruptions (**Supplementary Table S13**). Alopecia was observed on the scalp, arms, and lower legs, and was typically diffuse rather than patchy. Grade 1 alopecia occurred in 15 patients (55.6%) and grade 2 in 1 patient (3.7%). Alopecia tended to lessen with treatment interruption; in some patients, recovery was noted, with regrowth of fine hair within 1–2 months. Arthralgia was reported mainly in the trunk, including the neck, back, and lumbar regions. These events were predominantly grade 1 or 2 and generally persisted during treatment but showed improvement within approximately 12 weeks of treatment interruption. Skin hyperpigmentation presented either as localized spots or as diffuse darkening resembling tanning of the entire face. Grade 1 skin hyperpigmentation occurred in 12 patients (44.4%) and grade 2 in 1 patient (3.7%). These events improved following treatment interruption. These observations regarding alopecia, arthralgia, and skin hyperpigmentation were based on data available up to the data cutoff, supplemented by findings from the phase I study, although detailed information was not uniformly available for all patients.

Nine (33.3%) experienced TEAEs leading to dose reductions. The TEAEs associated with the study treatment dose reduction by PT were arthralgia (three patients [11.1%]), alopecia, pruritus, back pain, myalgia, rotator cuff syndrome, and “alanine aminotransferase increased” (one patient [3.7%] each) (**Supplementary Table S13**). Sixteen (59.3%) experienced TEAEs leading to interruption of the study treatment dose. The TEAEs associated with the study treatment dose interruption by PT were arthralgia (nine patients [33.3%]), alanine aminotransferase increased (four patients [14.8%]), hepatic function abnormal and aspartate

aminotransferase increased (two patients [7.4%] each), COVID-19, irritable bowel syndrome, alopecia, myalgia, neck pain, and blood creatine phosphokinase increased (one patient [3.7%] each) (**Supplementary Table S13**). The pain-related TEAEs are summarized in **Supplementary Table S14**. Pain-related events were observed in 22 patients (81.5%). All of these events were grade 1 or 2, except for one patient who experienced a grade 3 event.

Discussion

This was a Phase II, multicenter, open-label, single-arm study to investigate the efficacy and safety of safusidenib in patients with chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas after surgical resection. The observed efficacy outcomes highlighted the long-term benefits of this study. The confirmed ORR and CBR, evaluated based on RANO-LGG criteria, indicated that the treatment not only achieved significant tumor shrinkage but also provided sustained disease control for a substantial proportion of patients. These findings suggest that many patients were able to maintain control over their tumor burden for an extended period, reflecting the potential durability of the therapeutic effect.

Although no direct comparison between vorasidenib and safusidenib is available, cross-trial observations suggest potential differences in efficacy. In the phase III INDIGO trial, vorasidenib demonstrated an ORR of approximately 10%.[3] By contrast, in this phase II trial of safusidenib, the ORR was 44.4%. This comparatively higher response rate suggests that tumor reduction may be a distinguishing clinical feature and a potential advantage relative to vorasidenib. These comparisons, however, should be interpreted with caution because of differences in study design and patient populations.

In the secondary analysis of ORR at subsequent time points after treatment initiation, the observed decline in ORR between 12 and 24 months does not necessarily indicate tumor progression. Rather, it primarily reflects variability around the predefined response threshold and the requirement for confirmation under the study's response assessment rules. In this study, some patients initially categorized as minor responders subsequently fluctuated around the 25% reduction cutoff and were reassessed as having SD at later time points, whereas others lacked follow-up imaging for confirmation. These findings suggest that the apparent decrease in ORR is more likely attributable to assessment methodology and data availability than to a true loss of efficacy. Based on the TTR and DoR results, although limited to 12 responders, the median TTR was approximately 12 months, and responses appeared to be maintained at 24 months. The durability of response is an important finding, and confirmation with longer follow-up is warranted.

Discrepancies between local and central assessments of cancer type were observed. These differences may be attributable to the distinct evaluation methods: central review was based on an integrated approach that included hematoxylin and eosin staining, phospho-histone H3 (pHH3) immunohistochemistry, and 1p/19q FISH assay, whereas local assessments followed routine clinical practice at each institution. Similar discrepancies between institutional and central pathology reviews have been reported in glioma trials.[11,12] Such discrepancies underscore the value of central histomolecular review for ensuring consistency across sites, while also indicating that results based on local assessments should be interpreted with caution.

The safety profile observed in this study demonstrated that the majority of TEAEs were mild to moderate in severity and manageable, allowing most patients to continue treatment. Pain-related events, reported under various PTs, were frequently observed. Although pain-related TEAEs have also been described with other mutant IDH inhibitors, such as

vorasidenib and olutasidenib, the incidence with safusidenib appeared substantially higher (81.5%). For comparison, vorasidenib reported a grouped “musculoskeletal pain” category in 26% of patients,[13] and olutasidenib reported “arthralgia” in 28%.[14] However, because terminology and the aggregation of pain-related events differ across reports, cross-trial comparisons should be interpreted with caution. These events predominantly affected the trunk region, including the neck, back, and lumbar areas. Although the mechanisms underlying these events remain unknown, pain-related grade 1 or 2 TEAEs generally improved or resolved with temporary interruption of the study drug. Many patients continued treatment by repeating cycles of interruption and resumption of the study drug when adverse events recurred after restarting treatment. Treatment interruption of up to 12 weeks was permitted, in accordance with the guidelines defined in the study protocol. Serious TEAEs occurred in a limited number of cases and were successfully managed with strategies such as dose interruptions. For example, “hepatic function abnormal” resolved with appropriate intervention. Notably, no TEAEs associated with death were reported. These findings suggest that although adverse events were common, they were generally non-severe and did not substantially interfere with treatment continuation in most patients, underscoring the overall tolerability of the treatment. Differences in safety profiles have been observed among IDH inhibitors. Although allosteric IDH inhibitors target the same dimer-interface pocket, their chemotypes, isoform selectivities, and binding geometries differ considerably, which likely contributes to the distinct safety profiles observed across this drug class.[15] In the phase III INDIGO trial, vorasidenib was most frequently associated with ALT elevations (38.9%), along with COVID-19 infection and fatigue.[3] Olutasidenib was associated with frequent gastrointestinal and fatigue-related adverse events (nausea 54%, fatigue 50%, diarrhea 31%), with ALT elevations also notable,[16] whereas ivosidenib has been linked to differentiation syndrome as a characteristic risk in AML (approximately 19%).[17] By contrast, safusidenib

has consistently demonstrated dermatologic adverse events, such as alopecia and skin hyperpigmentation, as its most frequent findings across clinical development,[5] while hepatic laboratory abnormalities, including ALT/AST elevations, were observed at a relatively high incidence in the present phase II study. These findings suggest that differences in binding mode, selectivity, and chemotype may underpin the divergent safety patterns observed across IDH inhibitors. Due to GCP noncompliance in the collection of adverse events identified in the present Phase II study, a re-investigation was conducted, and adverse events were recollected in accordance with the study protocol. To ensure transparency, adverse events reported in the Phase I and Phase II studies are shown in **Table 3**. Although direct comparison should be interpreted with caution because of the differences in dosing, 125–1,400 mg twice daily in the Phase I study and a fixed dose of 250 mg twice daily in the Phase II study, the incidence and types of adverse events were generally consistent between the two studies.

IDH1-mutated WHO grade 2 gliomas occur most commonly in young adults in their third decade.[18] They generally grow slowly in the early stages; however, they are characterized by persistent tumor growth and eventual malignant progression. As tumor cells grow invasively in the normal brain, complete surgical resection of tumors is difficult. Most of the remaining tumors evolve into higher-grade tumors (malignant transformation) during the process of repeated recurrence or progression, eventually leading to patient death, although patients can survive long after the first resection.[19] Postoperative therapy is needed to prevent the increase in the remaining tumors and delay recurrence and malignant transformation. Currently, postoperative therapy consists of radiotherapy and chemotherapy. However, postoperative radiotherapy raises concerns regarding late toxicities.[20,21] Alkylating agents, such as temozolomide and nitrosoureas, are commonly used as postoperative chemotherapy. However, these agents can cause DNA damage, which may lead to mutagenic and carcinogenic risks. Owing to their cumulative genotoxicity and the associated risk of

secondary malignancies,[22] they are generally not recommended for prolonged treatment. Safusidenib demonstrated tumor-reducing effects in patients who had not undergone radiation therapy or chemotherapy after surgery. Therefore, safusidenib may enable long-term disease control without the need for radiation or chemotherapy, delay the progression of residual tumors to malignancy, and postpone the initiation of radiation and chemotherapy. By delaying the toxicities associated with these treatments, safusidenib has the potential to improve patients' quality of life. In addition, safusidenib has demonstrated promising PFS outcomes. This study showed that at 24 months, 87.9% of patients treated with safusidenib remained progression-free, with the median PFS not yet reached. These findings suggest that safusidenib has the potential to achieve sustained disease control in patients with IDH1-mutant gliomas.

Safusidenib is a potential new treatment option for chemotherapy- and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas that can be used long-term, leading to delayed tumor recurrence and progression. The use of safusidenib as postoperative therapy prior to radiotherapy and chemotherapy allows these therapies to be deferred until recurrence, thereby delaying toxicities and potentially prolonging survival.

Limitations

An internal audit of the DS1001-A-J201 clinical trial identified a serious GCP noncompliance issue related to adverse event reporting. The criteria for collecting adverse events that differed from the provisions of the clinical trial protocol were explained to all clinical investigator sites conducting the DS1001-A-J201 study by the sponsor, and interfered with the investigator's medical judgment (such as the decision to accept or reject adverse events). This interference did not align with the clinical trial protocol, and the collected data contained potential bias from the sponsor, which compromised the evaluation of the clinical trial data. Therefore, the data used in the manuscript are based on the re-investigation of

adverse events in source documents and the re-collection of adverse events according to the protocol. However, this study is judged to be in GCP noncompliance by Daiichi Sankyo Co., Ltd. We also note a limitation that although the best overall response and ORR were analyzed by histologic subtype (oligodendrogliomas and astrocytomas), other outcomes such as PFS and OS were not examined by subtype. In addition, 1p/19q data were not available for all patients at the time of enrollment because some local assessments were missing. Another limitation is that the timing of tumor assessments in the INDIGO trial differed from that in our study. In addition, differences in study design and patient population further limit the comparability of efficacy outcomes. Therefore, direct numerical comparisons between the studies should be interpreted with particular caution.

In conclusion, this study demonstrated that safusidenib has the potential to achieve significant tumor shrinkage and sustained disease control, suggesting a durable therapeutic efficacy. Most TEAEs are mild to moderate and manageable, allowing treatment continuation in the majority of patients. Serious TEAEs were managed appropriately, with no treatment-related deaths reported, highlighting the overall tolerability of the treatment. These results indicated that safusidenib is a potential treatment option for patients with chemotherapy- and radiotherapy- naïve IDH1-mutated WHO grade 2 gliomas.

Ethics

This study was conducted in compliance with the ethical guidelines outlined in the Declaration of Helsinki and in accordance with the principles of GCP. However, cases of noncompliance with GCP requirements were identified and addressed to minimize their impact on study outcomes. The patients provided voluntary informed consent by signing a relevant document before participating in the study.

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Conflicts of Interest

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Authorship

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Data Availability

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 Co., Ltd. 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 address: https://vivli.org/ourmember/daiichi-sankyo/.

References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021; 23(8): 1231–1251.
2. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021; 18(3): 170–186.
3. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant Low-Grade Glioma. N Engl J Med. 2023; 389(7): 589–601.
4. Machida Y, Nakagawa M, Matsunaga H, et al. A Potent Blood-Brain Barrier-Permeable Mutant IDH1 Inhibitor Suppresses the Growth of Glioblastoma with IDH1 Mutation in a Patient-Derived Orthotopic Xenograft Model. Mol Cancer Ther. 2020; 19(2): 375–383.
5. Natsume A, Arakawa Y, Narita Y, et al. 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. Neuro Oncol. 2023; 25(2): 326–336.
6. Suzuki H, Aoki K, Chiba K, et al. Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet. 2015; 47(5): 458–468.
7. Arita H, Narita Y, Fukushima S, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total lp19q loss. Acta Neuropathol. 2013; 126(2): 267–276.
8. Wakimoto H, Tanaka S, Curry WT, et al. Targetable signaling pathway mutations are associated with malignant phenotype in IDH-mutant gliomas. Clin Cancer Res. 2014; 20(11): 2898–2909.
9. Bai H, Harmancı AS, Erson-Omay EZ, et al. Integrated genomic characterization of IDH1- mutant glioma malignant progression. Nat Genet. 2016; 48(1): 59–66.
10. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology

(a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011; 12(6): 583–593.

11. van den Bent MJ. Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. Acta Neuropathol. 2010; 120(3): 297–304.
12. Gupta T, Nair V, Epari S, Pietsch T, Jalali R. Concordance between local, institutional, and central pathology review in glioblastoma: implications for research and practice: a pilot study. Neurol India. 2012; 60(1): 61–65.
13. US Food and Drug Administraition. VORANIGO (vorasidenib) tablets: Prescribing information. Revised 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218784s002lbl.pdf.
14. US Food and Drug Administraition. REZLIDHIA (olutasidenib) capsules: Prescribing information. Revised 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215814s000lbl.pdf.
15. Xie X, Baird D, Bowen K, et al. Allosteric Mutant IDH1 Inhibitors Reveal Mechanisms for IDH1 Mutant and Isoform Selectivity. Structure. 2017; 25(3): 506–513.
16. de la Fuente MI, Colman H, Rosenthal M, et al. Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial. Neuro Oncol. 2023; 25(1): 146–156.
17. Norsworthy KJ, Mulkey F, Scott EC, et al. Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis. Clin Cancer Res. 2020; 26(16): 4280–4288.
18. Gakinya S, Mutuiri A, Onyuma T, Cheserem B, Mogere E. Frequency of IDH1 mutation in adult-type diffuse astrocytic gliomas in a tertiary hospital in Kenya. Front

Med (Lausanne). 2024; 11: 1305714.

19. Nakasu S, Nakasu Y. Malignant Progression of Diffuse Low-grade Gliomas: A Systematic Review and Meta-analysis on Incidence and Related Factors. Neurol Med Chir (Tokyo). 2022; 62(4): 177-185.
20. Wilke C, Grosshans D, Duman J, Brown P, Li J. Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. Neuro Oncol. 2018; 20(5): 597–607.
21. Seland M, Bjøro T, Furre T, et al. Hormonal dysfunction is frequent in cancer survivors treated with radiotherapy to the head and neck region. J Cancer Surviv. 2015; 9(4): 630–640.
22. Momota H, Narita Y, Miyakita Y, Shibui S. Secondary hematological malignancies associated with temozolomide in patients with glioma. Neuro Oncol. 2013; 15(10): 1445–1450.

Figure legends

Figure 1: Waterfall and Spider Plots of Percent Change in the Sum of the Product of Perpendicular Diameters of Target Lesions (Central Assessment)

(A) Waterfall plots

Bars are sorted by value and best overall response per RANO-LGG criteria (two-dimensional assessment). The best overall response of each patient is differentiated by the color of bars. Baseline is defined as the last measurement taken before the first dose of the study drug. n = 27, Red: CR; Orange: PR; Green: MR; Blue: SD; Grey: PD, *: Indicates that treatment continues.

CR, Complete Response; MR, Minor Response; PR, Partial Response; PD, Progressive Disease; SD, Stable Disease.

(B) Spider plots

Best overall response per RANO-LGG criteria (two-dimensional assessment) of each patient is differentiated by the color of lines. Baseline is defined as the last measurement taken before the first dose of the study drug. n = 27, Red: CR, Orange: PR, Green: MR, Blue: SD, Grey: PD

CR, Complete Response; MR, Minor Response; PR, Partial Response; PD, Progressive Disease; SD, Stable Disease.

Figure 2: Swimmer Plot of Treatment Duration (Central Assessment)

A swimmer plot of treatment duration (months) for individual patients. Time of first MR, PR, CR, and PFS event, and whether treatment is ongoing at the time of the data cutoff, is displayed. Arrows indicate that treatment continues. The color of the bar depends on the best response as follows. Red: CR, Orange: PR, Green: MR, Blue: SD, Grey: PD

●: PFS event, ◇: First CR, ○: First PR, △: First MR

659 CR, Complete Response; MR, Minor Response; PR, Partial Response; PD, Progressive
660 Disease; SD, Stable Disease.
661
662 **Figure 3:** Kaplan–Meier Plot of Progression-free Survival (Central Assessment)
663 The time from the study treatment start date to the date of the first PD or death due to any
664 cause, whichever occurred first, is shown. Median PFS was not reached. The event-free
665 probability at 24 months was 87.9% (95% CI: 67.0%–96.0%).
666

Table 1 Patient Demographics and Baseline Characteristics

Category	(N = 27)[a]
Age at Enrollment (years)	
Mean	41.1
Standard Deviation	8.54
Minimum	24
Median	41.0
Maximum	58
Sex (n, %)	
Male	14 (51.9)
Female	13 (48.1)
ECOG PS (n, %)	
0	26 (96.3)
1	1 (3.7)
≥2	0 (0.0)
Karnofsky Performance Status (n, %)	
80	1 (3.7)
90	7 (25.9)
100	19 (70.4)
Time Since Latest Diagnosis (months)[b]	
Mean	28.2
Standard Deviation	27.0
Minimum	4
Median	24.2
Maximum	119
SPD (mm^2)	
Mean	1222.7
Standard Deviation	885.8
Minimum	130.1
Median	1011.5
Maximum	3866.8

Cancer Types[c] (Latest Diagnosis) (Local Judgment) (n, %)	
Oligodendroglioma (OL)	17 (63.0)
Diffuse Astrocytoma (DA)	10 (37.0)
IDH1-R132 Mutation Status (Central Assessment) (n, %)	
Mutant	27 (100.0)
R132H	26 (96.3)
R132C	1 (3.7)
1p/19q-codeletion Status (Local Judgment) (n, %)	
Non-codeletion	7 (25.9)
Codeletion	12 (44.4)
Missing	8
Prior Radiation Therapy for This Cancer (n, %)	
Yes	0 (0.0)
No	27 (100.0)
Prior Systemic Therapy for This Cancer (n, %)	
Yes	0 (0.0)
No	27 (100.0)

[a]All patients had measurable non-enhancing disease at baseline.

[b]Time since the latest diagnosis refers to the interval from the most recent histopathological diagnosis (i.e., date of surgery) to study treatment initiation.

[c]Cancer types were classified based on the 2016 WHO classification.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; SPD, sum of the products of perpendicular diameters; IDH1, isocitrate dehydrogenase 1.

Table 2 Objective response rate by RANO-LGG (Central Assessment)

	(N = 27)
Confirmed Best Overall Response (n, %)	
Complete Response (CR)	0 (0.0)
Partial Response (PR)	4 (14.8)
Minor Response (MR)	8 (29.6)
Stable Disease (SD)	14 (51.9)
Progressive Disease (PD)	1 (3.7)
Not Evaluable (NE)	0 (0.0)
Confirmed Objective Response Rate (n, %)	
Responder	12 (44.4)
95% CI[a]	(25.5, 64.7)
P value[b]	P<0.0001
Confirmed Clinical Benefit Rate (n, %)	
CR+PR+MR+SD with <0% of Tumor Size Change	22 (81.5)
95% CI[a]	(61.9, 93.7)

Percentage is calculated using the number of patients in the column heading as the denominator.

[a]95% confidence interval based on Clopper-Pearson method.

[b]The binomial test with a one-sided significance level of 5% under the null hypothesis that the objective response rate is 5% or less.

RANO-LGG, Response Assessment in Neuro-Oncology criteria for low-grade gliomas; CI, confidence interval.

Table 3 Comparison of Treatment-emergent Adverse Events Occurring in ≥20% of Patients in Phase I or Phase II Trials

	Phase I[a]		Phase II	
	N = 47, n (%)[b]		N = 27, n (%)[b]	
Preferred Term	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**
All TEAEs	20 (42.6)	45 (95.7)	10 (37.0)	26 (96.3)
Alopecia	0 (0.0)	13 (27.7)	0 (0.0)	16 (59.3)
Arthralgia	1 (2.1)	13 (27.7)	1 (3.7)	15 (55.6)
Skin hyperpigmentation	0 (0.0)	25 (53.2)	0 (0.0)	13 (48.1)
Alanine aminotransferase increased	3 (6.4)	4 (8.5)	2 (7.4)	11 (40.7)
Rash	0 (0.0)	11 (23.4)	0 (0.0)	10 (37.0)
Aspartate aminotransferase increased	2 (4.3)	3 (6.4)	1 (3.7)	9 (33.3)
Pruritus	0 (0.0)	14 (29.8)	0 (0.0)	9 (33.3)
Back pain	0 (0.0)	10 (21.3)	0 (0.0)	7 (25.9)
Neutrophil count decreased	6 (12.8)	7 (14.9)	0 (0.0)	7 (25.9)
Diarrhoea	2 (4.3)	22 (46.8)	0 (0.0)	6 (22.2)
Nausea	0	12 (25.5)	0 (0.0)	5 (18.5)
Dry skin	0	10 (21.3)	0 (0.0)	4 (14.8)
Headache	1 (2.1)	11 (23.4)	1 (3.7)	4 (14.8)

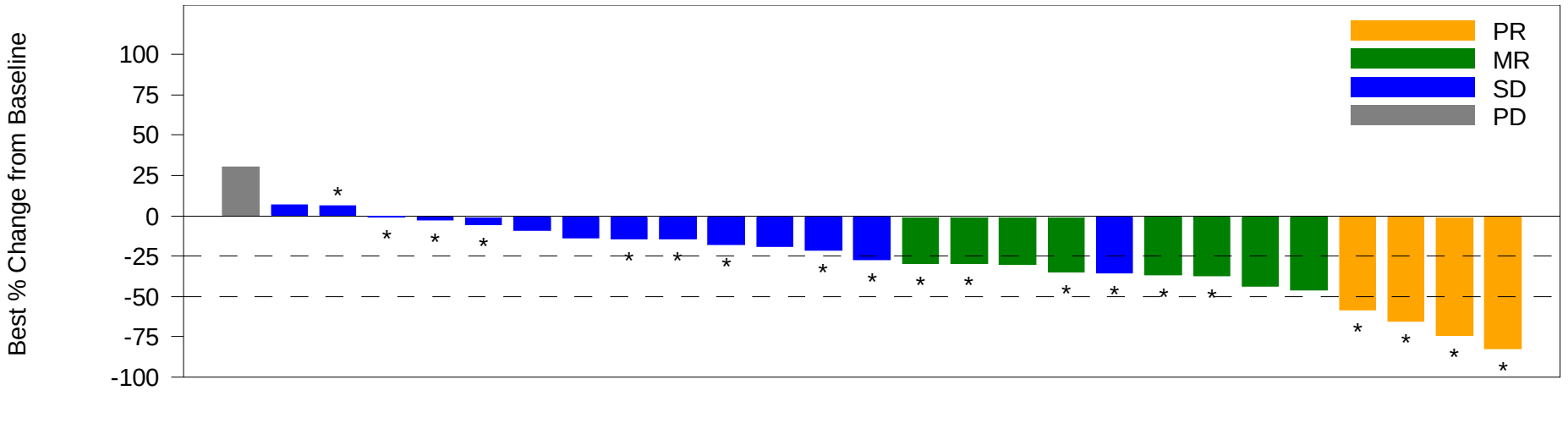
[a]Phase I data are adapted from Natsume et al., 2022.

[b]Patient may experience more than one event per preferred term. At each level of patient summarization, the patient is counted once at the worst Common Terminology Criteria for Adverse Events grade.

TEAE, treatment-emergent adverse events.

Figure 1 Waterfall and Spider Plots of Percent Change in the Sum of the Products of Perpendicular Diameters of Target Lesions (Central Assessment)

(A)



(B)

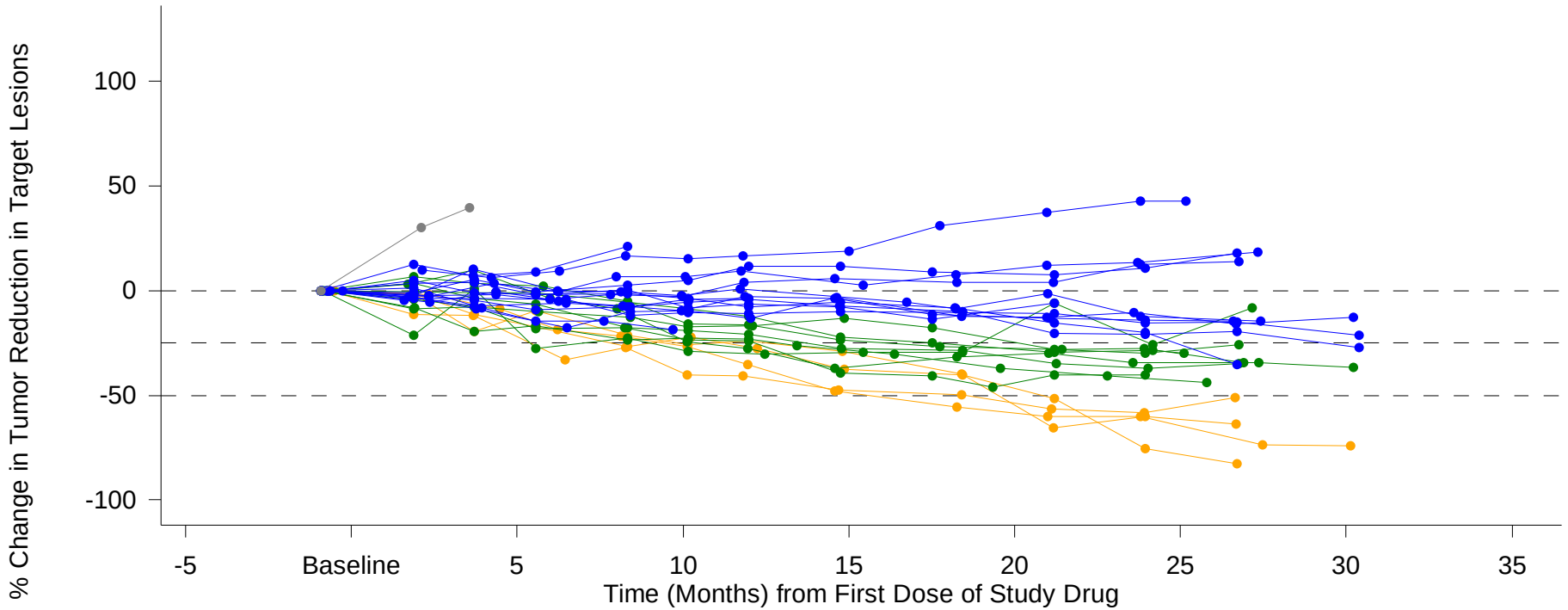
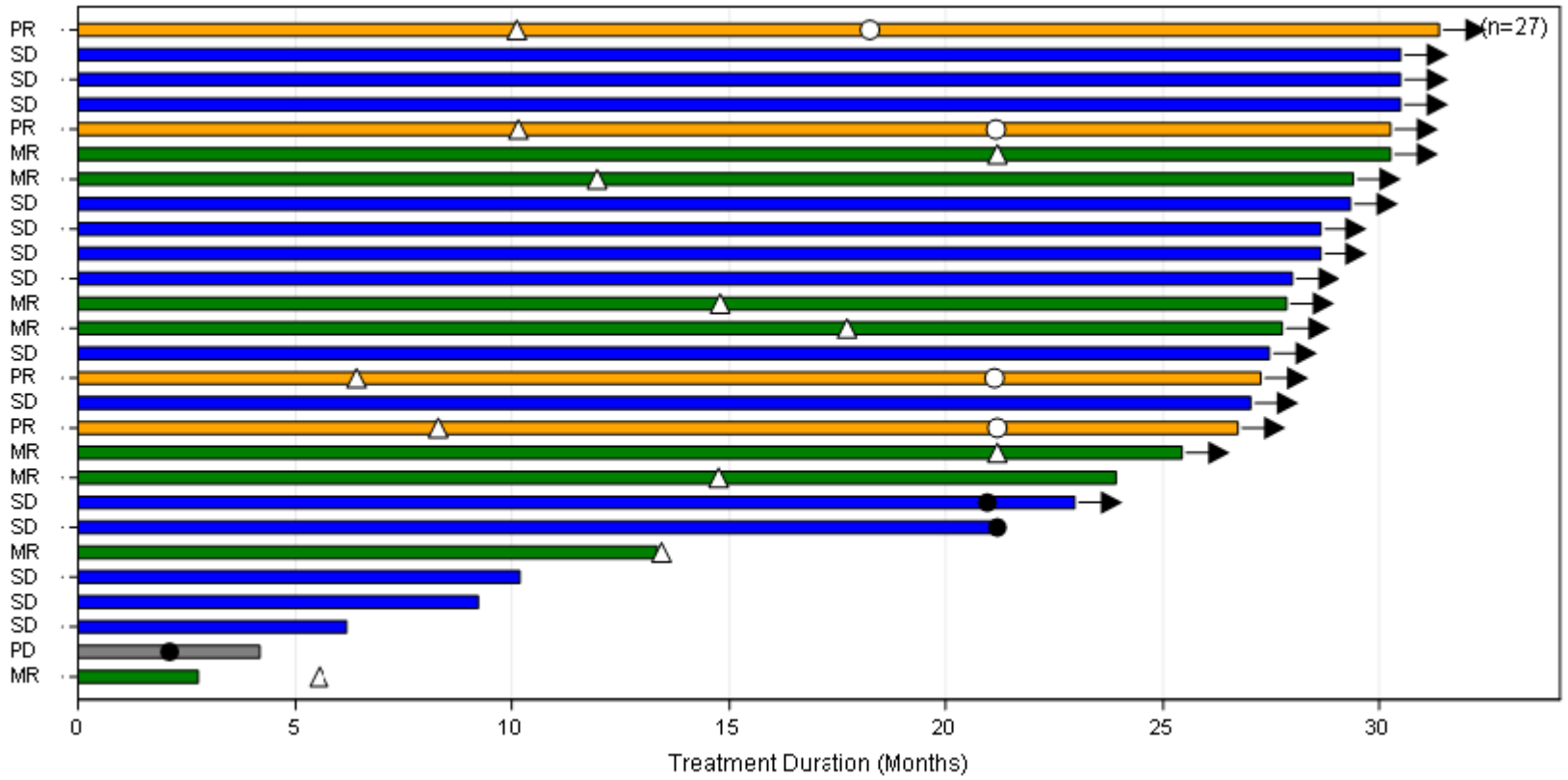


Figure 2 Swimmer Plot of Treatment Duration (Central Assessment)



Arrows indicate treatment continues. The color of the bar depends on best response as follows. Red: CR Orange: PR Green: MR Blue: SD Grey: PD
●: PFS event, ◇: First CR, ○: First PR, △: First MR
CR = Complete Response; MR = Minor Response; PR = Partial Response; PD = Progressive Disease; SD = Stable Disease

Figure 3 Kaplan-Meier Plot of Progression-free Survival (Central Assessment)