STELLAR: Phase III, Randomized, Open-Label Study of Eflornithine Plus Lomustine Versus Lomustine Alone in Patients With Recurrent Grade 3 Astrocytoma

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ABSTRACT

PURPOSE STELLAR (ClinicalTrials.gov identifier: NCT02796261) was a phase III, randomized, open-label trial of eflornithine + lomustine versus lomustine monotherapy in patients with recurrent grade 3 astrocytoma.

METHODS At trial initiation, eligibility criteria included: age ≥18 years, anaplastic astrocytoma (2016 WHO CNS Tumor classification [WHO CNS4]), first recurrence ≥6 months after radiation and temozolomide (TMZ), Karnofsky performance status ≥70, and no imaging findings consistent with grade 4 glioblastoma. Random assignment (1:1) was stratified by *isocitrate dehydrogenase* (*IDH*) mutation, age, resection extent, and geography. Patients received eflornithine (2.8 g/m² orally, every 8 hours [2 weeks on, 1 week off]) + lomustine (90 mg/m² orally, once every 6 weeks), or lomustine monotherapy (110 mg/m² once every 6 weeks). The primary end point was overall survival (OS).

RESULTS Among 343 patients randomly assigned across 74 sites in eight countries, there was no difference in survival between eflornithine + lomustine and lomustine monotherapy (median OS 23.4 *v* 20.3 months, hazard ratio [HR], 0.94). Following changes in classification and grading in the 2021 WHO CNS5, a subset analysis of patients with *IDH*-mutant, grade 3 astrocytoma (n = 196), defined in 2024, before unblinding, showed clinically meaningful improvements in median OS with eflornithine + lomustine versus lomustine monotherapy (34.9 *v* 23.5 months, HR, 0.64) and median progression-free survival (PFS, 15.8 *v* 7.2 months, HR, 0.57). No differences were observed among patients with CNS grade 4 disease. Grade ≥3 treatment-emergent adverse events of relevance were related to reversible myelosuppression (eflornithine + lomustine 42% *v* lomustine monotherapy 29% of patients) and hearing impairment (24% *v* 0%). No new safety signals were identified.

CONCLUSION Clinically meaningful improvements were observed; eflornithine + lomustine doubled PFS and improved OS in patients with recurrent *IDH*-mutant, grade 3 astrocytoma, but not grade 4 tumors, after prior radiotherapy and TMZ, consistent with its cytostatic mechanism of action.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Grade 3 astrocytomas (formerly anaplastic astrocytomas) are an aggressive and high-grade primary brain tumor of the glioma family with an incidence of at least 0.41 per 100,000 population and approximately 1,359 newly diagnosed patients in the United States annually.[1] Despite multimodality treatment, virtually all of these recur and result in a high degree of morbidity and mortality.[2] At recurrence, options are limited with a median overall survival (OS) of approximately 7 months.[3,4]

Diagnostic and grading criteria of astrocytomas have evolved significantly in the past decade, because of improved understanding of the biological and molecular alterations in different astrocytoma subtypes. Although the diagnosis

CONTEXT

Key Objective

To determine whether administration of eflornithine in combination with lomustine is superior to lomustine monotherapy in patients with recurrent grade 3 anaplastic astrocytoma (either *IDH*-wild type or *IDH*-mutant per 2016 WHO CNS4).

Knowledge Generated

Eflornithine combined with lomustine improved overall and progression-free survival in patients with *IDH*-mutant, grade 3 astrocytoma (predefined subset analysis, defined before unblinding). Patients with grade 4 astrocytoma and grade 4 glioblastoma did not benefit.

Relevance *(R.G. Maki)*

These data provide further evidence of the clinical relevance of the newest WHO classification of gliomas, in which activity of lomustine was active in grade 3 astrocytoma but not in grade 4 gliomas. These are hopeful data in a challenging area of oncology.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

anaplastic astrocytoma was used for many decades, it was removed in the 2021 WHO CNS Tumor Classification Fifth Edition (CNS5) update[5] and tumors previously diagnosed under this classification now fall into one of several diagnoses, distinguished by *isocitrate dehydrogenase* (*IDH*) mutation status and a combination of histologic and molecular criteria (Appendix Fig A1, online only).[5] In addition, the loss of *cyclin-dependent kinase inhibitor 2A/B* (*CDKN2A/B*) is a newly recognized and negative prognostic biomarker, with homozygous *CDKN2A/B* deletion defining grade 4 disease among *IDH*-mutant (*IDH*-mut) tumors, regardless of histopathologic findings.[5]

Eflornithine is an inhibitor of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine biosynthesis.[6] Elevated levels of polyamines result in rapid cell proliferation, and RNA, DNA, and protein synthesis.[7] Eflornithine inhibits polyamine synthesis, leading to reduced cell division and proliferation.[7] In addition, ODC activity and polyamine levels increase with grade of glial malignancy[8,9] making inhibition of ODC activity an attractive target for an anticancer intervention. As eflornithine's mechanism of action is primarily cytostatic rather than cytotoxic,[10,11] it would be expected to demonstrate efficacy mainly in less aggressive, lower-grade tumors, where the disease is less likely to overwhelm the agent's activity.

Eflornithine is approved for African trypanosomiasis and facial hirsutism[12] and, since December 2023, is also approved as an oral tablet to reduce the risk of progressive disease in adult and pediatric patients with high-risk neuroblastoma.[13] Eflornithine has also been used clinically for 40 years in patients with glioma.[14-19] Previous studies demonstrated trends of improvement in OS and progression-free survival (PFS) especially among patients with grade 2-3 glioma (previously named low grade and anaplastic) rather than those of the highest grade (previously all named glioblastoma),[8,15,17] consistent with its cytostatic mechanism.

The Study To evaluate Eflornithine + Lomustine versus Lomustine in recurrent anaplastic Astrocytoma that progress/Recur after irradiation and adjuvant temozolomide (TMZ) chemotherapy (STELLAR) trial was initiated in 2016 (ClinicalTrials.gov identifier: NCT02796261). On the basis of previous trial results, the intended population was patients with grade 3 tumors, specifically, histologically defined grade 3 anaplastic astrocytomas as described in the Fourth Edition 2016 WHO CNS4 (Appendix Fig A1).[21] Prespecified subgroup analyses were planned by *IDH* mutation status; this stratification factor was incorporated into the statistical design to maintain balance between arms.[22]

Consequently, the 2021 WHO CNS5[5] changes resulted in a major reclassification of patients with the diagnosis of anaplastic astrocytoma to other tumor diagnoses. At the time of 2021 WHO CNS5 publication, STELLAR had reached around 98% enrollment and as a result, the intention-to-treat (ITT) population was ultimately a heterogeneous population of tumors under the updated criteria. The population included three diagnoses per the 2021 WHO criteria: (1) *IDH*-mut grade 3 astrocytoma (without *CDKN2A/B* homozygous deletion); (2) *IDH*-mut grade 4 astrocytoma (*CDKN2A/B* homozygous deletion); and (3) glioblastoma, *IDH*-wild-type (wt) grade 4 (with or without *CDKN2A/B* deletion). To accommodate for the changes in classification, the statistical analysis plan was updated before unblinding to include further analyses by *CDKN2A/B* status.

Here, we present the efficacy and safety of oral eflornithine in combination with lomustine versus lomustine monotherapy for adult patients with recurrent glioma, after prior

radiation and TMZ chemotherapy, including results from a 2021 WHO CNS5 diagnostic subset analysis (defined before unblinding) of patients with *IDH*-mut grade 3 (without *CDKN2A/B* homozygous deletion) astrocytoma.

METHODS

Study Design

STELLAR (ClinicalTrials.gov identifier: NCT02796261) was a prospective, randomized, open-label, phase III study to evaluate the efficacy and safety of eflornithine and lomustine compared with lomustine monotherapy in patients with first recurrent grade 3 astrocytoma. Patients were enrolled from 74 centers in North America (the United States and Canada) and Europe (Belgium, Germany, France, Italy, the Netherlands, and the United Kingdom). The study design is shown in Appendix Figure A2, and further detail is provided in the protocol. Treatment was intended to continue until disease progression, intolerable toxicity, or a maximum of 2 years for eflornithine and up to 12 months (or six cycles) of lomustine. After the treatment period, patients were followed for survival until death, loss to follow-up, or withdrawal of consent. The study protocol was approved by the institutional review board at each site, and the study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice, the Declaration of Helsinki, and local regulations. All patients provided written informed consent before participation.

Patients

Eligible patients were age ≥18 years, diagnosed with anaplastic astrocytoma on the basis of 2016 WHO CNS4 definition with first progression of disease after TMZ and prior radiotherapy (≤6 months before random assignment to guard against pseudoprogression[23]) and a life expectancy ≥6 months. To reduce unintentional enrollment of patients with grade 4 tumors, magnetic resonance imaging (MRI) criteria were added as described in the protocol. Key exclusion criteria included MRI findings at progression consistent with grade 4 (glioblastoma) disease or radiation necrosis, prior lomustine use, and prior systemic therapy for recurrent disease. Central testing for *1p/19q* status was not performed, but histopathologic confirmation of anaplastic astrocytoma was performed by central referee pathologists. Testing of tumor samples assessed several biomarkers including *IDH1/2* and *α-Thalassemia Retardation X-linked* (*ATRX*) mutation, the latter of which is commonly understood to be mutually exclusive with *1p/19q* co-deletion, in the majority of cases.[24-26] Full inclusion and exclusion criteria are provided in the protocol.

Procedures

The random assignment ratio was 1:1, and patients were assigned centrally using an interactive web response. Random assignment was stratified by: age ≤45 years or >45 years, region (US *v* ex-US), *IDH* status (*wt v mut*), and number of prior surgeries (biopsy *v* one or 2) using a block size of four. Eflornithine (Orbus Therapeutics, North Fair Oaks, CA) was provided as an oral solution (150 mg/mL) and administered at 2.8 g/m² body surface area every 8 hours (i.e., 3 times per day), on Days 1-14 and 22-35 of each 42-day cycle, for up to 2 years. Lomustine (oral, commercially sourced) combined with eflornithine was initially dosed at 110 mg/m² on Day 15 of 42 (one administration per cycle; never on the same day as eflornithine) but reduced to 90 mg/m² in the combination arm after five patients experienced grade 4 thrombocytopenia in a preplanned safety analysis. Lomustine monotherapy was dosed at 110 mg/m² and administered on Day 15 and every 6 weeks thereafter for up to six cycles or 12 months, whichever came first. Doses could be modified for the next treatment, depending on the toxicities observed. Drug-specific monitoring, including hearing tests, was performed throughout. All procedures are listed in the protocol.

End Points

All efficacy end points were analyzed in the ITT population, which included all randomly assigned patients, irrespective of actual receipt of protocol-defined therapy. The primary end point was OS. Secondary end points included PFS and response determined by the investigator using Response Assessment in Neuro-Oncology criteria for high- and low-grade glioma,[23,27-30] and an adaptation of the Levin analog scale.[31] Following the ITT analyses, a subpopulation analysis (defined in 2024, before unblinding) was performed in patients with *IDH*-mut grade 3 (without *CDKN2A/B* homozygous deletion) astrocytoma as per 2021 WHO CNS5, hereafter referred to as the *IDH*-mut grade 3 subset. Outcomes (OS and PFS) were also compared between patients with *IDH*-mut and *IDH*-wt disease (regardless of *CDKN2A/B* status). Safety analyses included the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events using Common Terminology Criteria for Adverse Events v4.03 and were performed on all patients who underwent random assignment and received any dose of protocol-defined study treatment. TEAEs of relevance included those related to diarrhea, nausea, vomiting, hearing impairment, seizure, and myelosuppression.

Statistical Analysis

Sample size was calculated assuming true median OS of 12 months for the lomustine monotherapy (control) arm. Assuming that OS follows an exponential probability distribution for each treatment arm, such an improvement represented a true hazard ratio (HR) of 0.667 (combination arm/lomustine monotherapy arm). Inferential comparisons of OS were performed using a stratified log-rank test, on the basis of random assignment factors including age, *IDH* mutation status, and number of prior surgeries. Therefore, with a sample size of 340 patients (170 per arm), there was 90% power to detect a 33.3% reduction in risk of death (HR < 0.667) for the combination arm over lomustine monotherapy, on the basis of a two-sided overall type I error of 5% with adjustment for one interim analysis for superiority at 75% of total deaths, using O'Brien-Fleming

stopping boundary (SEQDESIGN procedure, SAS version 9.4).[32] The boundary for declaring superiority was alpha = 0.020 for the interim analysis, and alpha = 0.044 for the primary analysis, on the basis of the two-sided *P* value. For multiplicity, the overall type I error rate for the study was set at 0.05 (two-sided). If superiority of OS was demonstrated at either analysis, formal inferential comparisons between treatment arms were planned for the secondary end points. Tests were performed in a sequential hierarchical manner on the basis of a closed testing procedure, to maintain strict control of the overall type I error rate to account for hypothesis testing of multiple secondary end points. To ascertain the strength of evidence for detecting a true difference in OS and PFS outcomes between the three patient populations as defined by 2021 WHO CNS5, post hoc sensitivity analyses were completed using multivariable Cox model interaction tests. Bayesian shrinkage analyses were also performed to check the magnitude of the estimated HR in predefined analysis populations.[33] Additional subgroup analyses are considered exploratory; HRs and *P* values are included to provide an objective measure of the magnitude of effect size and relation to variance/standard deviation.

RESULTS

Patient Demographics

Between 2016 and 2022, 343 patients were randomly assigned and 319 (93.0%) treated per the ITT protocol. Among the 343 patients, 169 patients (98.3%) were treated in the eflornithine + lomustine arm and 150 patients (87.7%) in the lomustine monotherapy arm. A total of 154 patients (91.1%) in the eflornithine + lomustine arm and 106 patients (70.6%) in the lomustine monotherapy arm discontinued study treatment. Further details regarding discontinuation are provided in Figure 1. An interim analysis was completed by an Independent Data Monitoring Committee on 13 June 2022 after the prespecified 196 deaths (75% of total deaths) had occurred; findings were not reported or published and the sponsor remained blinded to the results.

The *IDH*-mut grade 3 subset included 196 randomly assigned patients (96 to eflornithine + lomustine, 100 to lomustine monotherapy; Fig 1). Patient demographics and baseline characteristics were balanced between treatment

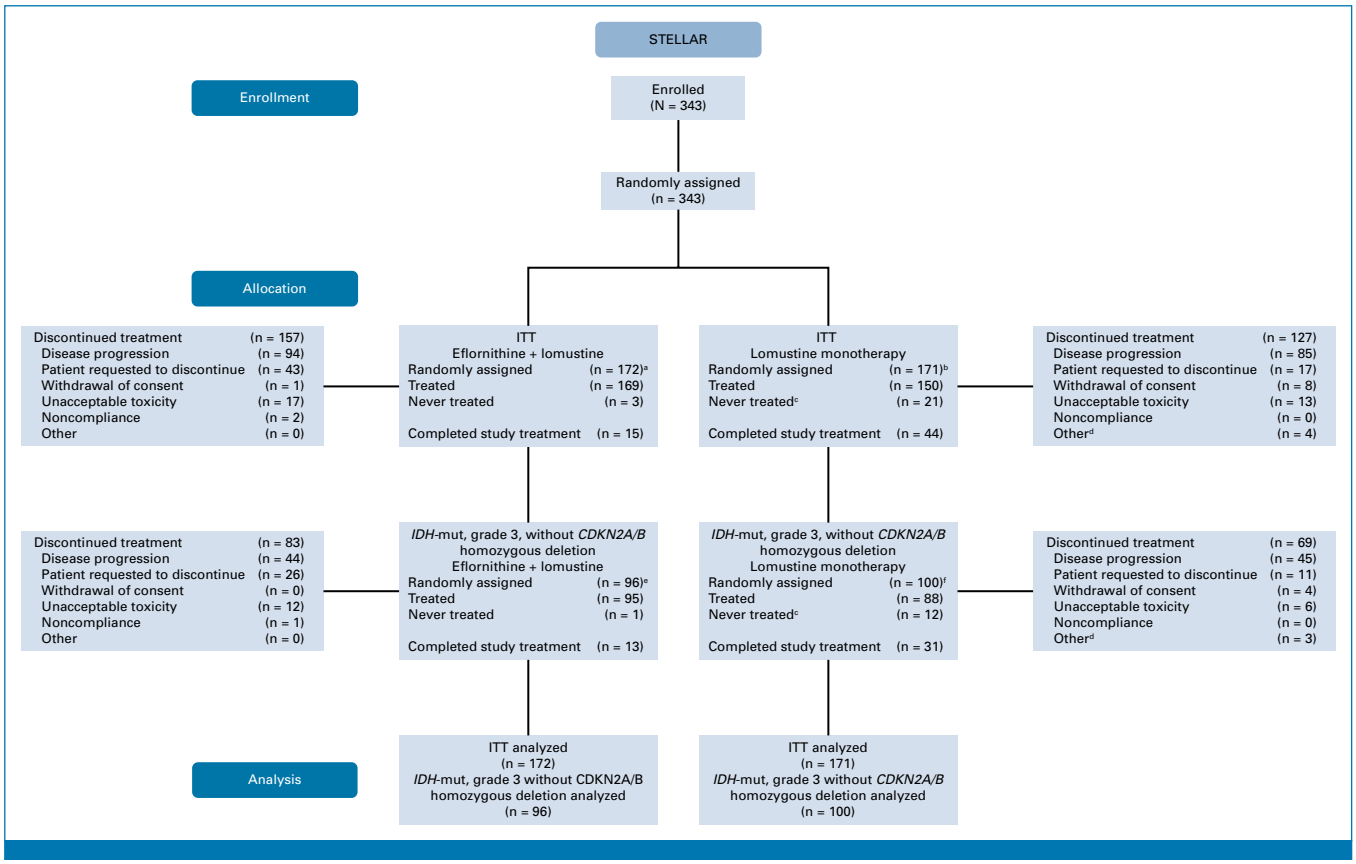


FIG 1. CONSORT diagram (ITT population and *IDH*-mut grade 3 subset). [a]ITT: Eflornithine + lomustine, deaths by EOS (n = 129). [b]ITT: Lomustine monotherapy, deaths by EOS (n = 128). [c]Never treated: the most common reason was due to the open-label nature of the study, larger numbers of patients withdrew in the lomustine monotherapy arm as they did not want to be treated with lomustine only. [d]Includes: patient with kidney stones (lomustine); patient diffusion capacity of carbon monoxide was too low and was not eligible for trial; patient did not wait/never received the study drug; patient died while on treatment. [e]IDH-mut grade 3 without *CDKN2A/B* subset, eflornithine + lomustine, deaths by EOS (n = 59). [f]IDH-mut grade 3 without CDKN2A/B subset, lomustine monotherapy, deaths by EOS (n = 72). *CDKN2A/B*, *cyclin-dependent kinase inhibitor 2A/B*; *IDH*, *isocitrate dehydrogenase*; *IDH*-mut, *IDH* mutation; ITT, intention-to-treat population; N, total number of patients.

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	ITT Population			*IDH*-mut Grade 3 Subset		
	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Total (N = 343)	Eflornithine + Lomustine (n = 96)	Lomustine Monotherapy (n = 100)	Total (N = 196)
Age, years						
No.	172	171	343	96	100	196
Mean (SD)	45.2 (12.6)	44.5 (12.3)	44.9 (12.5)	41.6 (9.4)	39.8 (9.9)	40.7 (9.7)
Range	19-77	20-78	19-78	21-69	20-64	20-69
Age group, years, No. (%)						
≤45	95 (55.2)	97 (56.7)	192 (56.0)	65 (67.7)	73 (73.0)	138 (70.4)
>45	77 (44.8)	74 (43.3)	151 (44.0)	31 (32.3)	27 (27.0)	58 (29.6)
<65	153 (89.0)	162 (94.7)	315 (91.8)	94 (97.9)	100 (100.0)	194 (99.0)
≥65	19 (11.0)	9 (5.3)	28 (8.2)	2 (2.1)	0	2 (1.0)
Sex, No. (%)						
Male	69 (40.1)	65 (38.0)	134 (39.1)	38 (39.6)	40 (40.0)	78 (39.8)
Female	103 (59.9)	106 (62.0)	209 (60.9)	58 (60.4)	60 (60.0)	118 (60.2)
Ethnicity, No. (%)						
Hispanic or Latino	145 (84.3)	147 (86.0)	292 (85.1)	77 (80.2)	86 (86.0)	163 (83.2)
Not Hispanic or Latino	9 (5.2)	14 (8.2)	23 (6.7)	8 (8.3)	7 (7.0)	15 (7.7)
Not reported/unknown	18 (10.5)	10 (5.8)	28 (8.2)	11 (11.5)	7 (7.0)	18 (9.2)
Race, No. (%)						
Asian	2 (1.2)	5 (2.9)	7 (2.0)	0	3 (3.0)	3 (1.5)
Black or African American	3 (1.7)	3 (1.8)	6 (1.7)	2 (2.1)	2 (2.0)	4 (2.0)
White	150 (87.2)	146 (85.4)	296 (86.3)	83 (86.5)	84 (84.0)	167 (85.2)
Other	1 (0.6)	2 (1.2)	3 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
Not reported/unknown	16 (9.3)	15 (8.8)	31 (9.0)	10 (10.4)	10 (10.0)	20 (10.2)
Region, No. (%)						
US	114 (66.3)	113 (66.1)	227 (66.2)	60 (62.5)	62 (62.0)	122 (62.2)
Non-US	58 (33.7)	58 (33.9)	116 (33.8)	36 (37.5)	38 (38.0)	74 (37.8)

Abbreviations: *CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B*; *IDH, isocitrate dehydrogenase*; *IDH*-mut, *IDH* mutation; ITT, intention-to-treat; N, total number of patients; SD, standard deviation; US, United States.

arms for the ITT population and the *IDH*-mut grade 3 subset (Table 1). In the overall ITT population, there were 237 patients with *IDH* mutations, of which 235 patients had *IDH1*-mutant tumors and two had an *IDH2* mutation (Appendix Table A1). For the ITT population, approximately 66% of patients were from the United States, around 60% were male, and the majority (>86%) were White. Relative to the ITT population, the *IDH*-mut grade 3 subset had a higher proportion of patients younger than 65 years (99% *v* 92%), which is consistent with *IDH*-mut tumors presenting more commonly in younger patients. The median time from end of last radiation treatment to random assignment in this subset was 42.7 months in the eflornithine + lomustine arm and 35.1 months in the lomustine monotherapy arm (Appendix Table A2).

Efficacy

Overall Survival

OS was mature (75% died); the median duration of follow-up was 55.2 months [95% CI, 45.9 to 70.7] for eflornithine + lomustine and 54.4 months [95% CI, 47.6 to 63.8] for lomustine monotherapy. There was no difference in median OS between treatment arms in the ITT population (23.4 months [95% CI, 20.5 to 28.2] for eflornithine + lomustine *v* 20.3 months [95% CI, 16.5 to 25.4] for lomustine monotherapy; HR, 0.95 [95% CI, 0.74 to 1.23]; stratified log-rank $P = .703$; Appendix Table A3 and Fig 2A).

However, in the *IDH*-mut grade 3 subset, median OS was considerably improved with eflornithine + lomustine versus lomustine monotherapy (34.9 months [95% CI, 28.2 to 47.6] *v* 23.5 months [95% CI, 18.3 to 31.0]; HR, 0.64 [95% CI, 0.44 to 0.91]; Appendix Table A3, Fig 2B).

OS was also analyzed for 237 patients with *IDH*-mut (regardless of *CDKN2A/B* status) and 106 patients with *IDH*-wt (regardless of *CDKN2A/B* status) disease (Appendix Table A4). Median OS was numerically higher for patients with *IDH*-mut disease treated with eflornithine + lomustine versus lomustine monotherapy (28.5 *v* 22.3 months; HR, 0.76 [95% CI, 0.55 to 1.05]). No OS difference

was observed between treatments for patients with *IDH*-wt (WHO 2021 glioblastoma, 13.4 *v* 13.6 months, HR, 1.40 [95% CI, 0.92 to 2.14]).

Progression-Free Survival

In the ITT population, there was no statistically significant benefit in median PFS after treatment with eflornithine + lomustine compared with lomustine monotherapy (HR, 0.88 [95% CI, 0.65 to 1.20]; stratified log-rank $P = .432$; Table 2 and Fig 3A). However, consistent with the OS results, a substantial improvement in PFS was observed in the *IDH*-mut grade 3 subset for eflornithine + lomustine versus lomustine monotherapy (median PFS 15.8 months *v* 7.2 months, respectively; HR, 0.57 [95% CI, 0.36 to 0.88]; Table 2 and Fig 3B).

PFS for patients with *IDH*-mut (regardless of *CDKN2A/B* status) and *IDH*-wt (regardless of *CDKN2A/B* status) is shown in Appendix Table A4. Median PFS was considerably higher for patients with *IDH*-mut treated with eflornithine + lomustine versus lomustine monotherapy (12.3 *v* 7.3 months, respectively; HR, 0.68 [95% CI, 0.46 to 1.00]). Consistent with the OS results in patients with *IDH*-wt tumors, PFS was similar between treatment arms. However, median PFS was shorter with eflornithine + lomustine versus lomustine monotherapy (3.4 *v* 6.8 months, respectively; HR, 1.41 [95% CI, 0.84 to 2.37]).

Radiographic responses were more common in the eflornithine arm, in both the ITT population and the *IDH*-mut grade 3 subset, showing consistency with OS and PFS (Table 2 and Appendix Table A5).

Sensitivity analyses demonstrated consistency with the results above (Appendix Results: Sensitivity Analyses, Appendix Figs A3 and A4).

Adverse Events

Following completion of a preplanned safety analysis including 42 patients, the dose of lomustine was reduced in the combination group from 110 mg/m² to 90 mg/m² (one adminstration on Day 15 of a 42-day cycle) after five patients experienced grade 4 thrombocytopenia.

The safety analysis included the 319 patients who received treatment. A similar percentage of patients in the eflornithine + lomustine and lomustine monotherapy arms reported TEAEs (99% *v* 93%, respectively); frequently reported TEAEs of relevance included diarrhea (80% *v* 7%), nausea (52% *v* 31%), and fatigue (41% *v* 36%).

Details regarding grade 3 and 4 TEAEs are shown in Table 3. No grade 5 TEAEs occurred. Among patients in the eflornithine + lomustine and lomustine monotherapy groups, respectively, the most common grade 3 and 4 TEAEs were related to myelosuppression (42% *v* 29%) and hearing impairment (24% *v* 0%).

Serious TEAEs were reported by 19% of patients in the eflornithine + lomustine arm and 8% of patients in the lomustine monotherapy arm. Frequently reported events (>3% incidence) included seizures (4% *v* <1%), pulmonary embolism (4% *v* 0%), and vomiting (3% *v* 0%) among the eflornithine + lomustine and lomustine monotherapy groups, respectively. No new safety signals were identified.

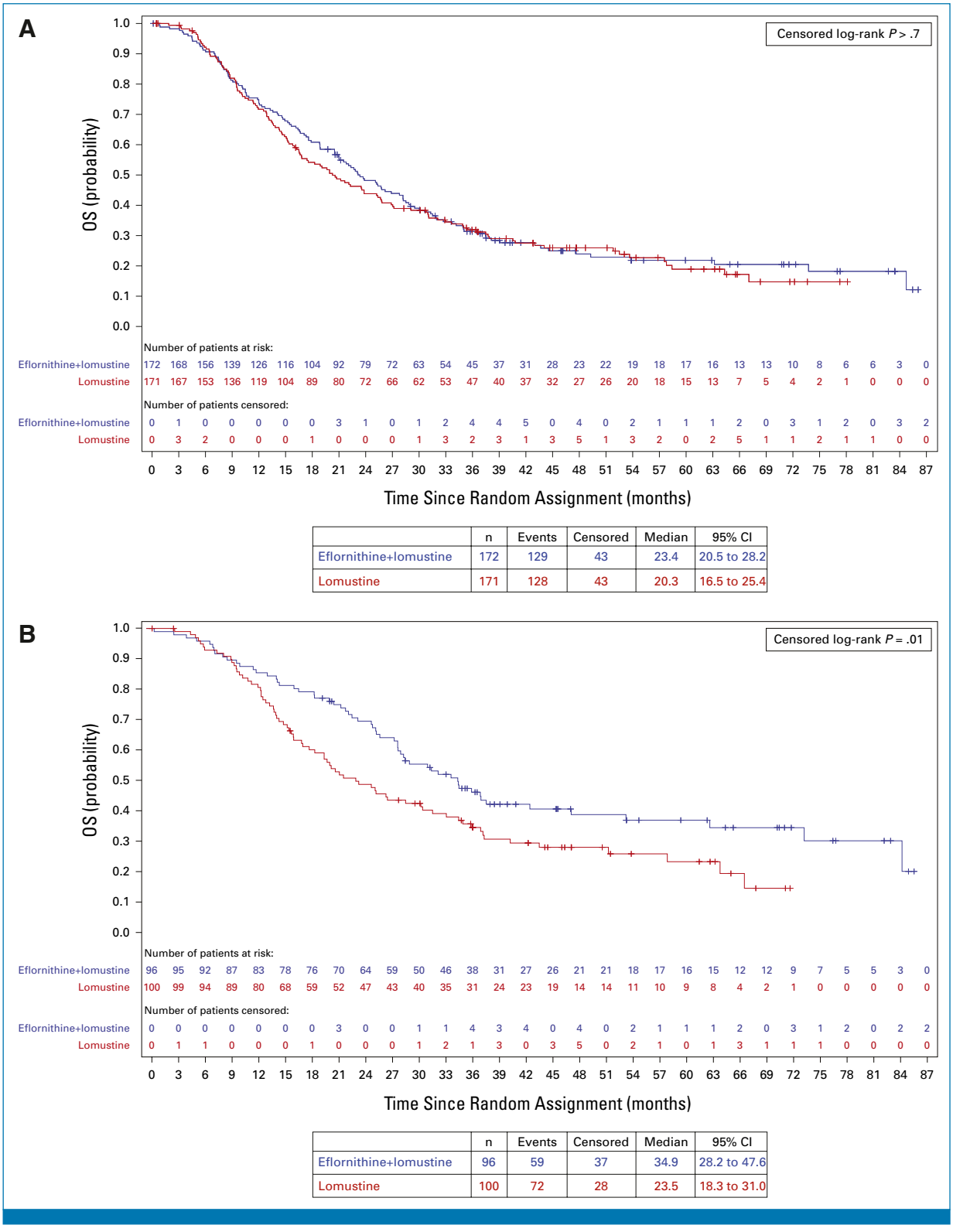
DISCUSSION

In this large randomized, open-label, phase III study of eflornithine + lomustine versus lomustine monotherapy for first recurrence of anaplastic astrocytoma (on the basis of WHO 2016 criteria), there was no overall difference in PFS or OS between arms in the ITT population. However, as described earlier, the ITT population according to WHO 2021 CNS5 consisted of three distinct tumor populations. Prior clinical evidence[10,15,17] had demonstrated that grade 4 gliomas were likely to be relatively insensitive to eflornithine; therefore, inclusion criteria were devised to exclude grade 4 *IDH*-wt tumors. Following the 2021 WHO CNS5 addition of *CDKN2A/B* homozygous deletion as a new molecular criteria for grade 4 *IDH*-mut astrocytomas, when this new category of patients were analyzed in STELLAR, no benefit was observed, which is congruous with eflornithine's cytostatic mechanism of action.[10,11]

However, among patients with the intended target tumor population (per WHO 2021 CNS5 and defined before unblinding: *IDH*-mut, grade 3 astrocytomas), eflornithine improved OS by a median of 11.4 months, a clinically meaningful finding. Similarly, median PFS was more than doubled (8.6-month difference between treatment arms). These results indicate that eflornithine is more efficacious in slower-growing gliomas that do not overwhelm the cytostatic ability of the drug. Furthermore, as the three disease cohorts are biologically distinct, the results must be considered separately.[22,34] The robust size of the *IDH*-mut grade 3 subgroup combined with the sensitivity analyses indicate that the benefits of eflornithine observed in this patient population are real and important, with a concordance of efficacy outcomes across OS, PFS, and radiographic responses.

Of note, in patients with *IDH*-wt disease (glioblastoma, grade 4), median PFS was numerically shorter in the eflornithine + lomustine arm compared with the lomustine monotherapy arm (3.4 *v* 6.8 months), which negatively affected the results in the entire ITT population. Potentially, this could be due to the differing lomustine dose per cycle in the two treatment groups (90 mg/m² *v* 110 mg/m² in the monotherapy arm), where the lower lomustine dose, required in the combination group because of potential toxicity, may have negatively affected the overall outcomes.

In the *IDH*-mut grade 3 subset, the median time from last radiation to random assignment was nominally higher in the



	n	Events	Censored	Median	95% CI
Eflornithine+lomustine	172	129	43	23.4	20.5 to 28.2
Lomustine	171	128	43	20.3	16.5 to 25.4

	n	Events	Censored	Median	95% CI
Eflornithine+lomustine	96	59	37	34.9	28.2 to 47.6
Lomustine	100	72	28	23.5	18.3 to 31.0

FIG 2. Kaplan-Meier curves of OS for the (A) ITT population and (B) *IDH*-mut grade 3 subset (investigator assessment by treatment). *P* values are from the log-rank test stratified by age (≤45 *v* > 45) and number of prior surgeries. For the ITT population *P* value was also stratified by *IDH* status (mutant *v* wild-type). *CDKN2A/B*, *cyclin-dependent kinase inhibitor 2A/B*; *IDH*-mut, *isocitrate dehydrogenase* mutation; ITT, intention-to-treat; N, total number of patients; OS, overall survival.

TABLE 2. Summary of Secondary Efficacy Endpoint Results

End Point	ITT Population		*IDH*-mut Grade 3 Subset	
	Eflornithine + Lomustine (N = 172)	Lomustine Monotherapy (N = 171)	Eflornithine + Lomustine (N = 96)	Lomustine Monotherapy (N = 100)
PFS				
Median, months (95% CI)	8.9 (4.6 to 12.1)	7.2 (5.5 to 10.4)	15.8 (11.8 to 24.2)	7.2 (3.7 to 11.1)
Log-rank *P* value[a]	.4319		.0113	
HR (95% CI)[b]	0.88 (0.65 to 1.20)		0.57 (0.36 to 0.88)	
Cox regression *P* value	.4326		.0125	
Objective response[c]				
No. of patients with ≥1 MRI evaluation	158	147	92	86
Patients with objective response, n (%)	19 (12.0)	13 (8.8)	16 (17.4)	8 (9.3)
95% CI for objective response Rate	7.4 to 18.1	4.8 to 14.6	10.3 to 26.7	4.1 to 17.5
P	.3456		.1037	
Duration of objective response				
Median (months) (95% CI)	14.09 (7.23 to 18.60)	NR (5.72 to NE)	16.36 (8.28 to NE)	NR (NE to NE)
Log-rank *P* value[a]	.2856		.3076	
HR (95% CI)[b]	3.00 (0.36 to 24.71)		1.323e7 (0.00 to NE)	
Cox regression *P* value	.3078		.9963	
Clinical benefit[d]				
Patients with clinical benefit, n (%)	86 (54.4)	83 (56.5)	60 (65.2)	49 (49.0)
95% CI for clinical benefit rate	46.3 to 62.4	48.0 to 64.6	54.6 to 74.9	45.8 to 67.6
P	.7235		.2439	
Duration of clinical benefit				
Median, months (95% CI)	21.91 (12.32 to NE)	11.30 (10.41 to NE)	24.18 (17.12 to NE)	12.06 (10.41 to NE)
Log-rank *P* value[a]	.0385		.0083	
HR (95% CI)[b]	0.59 (0.35, 0.98)		0.40 (0.19, 0.80)	
Cox regression *P* value	.0405		.0101	

Abbreviations: BOR, best overall response; HR, hazard ratio; *IDH*, *isocitrate dehydrogenase*; ITT, intention-to-treat; MRI, magnetic response imaging; n, number of patients; N, total number of patients; NE, non-evaluable; NR, not reported; PFS, progression-free survival.

[a]Log-rank test stratified by age (≤45 *v* >45 years), *IDH* status, and number of prior surgeries.

[b]Cox regression analysis stratified by age (≤45 *v* >45 years), *IDH* status, and number of prior surgeries without covariate.

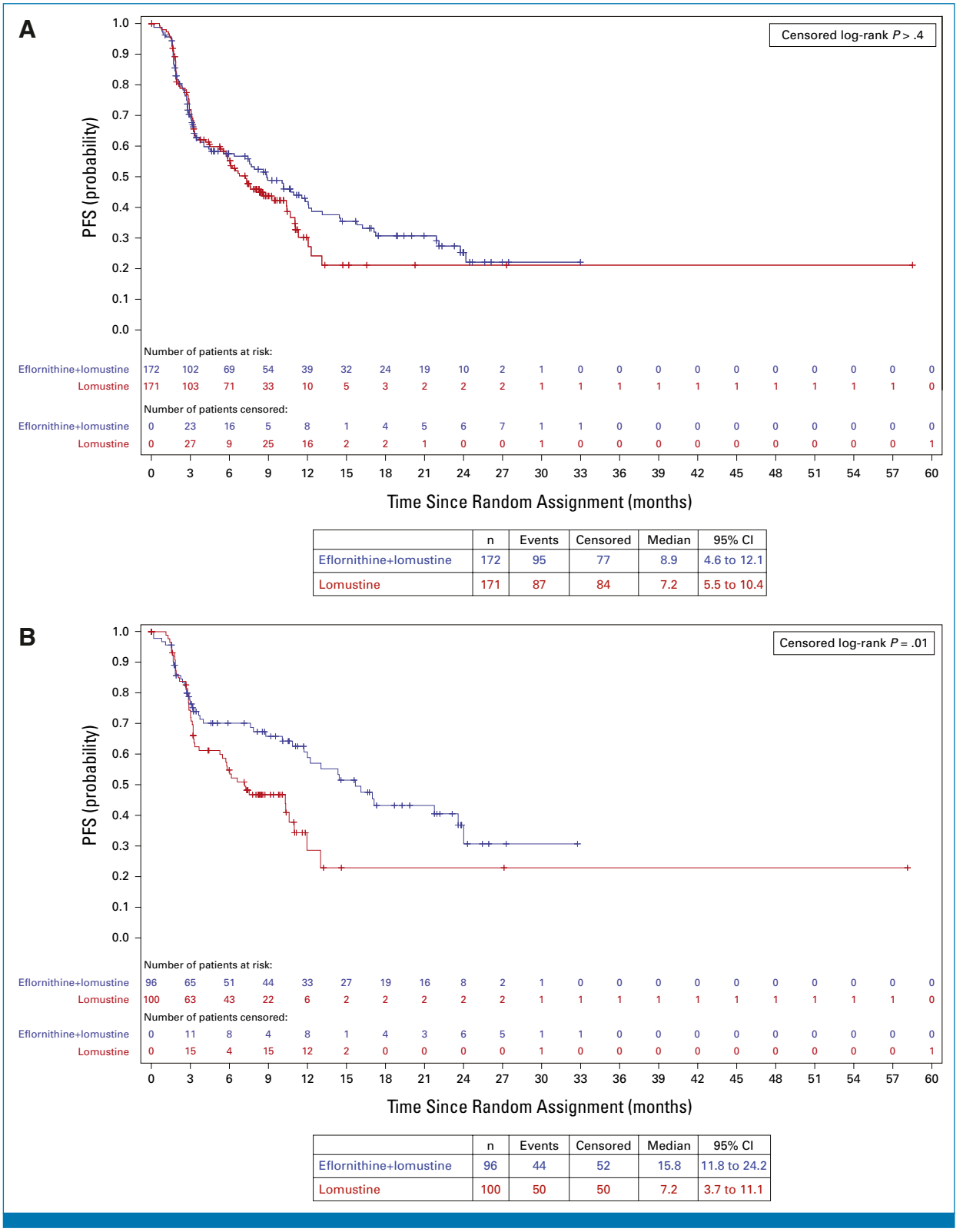
[c]Objective response = partial or complete response in the MRI scan.

[d]Patients who qualified for clinical benefit responses were those with a BOR of complete response, partial response, minor response, or stable disease for 120 days without progressive disease. To qualify as stable disease for 120 days without progressive disease, a patient was required to have a tumor assessment on study Day 120 or later with no prior progressive disease as assessed by investigator.

eflornithine arm versus the lomustine monotherapy arm (42.7 *v* 35.1 months, respectively). However, the mean time from last radiation to random assignment was very similar (48.5 *v* 46.3 months). To understand the potential difference between the two treatment groups, Wilcoxon rank-sum tests were run and showed no evidence that the median time to random assignment was materially different between the two treatment groups ($P = .3176$) and therefore, unlikely to impact the *IDH*-mut grade 3 subset results.

The current initial standard treatment for grade 3 astrocytoma is radiation and chemotherapy, either procarbazine, lomustine, and vincristine (PCV) or TMZ.[34,35] The efficacy of adjuvant TMZ was demonstrated in the CATNON trial, especially among patients with *IDH*-mut tumors when administered after radiotherapy.[34,36] At recurrence, the same therapies are often used that is, TMZ is considered if patient relapse follows PCV and vice versa, with single-agent lomustine as a common salvage therapy.[3,37] Therefore, there is a distinct unmet need for chemotherapeutic treatment options in this population.[3] Our results demonstrate that the addition of eflornithine can improve median OS and PFS in select patients with recurrent astrocytoma.

There were no unexpected safety signals, and no grade 5 TEAEs reported. The most common grade 3 and 4 TEAEs of relevance were related to myelosuppression and hearing impairment, which are known toxicities of eflornithine and occurred at a frequency consistent with prior experience.[15-17,19,38-40] Importantly, on the basis of previous evidence, hearing impairment because of eflornithine is nearly always reversible, with only one prior case report of irreversible hearing loss.[10,41,42] However, the follow-up period for STELLAR is insufficient to draw conclusions about



	n	Events	Censored	Median	95% CI
Eflornithine+lomustine	172	95	77	8.9	4.6 to 12.1
Lomustine	171	87	84	7.2	5.5 to 10.4

	n	Events	Censored	Median	95% CI
Eflornithine+lomustine	96	44	52	15.8	11.8 to 24.2
Lomustine	100	50	50	7.2	3.7 to 11.1

FIG 3. Kaplan-Meier curves of PFS for the (A) ITT population and (B) *IDH*-mut grade 3 subset (investigator assessment by treatment). *P* values are from the log-rank test stratified by age (≤45 *v* > 45) and number of prior surgeries. For the ITT population *P* value was also stratified by *IDH* status (mutant *v* wild-type). *CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B*; *IDH*-mut, *isocitrate dehydrogenase* mutation; ITT, intention-to-treat; N, total number of patients; PFS, progression-free survival.

TABLE 3. Safety Summary (all treated patients)

TEAE	Eflornithine + Lomustine (n = 169), No. (%)	Lomustine Monotherapy (n = 150), No. (%)
Any TEAEs	168 (99.4)	140 (93.3)
Any eflornithine-related TEAEs	158 (93.5)	0
Any lomustine-related TEAEs	135 (79.9)	126 (84.0)
Any grade 3 and 4[a] TEAEs	123 (72.8)	61 (40.7)
Any grade 3 and 4[a] eflornithine-related TEAEs	86 (50.9)	0
Any grade 3 and 4[a] lomustine-related TEAEs	77 (45.6)	50 (33.3)
Grade 3 and 4[a] TEAEs of relevance	111 (65.7)	46 (30.7)
TEAEs related to myelosuppression[b]	71 (42.0)	44 (29.3)
TEAEs related to hearing impairment[c]	40 (23.7)	0
TEAEs related to diarrhea[c]	16 (9.5)	0
TEAEs related to nausea[c]	6 (3.6)	1 (0.7)
TEAEs related to vomiting[c]	6 (3.6)	0
TEAEs related to seizure	6 (3.6)	2 (1.3)
Any serious TEAEs	32 (18.9)	12 (8.0)
Any serious eflornithine-related TEAEs	13 (7.7)	0
Any serious lomustine-related TEAEs	6 (3.6)	4 (2.7)

NOTE. For each category, patients were counted only once, even if they experienced multiple events in the same category. Treatment-emergence was defined as any event that started between the first dose and 30 days after the last dose of study treatment(s).
Abbreviations: MedDRA, medical dictionary for regulatory activities; n, number of patients; N, total number of patients; TEAE, treatment-emergent adverse event.
[a]No grade 5 toxicities occurred.
[b]TEAEs related to myelosuppression were defined as any TEAEs related to pancytopenia, TEAEs related to thrombocytopenia, TEAEs related to neutropenia, and TEAEs related to anemia.
[c]Defined by selected MedDRA preferred terms.

the reversibility of hearing loss cases reported in the trial. Myelosuppression, frequently reported in both treatment arms, is an expected side effect of chemotherapeutic drugs and was managed with typical supportive measures.[43-45]

The most relevant limitation of this study is that the target population was recategorized during trial conduct. As a result, the overall trial population was divided into three distinct disease cohorts, one of which became the *IDH*-mut grade 3 subset of interest presented here. However, the subset analysis was not powered to detect differences between the treatment arms. Therefore, although the analysis in the *IDH*-mut grade 3 subset demonstrated clinical superiority with respect to OS and PFS with eflornithine + lomustine versus lomustine monotherapy, because the statistical comparison was not prespecified, the *P* value (0.014) cannot be considered statistically significant. Additionally, there was no prespecified target patient recruitment for the *IDH*-mut and *IDH*-wt groups nor for patients with varying *CDKN2A/B* statuses. Finally, the open-label trial design meant that some patients withdrew after random assignment as they did not want to receive lomustine monotherapy.

In conclusion, patients with recurrent grade 3 astrocytoma (*IDH*-mut, without *CDKN2A/B* homozygous deletion) randomly assigned to eflornithine + lomustine had substantially longer PFS and OS than with lomustine monotherapy. This is a clinically meaningful result, representing a potential new treatment option in this patient population with considerable unmet need. No benefits were observed in patients with grade 4 disease (*IDH*-mut, with *CDKN2A/B* homozygous deletion or *IDH*-wt regardless of *CDKN2A/B* status) or with all three diagnoses combined (primary end point in the ITT population).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

STELLAR: Phase III, Randomized, Open-Label Study of Eflornithine Plus Lomustine Versus Lomustine Alone in Patients With Recurrent Grade 3 Astrocytoma

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Speakers' Bureau: Chimerix
Research Funding: Orbus Therapeutics (Inst), Biodexa (Inst), Exvade (Inst)
Patents, Royalties, Other Intellectual Property: US 15/428510—Method of Treating Solid Tumor w/Oncolytic Poliovirus licensed to Istari, a patent, CA 2,892,183—Method of Treating Solid Tumor w/Oncolytic Poliovirus licensed to Istari, a patent, EP 13856989.2—Method of Treating Solid Tumor w/Oncolytic Poliovirus licensed to Istari, a patent, HK 15112399.5—Method of Treating Solid Tumor w/Oncolytic Poliovirus licensed to Istari, a patent, US 16/505,771 ONCOLYTIC POLIOVIRUS FOR HUMAN TUMORS, US 17/044,645 NEOADJUVANT CANCER TREATMENT, AU 2019247039 NEOADJUVANT CANCER TREATMENT, JP 2020-554198 NEOADJUVANT CANCER TREATMENT, South Korea 10-2020-7031272 NEOADJUVANT CANCER TREATMENT, Canada NEOADJUVANT CANCER TREATMENT, PCT/US2019/025402 NEOADJUVANT CANCER TREATMENT, US 62/823,277 NEOADJUVANT CANCER TREATMENT, US 17/016,699 ONCOLYTIC POLIOVIRUS FOR HUMAN TUMORS, US 16/086,735 SEQUENTIAL ANTI-CANCER TREATMENT, China NEOADJUVANT CANCER TREATMENT, US 62/651,470

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Patents, Royalties, Other Intellectual Property: Patents with my name on them have been filed by Orbus Therapeutics. I do not and will not receive royalties on these patents as they are held by Orbus Therapeutics
Travel, Accommodations, Expenses: Orbus Therapeutics
Other Relationship: Orbus Therapeutics
Uncompensated Relationships: Orbus Therapeutics

No other potential conflicts of interest were reported.

APPENDIX

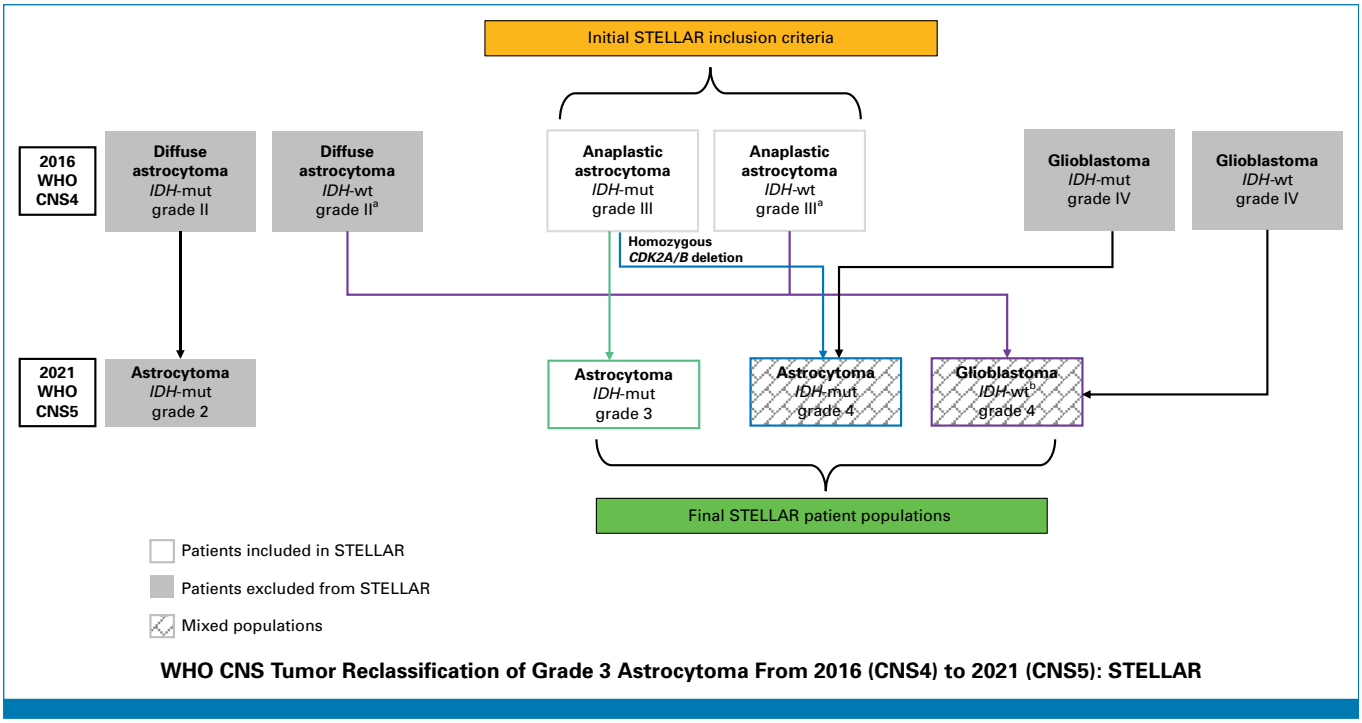
Supplementary Results: Sensitivity Analyses

As no hierarchy was prespecified for the treatment comparisons in subgroups, a conservative post hoc Bonferroni alpha adjustment was applied. Based on this adjustment, a treatment comparison for OS for a particular subgroup was deemed statistically important if $P < .0167$ (adjusted for three log-rank tests in the *IDH*-mut grade 3 astrocytoma, grade 4 astrocytoma and glioblastoma, and *IDH*-wt). With $P = .0136$ for the log-rank test for patients with *IDH*-mut grade 3 astrocytoma, a treatment benefit for eflornithine + lomustine versus lomustine in patients with *IDH*-mut grade 3 astrocytoma was justifiably demonstrated.

To verify if the treatment outcome effects observed in the *IDH*-mut grade 3 without homozygous *CDKN2A/B* deletion subset were different from those observed in the remaining patients (grade 4 astrocytoma and glioblastoma), a treatment-by-subgroup interaction test was performed using multivariate Cox regression models.

The treatment effect of eflornithine + lomustine over lomustine monotherapy on OS differed between the subgroups of *IDH*-mut grade 3 astrocytoma and grade 4 astrocytoma and glioblastoma ($P = .0010$ interaction test). This was supported by a HR = 0.664 in the *IDH*-mut grade 3 astrocytoma subgroup, a HR = 1.538 in the grade 4 astrocytoma and indicates that the glioblastoma subgroup should be analyzed separately (data not shown). Similarly, the treatment effect of eflornithine + lomustine over lomustine monotherapy on PFS differed between the subgroups of *IDH*-mut grade 3 astrocytoma and grade 4 astrocytoma and glioblastoma ($P = .0064$ interaction test). Again, this was supported by a HR = 0.587 in *IDH*-mut grade 3 astrocytoma subgroup, a HR = 1.337 in grade 4 astrocytoma and indicates that the glioblastoma subgroup should be analyzed separately (data not shown).

To further confirm the robustness of results, Bayesian shrinkage analysis was performed and demonstrated that the results in this subpopulation were not random. Bayesian shrinkage analysis assumed a noninformative prior distribution for the parameters, such that the HR estimated from the posterior distribution is more conservative. The degree of shrinkage indicates how much of the HR estimate is due to random variation (Appendix Figs A2 and A3).



WHO CNS Tumor Reclassification of Grade 3 Astrocytoma From 2016 (CNS4) to 2021 (CNS5): STELLAR

FIG A1. WHO CNS Tumor Reclassification of grade 3 astrocytoma from 2016 (CNS4) to 2021 (CNS5): STELLAR. STELLAR began enrolling patients in September 2016 on the basis of the 2016 WHO CNS4 criteria and completed enrollment of 343 patients in January 2022. When the 2021 WHO CNS5 was published in August 2021, STELLAR had already enrolled 333 patients, and thus, the study was at 98% of its enrollment target. The statistical analysis plan was proactively amended before unblinding to evaluate the impact of tumor molecular characteristics on OS and PFS, including homozygous deletion status of *CDKN2A/B*. This allowed analysis of patients with different disease types enrolled in STELLAR study using the updated 2021 WHO CNS5. All patients enrolled in STELLAR had disease that progressed or recurred after irradiation and TMZ chemotherapy. [a]The large majority of *IDH*-wt astrocytoma histologically grade 2 or 3 tumors are reclassified to grade 4, as defined by molecular features. [b]*IDH*-wt is diagnosed in the setting of an *IDH*-wt diffuse and astrocytic glioma in adults if there is microvascular proliferation or necrosis or *TERT* promoter mutation or *EGFR* gene amplification or +7/-10 chromosome copy number change. *CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor*; *IDH, isocitrate dehydrogenase; IDH*-mut, *IDH* mutation; IDH-wt, *IDH*-wild-type; PFS, progression-free survival; OS, overall survival; *TERT, telomerase reverse transcriptase*; TMZ, temozolomide.

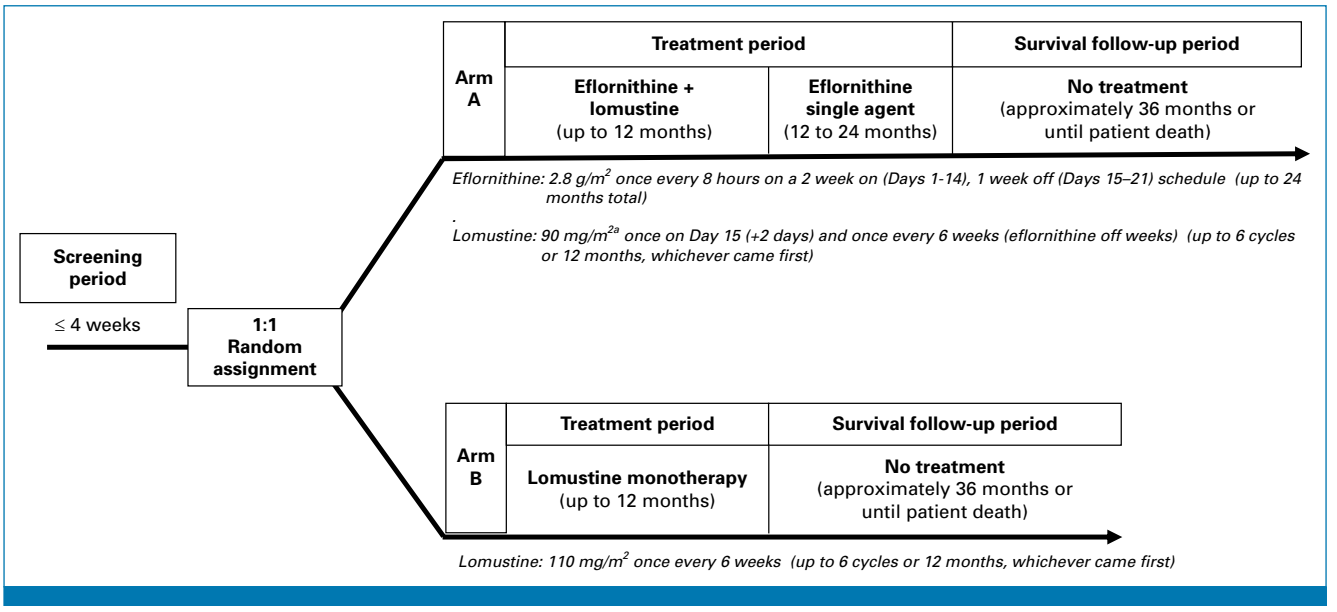
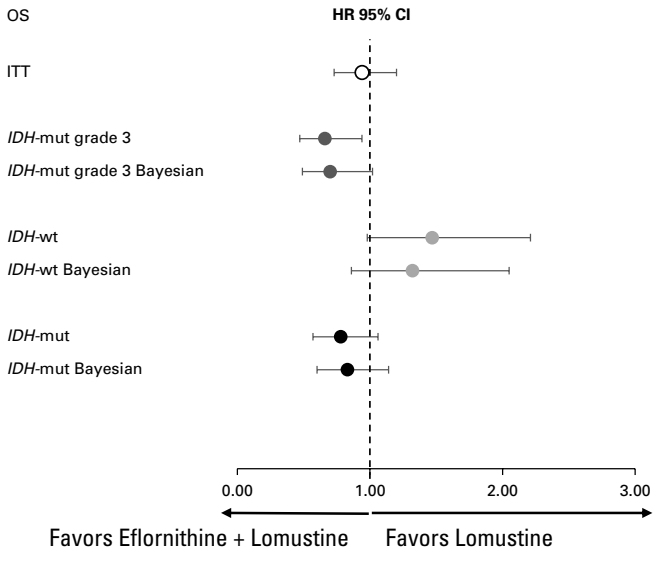
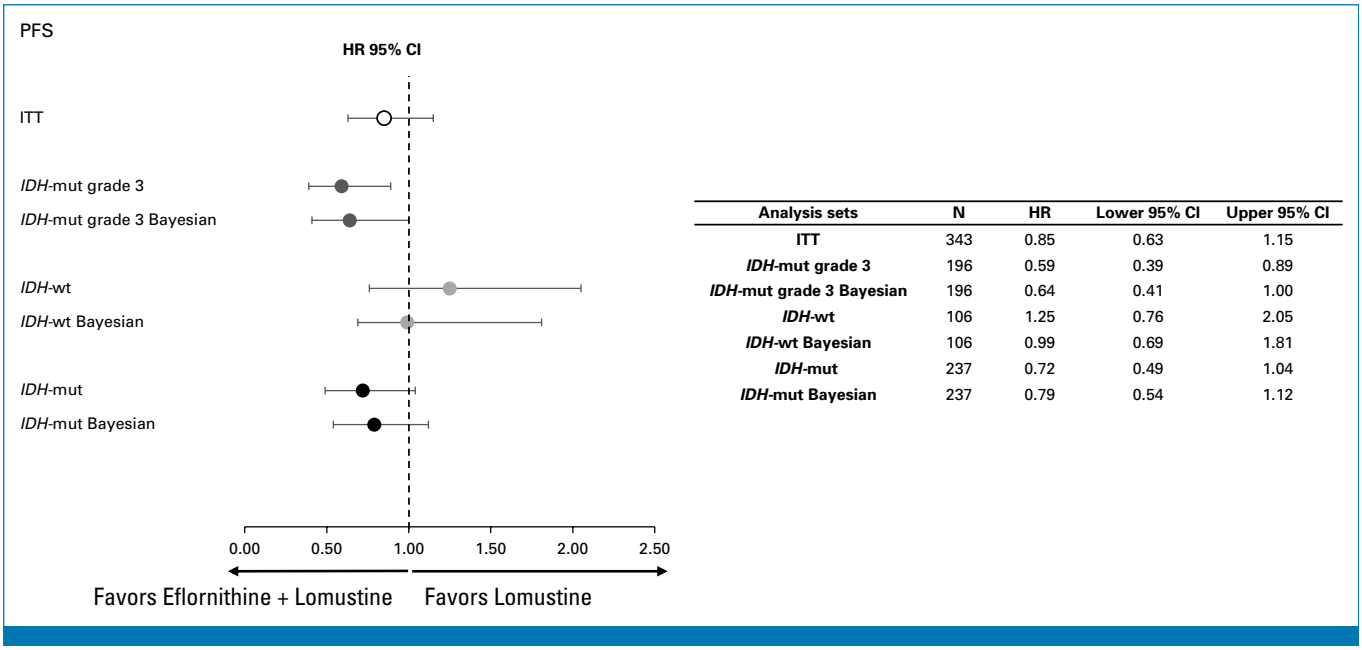


FIG A2. STELLAR study design. [a]Initial lomustine dose was 110 mg/m^2. Following a preplanned safety analysis, the dose of lomustine was reduced after five patients experienced grade 4 thrombocytopenia.



Analysis sets	N	HR	Lower 95% CI	Upper 95% CI
ITT	343	0.94	0.73	1.2
***IDH*-mut grade 3**	196	0.66	0.47	0.94
***IDH*-mut grade 3 Bayesian**	196	0.7	0.49	1.02
***IDH*-wt**	106	1.47	0.98	2.21
***IDH*-wt Bayesian**	106	1.32	0.86	2.05
***IDH*-mut**	237	0.78	0.57	1.06
IDH-mut Bayesian	237	0.83	0.6	1.14

FIG A3. Bayesian analysis: Forest plot for OS HRs by subgroup (ITT; *IDH*-mut grade 3; *IDH*-wt and *IDH*-mut). Parameters were estimated using the simple contrast comparing eflornithine + lomustine with lomustine monotherapy from the Cox model with treatment, subgroup, and treatment-by-subgroup interaction terms. Bayesian shrinkage analysis assumed a noninformative prior distribution for the parameters, such that the HR estimated from the posterior distribution is more conservative. The degree of shrinkage indicates how much of the HR estimate is due to random variation. HR, hazard ratio; *IDH*-mut, *IDH* mutation; *IDH*-wt, *IDH*-wild-type; ITT, intent-to-treat; N, total number of patients; OS, overall survival.



Analysis sets	N	HR	Lower 95% CI	Upper 95% CI
ITT	343	0.85	0.63	1.15
***IDH*-mut grade 3**	196	0.59	0.39	0.89
***IDH*-mut grade 3 Bayesian**	196	0.64	0.41	1.00
***IDH*-wt**	106	1.25	0.76	2.05
***IDH*-wt Bayesian**	106	0.99	0.69	1.81
***IDH*-mut**	237	0.72	0.49	1.04
***IDH*-mut Bayesian**	237	0.79	0.54	1.12

FIG A4. Bayesian analysis: forest plot for PFS HRs by subgroup (ITT; *IDH*-mut grade 3; *IDH*-wt and *IDH*-mut). Parameters were estimated using the simple contrast comparing eflornithine + lomustine with lomustine monotherapy from the Cox model with treatment, subgroup, and treatment-by-subgroup interaction terms. Bayesian shrinkage analysis assumed a noninformative prior distribution for the parameters, such that the HR estimated from the posterior distribution is more conservative. The degree of shrinkage indicates how much of the HR estimate is due to random variation. HR, hazard ratio; *IDH*-mut, *IDH* mutation; *IDH*-wt, *IDH*-wild-type; ITT, intent-to-treat, N, total number of patients; PFS, progression-free survival.

TABLE A1. Key Biomarkers for the ITT Population

Biomarker	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Overall (N = 343)
IDH-wt	54 (31.4)	52 (30.4)	106 (30.9)
IDH mutation	118 (68.6)	119 (69.6)	237 (69.1)
IDH1	116 (67.4)	119 (69.6)	235 (68.5)
IDH2	2 (1.2)	0	2 (0.6)
Known *ATRX* status	111 (64.5)	115 (67.3)	226 (66.9)
Known *CDKN2A/B* homozygous deletion	17 (9.9)	16 (9.4)	33 (9.6)
ATRX intact	4 (2.3)	5 (2.9)	9 (2.6)
ATRX mutated	13 (7.6)	11 (6.4)	24 (7.0)
Known *CDKN2A/B* without homozygous deletion	96 (55.8)	100 (58.5)	196 (57.1)
ATRX intact	32 (18.6)	26 (15.2)	58 (16.9)
ATRX mutated	61 (35.5)	72 (42.1)	133 (38.8)

NOTE. All values presented are No. (%). All percentages are calculated from the number.
Abbreviations: *ATRX, α-Thalassemia Retardation X-linked*; *CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; IDH, isocitrate dehydrogenase*; N, total number of patients; n, number of patients with available data.

TABLE A2. Time From Last Radiotherapy to Random Assignment

Radiotherapy History	ITT Population		IDH-mut Grade 3 Subset		IDH-mut Population		IDH-wt Population	
	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Eflornithine + Lomustine (n = 96)	Lomustine Monotherapy (n = 100)	Eflornithine + Lomustine (n = 118)	Lomustine Monotherapy (n = 119)	Eflornithine + Lomustine (n = 54)	Lomustine Monotherapy (n = 52)
Time from end of last radiation to random assignment, months, No. (%)								
≤24	85 (49.4)	77 (45.0)	36 (37.5)	31 (31.0)	42 (35.6)	41 (34.5)	43 (79.6)	36 (69.2)
>24	87 (50.6)	94 (55.0)	60 (62.5)	69 (69.0)	76 (64.4)	78 (65.5)	11 (20.4)	16 (30.8)
Time from end of last radiation to random assignment, months								
n	172	171	96	100	118	119	54	52
Mean (SD)	38.9 (32.9)	39.3 (37.8)	48.5 (34.9)	46.3 (39.7)	48.0 (34.6)	45.9 (40.4)	18.8 (16.3)	24.2 (25.3)
Median	26.3	27.1	42.7	35.1	41.1	33.1	12.2	15.9
Min-max	1-140	5-197	6-140	6-197	1-140	5-197	5-84	6-169

Abbreviations: *IDH*-mut, *isocitrate dehydrogenase* mutation; *IDH*-wt, *isocitrate dehydrogenase* wild-type; ITT, intention-to-treat; max, maximum; min, minimum; N, total number of patients; n, number of patients with available data; SD, standard deviation.

TABLE A3. OS (ITT and *IDH*-mut Grade 3 Subset)

OS	ITT Population		*IDH*-mut Grade 3 Subset	
	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Eflornithine + Lomustine (n = 96)	Lomustine Monotherapy (n = 100)
Status, No. (%)				
Deaths	129 (75.0)	128 (74.9)	59 (61.5)	72 (72.0)
Censored	43 (25.0)	43 (25.1)	37 (38.5)	28 (28.0)
OS, months (95% CI)[a]				
Median	23.4 (20.5 to 28.2)	20.3 (16.5 to 25.4)	34.9 (28.2 to 47.6)	23.5 (18.3 to 31.0)
Stratified log-rank *P* value[b]	0.7032		0.0136	
Unstratified log-rank *P* value	0.6041		0.0140	
HR #1 (95% CI)[c]	0.95 (0.74 to 1.23)		0.64 (0.44 to 0.91)	
Stratified Cox regression Walds test *P* value	0.7033		0.0143	
HR #2 (95% CI)[c]	0.94 (0.73 to 1.20)		0.65 (0.46 to 0.92)	
Unstratified Cox regression Walds test *P* value	0.6041		0.0148	
Median duration of follow-up, months (95% CI)[d]	55.2 (45.9 to 70.7)	54.4 (47.6 to 63.8)	NA	NA

Abbreviations: HR, hazard ratio; *IDH*-mut, *isocitrate dehydrogenase* mutation; ITT, intention-to-treat; n, number of patients; N, total number of patients; NA, not applicable; OS, overall survival.

[a]OS was calculated as (date of death − date of random assignment + 1)/30.4375. Patients who were alive at the cutoff date were censored at the date of last observation. CIs were calculated using Greenwood's SE.

[b]Stratified analysis used age (≤45 *v* >45 years), *IDH* status (mutated *v* wild-type), and number of prior surgeries as stratification factors.

[c]HR and CI were estimated using the Cox proportional hazards model with treatment as main effect without covariate.

[d]Duration of follow-up was estimated using the same Kaplan-Meier method but reversing the censoring indicator.

TABLE A4. OS and PFS (*IDH*-mut and *IDH*-wt populations)

OS and PFS	*IDH*-mut Population		*IDH*-wt Population	
	Eflornithine + Lomustine (n = 118)	Lomustine Monotherapy (n = 119)	Eflornithine + Lomustine (n = 54)	Lomustine Monotherapy (n = 52)
Status, No. (%)				
Deaths	78 (66.1)	85 (71.4)	51 (94.4)	43 (82.7)
Censored	40 (33.9)	34 (28.6)	3 (5.6)	9 (17.3)
OS[a], months (95% CI)[b]				
Median	28.5 (23.1 to 35.1)	22.3 (18.3 to 30.8)	13.4 (9.7 to 17.6)	13.6 (9.4 to 25.4)
Stratified log-rank *P* value[c]	0.0937		0.1148	
Unstratified log-rank *P* value	0.0982		0.0625	
HR #1 (95% CI)[d]	0.76 (0.55 to 1.05)		1.40 (0.92 to 2.14)	
Stratified Cox regression Walds test *P* value	0.0953		0.1164	
HR #2 (95% CI)[d]	0.77 (0.57 to 1.05)		1.49 (0.98 to 2.28)	
Unstratified Cox regression Walds test *P* value	0.0993		0.0641	
PFS[e], months (95% CI)[b]				
Median	12.3 (7.9 to 17.1)	7.3 (5.5 to 11.1)	3.4 (2.8 to 6.4)	6.8 (2.9 to 9.3)
Stratified log-rank *P* value[c]	0.0494		0.1899	
Unstratified log-rank *P* value	0.0649		0.3623	
HR #1 (95% CI)[d]	0.68 (0.46 to 1.00)		1.41 (0.84 to 2.37)	
Stratified Cox regression Walds test *P* value	0.0511		0.1927	
HR #2 (95% CI)[d]	0.70 (0.48 to 1.02)		1.26 (0.76 to 2.07)	
Unstratified Cox regression Walds test *P* value	0.0667		0.3652	

Abbreviations: HR, hazard ratio; *IDH*-mut: *IDH* mutation; *IDH*-wt: *IDH*-wild type; MRI, magnetic resonance imaging; n, number of patients; N, total number of patients; OS, overall survival; PFS, progression-free survival.

[a]OS was calculated as (date of death − date of random assignment +1)/30.4375. Patients alive at cutoff date were censored at the date of last observation.

[b]CIs were calculated using Greenwood SE.

[c]Stratified analysis uses age (≤45 *v* > 45 years), *IDH* status (mutated *v* wild-type), and number of prior surgeries as stratification factors.

[d]HR and CI were estimated using the Cox proportional hazards model with treatment as main effect without covariate.

[e]PFS was calculated as: (date of first PD or death date of random assignment + 1)/30.4375. Patients who initiated other anticancer therapy or missed tumor assessment for six consecutive months before PD were censored at the last MRI assessment.

TABLE A5. Full Summary of Secondary Efficacy End Points

End Point	ITT Population		*IDH*-mut Grade 3 Subset	
	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Eflornithine + Lomustine (n = 96)	Lomustine Monotherapy (n = 100)
PFS, months (95% CI)				
Median	8.9 (4.6 to 12.1)	7.2 (5.5 to 10.4)	15.8 (11.8 to 24.2)	7.2 (3.7 to 11.1)
Log-rank *P* value[a]	0.4319		0.0113	
HR (95% CI)[b]	0.88 (0.65 to 1.20)		0.57 (0.36 to 0.88)	
Cox regression *P* value	0.4326		0.0125	
Objective response[c]				
No. of patients with ≥1 MRI evaluation	158	147	92	86
Patients with objective response, No. (%)	19 (12.0)	13 (8.8)	16 (17.4)	8 (9.3)
95% CI for objective response rate	7.4 to 18.1	4.8 to 14.6	10.3 to 26.7	4.1 to 17.5
Odds ratio (95% CI; eflornithine + lomustine/lomustine)[d]	1.44 (0.68 to 3.06)		2.13 (0.86 to 5.3)	
P value	0.3456		0.1037	
Duration observed, No. (%)	10 (52.6)	1 (7.7)	7 (43.8)	0 (0.0)
Duration censored, No. (%)	9 (47.4)	12 (92.3)	9 (56.3)	8 (100.0)
Duration of objective response, months (95% CI)				
Median	14.09 (7.23 to 18.60)	NR (5.72 to NE)	16.36 (8.28 to NE)	NR (NE to NE)
Log-rank *P* value[a]	0.2856		0.3076	
HR (95% CI)[b]	3.00 (0.36 to 24.71)		1.323e7 (0.00 to NE)	
Cox regression *P* value	0.3078		0.9963	
Clinical benefit[e]				
Patients with clinical benefit, No. (%)	86 (54.4)	83 (56.5)	60 (65.2)	49 (49.0)
95% CI for clinical benefit rate	46.3 to 62.4	48.0 to 64.6	54.6 to 74.9	45.8 to 67.6
Odds ratio (95% CI; eflornithine + lomustine/lomustine)[d]	0.92 (0.58 to 1.46)		1.44 (0.78 to 2.64)	
P value	0.7235		0.2439	
Duration observed, No. (%)	35 (40.7)	31 (37.3)	19 (31.7)	17 (34.7)
Duration censored, No. (%)	51 (59.3)	52 (62.7)	41 (68.3)	32 (65.3)
Duration of clinical benefit, months (95% CI)				
Median	21.91 (12.32 to NE)	11.30 (10.41 to NE)	24.18 (17.12 to NE)	12.06 (10.41 to NE)
Log-rank *P* value[a]	0.0385		0.0083	

(continued on following page)

TABLE A5. Full Summary of Secondary Efficacy End Points (continued)

End Point	ITT Population		*IDH*-mut Grade 3 Subset	
	Eflornithine + Lomustine (n = 172)	Lomustine Monotherapy (n = 171)	Eflornithine + Lomustine (n = 96)	Lomustine Monotherapy (n = 100)
HR (95% CI)[b]	0.59 (0.35 to 0.98)		0.40 (0.19 to 0.80)	
Cox regression *P* value	0.0405		0.0101	
BOR				
Objective response	19 (12.0)	13 (8.8)	16 (17.4)	8 (9.3)
CR	7 (4.4)	6 (4.1)	7 (7.6)	4 (4.7)
PR	12 (7.6)	7 (4.8)	9 (9.8)	4 (4.7)
Clinical benefit	86 (54.4)	83 (56.5)	60 (65.2)	49 (57.0)
CR	7 (4.4)	6 (4.1)	7 (7.6)	4 (4.7)
PR	12 (7.6)	7 (4.8)	9 (9.8)	4 (4.7)
MR	11 (7.0)	10 (6.8)	9 (9.8)	8 (9.3)
SD	56 (35.4)	60 (40.8)	35 (38.0)	33 (38.4)
SD	92 (58.2)	88 (59.9)	55 (59.8)	51 (59.3)
MR	11 (7.0)	10 (6.8)	9 (9.8)	8 (9.3)
SD	73 (46.2)	72 (49.0)	44 (47.8)	41 (47.7)
Minor progression	8 (5.1)	6 (4.1)	2 (2.2)	2 (2.3)
PD	47 (29.7)	46 (31.3)	21 (22.8)	27 (31.4)

Abbreviations: BOR, best overall response; CR, complete response; *IDH, isocitrate dehydrogenase*; ITT, intention-to-treat; MR, minor response; MRI, magnetic response imaging; n, number of patients; N, total number of patients; NE, nonevaluable; NR, not reported; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Log-rank test stratified by age (≤45 *v* > 45 years), *IDH* status, and number of prior surgeries.

[b]Cox regression analysis stratified by age (≤45 *v* > 45 years), *IDH* status, and number of prior surgeries without covariate.

[c]Objective response = partial or CR in the MRI scan.

[d]Odds ratio estimated from the logistic regression with treatment as main effect, age (≤45 *v* > 45 years), *IDH* status (mutated *v* wild-type), and number of prior surgeries as model covariates

[e]Patients who qualified for clinical benefit responses were those with a BOR of CR, PR, MR, or SD for 120 days without PD. To qualify as SD for 120 days without PD, a patient was required to have a tumor assessment on study Day 120 or later with no prior PD as assessed by investigator.