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Effect of Vocimagene Amiretrorepvec in Combination With Flucytosine vs Standard of Care on Survival Following Tumor Resection in Patients With Recurrent High-Grade Glioma

A Randomized Clinical Trial

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Article Information

Key Points

Question

Does treatment with vocimagene amiretrorepvec (Toca 511) and flucytosine (Toca FC), compared with standard of care (SOC), improve survival among patients with recurrent glioblastoma and anaplastic astrocytoma?

Findings

In this randomized open-label clinical trial of 403 patients assigned to receive Toca 511/FC or SOC, the primary end point of overall survival was not met (11.1 months for the Toca 511/FC group and 12.22 months for the SOC group). Secondary end points did not demonstrate statistically significant differences and rates of adverse events were similar in the 2 groups.

Meaning

Toca 511 and Toca FC treatment did not improve survival for patients with recurrent glioblastoma and anaplastic astrocytoma.

Abstract

Importance

New treatments are needed to improve the prognosis of patients with recurrent high-grade glioma.

Objective

To compare overall survival for patients receiving tumor resection followed by vocimagene amiretrorepvec (Toca 511) with flucytosine (Toca FC) vs standard of care (SOC).

Design, Setting, and Participants

A randomized, open-label phase 2/3 trial (TOCA 5) in 58 centers in the US, Canada, Israel, and South Korea, comparing posttumor resection treatment with Toca 511 followed by Toca FC vs a defined single choice of approved (SOC) therapies was conducted from November 30, 2015, to December 20, 2019. Patients received tumor resection for first or second recurrence of glioblastoma or anaplastic astrocytoma.

Interventions

Patients were randomized 1:1 to receive Toca 511/FC (n = 201) or SOC control (n = 202). For the Toca 511/FC group, patients received Toca 511 injected into the resection cavity wall at the time of surgery, followed by cycles of oral Toca FC 6 weeks after surgery. For the SOC control group, patients received investigators' choice of single therapy: lomustine, temozolomide, or bevacizumab.

Main Outcomes and Measures

The primary outcome was overall survival (OS) in time from randomization date to death due to any cause. Secondary outcomes reported in this study included safety, durable response rate (DRR), duration of DRR, durable clinical benefit rate, OS and DRR by *IDH1* variant status, and 12-month OS.

Results

All 403 randomized patients (median [SD] age: 56 [11.46] years; 62.5% [252] men) were included in the efficacy analysis, and 400 patients were included in the safety analysis (3 patients on the SOC group did not receive resection). Final analysis included 271 deaths (141 deaths in the Toca 511/FC group and 130 deaths in the SOC control group). The median follow-up was 22.8 months. The median OS was 11.10 months for the Toca 511/FC group and 12.22 months for the control group (hazard ratio, 1.06; 95% CI 0.83, 1.35; $P = .62$). The secondary end points did not demonstrate statistically significant differences. The rates of adverse events were similar in the Toca 511/FC group and the SOC control group.

Conclusions and Relevance

Among patients who underwent tumor resection for first or second recurrence of glioblastoma or anaplastic astrocytoma, administration of Toca 511 and Toca FC, compared with SOC, did not improve overall survival or other efficacy end points.

Trial Registration

ClinicalTrials.gov Identifier: NCT02414165

Introduction

High-grade gliomas (HGGs), including grade III anaplastic astrocytoma (AA) and grade IV glioblastoma, are the most aggressive malignant primary brain tumors.[1] Patients with glioblastoma and AA receive maximal safe resection plus radiotherapy with concurrent chemotherapy temozolomide, followed by maintenance temozolomide as standard of care (SOC) treatment. This results in a median overall survival (mOS) ranging from 12.7 months to 3.9 years depending on the tumor grade and the molecular and genetic profile.[2,3,4] Despite aggressive treatment, nearly all HGGs eventually recur, and there are no effective treatments for this population. For recurrent glioblastoma, the median progression-free survival is as short as 1.8 months[5] and mOS ranges from 7.1 to 9.8 months.[6,7,8] Chemotherapies such as lomustine and temozolomide have been approved by the US Food and Drug Administration for treating glioblastoma and AA, but the OS improvement in the recurrent setting is minimal.[9] New treatments are needed to improve the prognosis of this patient population.

Vocimagene amiretrorepvec (Toca 511) is an investigational γ retroviral replicating vector encoding a transgene for an optimized yeast cytosine deaminase, an enzyme that converts 5-fluorocytosine (5-FC) into 5-fluorouracil in the tumor microenvironment without systemic 5-fluorouracil ad-

verse effects.[10] Preclinical data indicated that Toca 511 and 5-FC treatment kills tumor cells and nearby immunosuppressive cells such as myeloid-derived suppressor cells and tumor-associated macrophages, leading to T-cell priming and durable systemic antitumor immune activity.[11] Multiyear durable complete responses have been observed in recurrent HGG patients in a phase 1 resection-injection trial (NCT01470794) with Toca 511/FC.[12] Integrated Toca 511 was commonly detected in tumor and transiently detected in blood. No evidence for clonal expansion of cells with integrated Toca 511 DNA, or preferential retrieval of integration sites near oncogenes was observed.[13]

A phase 2/3 randomized clinical trial of Toca 511 and Toca FC vs SOC for treatment of patients with recurrent glioblastoma and AA has been completed. Efficacy, safety, and baseline molecular and immunological results are reported here.

Methods

Study Design and Oversight

This was a multicenter, randomized, open-label study of Toca 511 and Toca FC vs SOC that was investigator's choice of single-agent chemotherapy (lomustine or temozolomide) or bevacizumab for patients with first or second recurrence of glioblastoma or AA. Patients were recruited from 67 centers in the US, Canada, Israel, and South Korea, with 58 sites enrolling patients. The trial was conducted from November 30, 2015, to December 20, 2019. This study was approved by the institutional review board and institutional biosafety committee for each site, and all patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. The trial protocol is available in Supplement 1.

Patient Selection and Follow-up

Patients aged 18 to 75 years with first or second recurrence of histologically proven glioblastoma or AA were eligible. Additional key inclusion criteria were prior first-line multimodal therapy; tumor size between 1 and 5 cm; adequate laboratory values for surgery; and Karnofsky Performance Status score of at least 70. Key exclusion criteria were multifocal tumor; any active infection requiring systemic antibiotic, antifungal, or antiviral therapy within the previous 4 weeks; or received bevacizumab in the recurrent setting.

Randomization and Masking

Patients were randomized at the time of resection in a 1:1 ratio to either Toca 511 and Toca FC (Toca 511/FC), or SOC group. Stratification was by isocitrate dehydrogenase 1 (*IDH1*) variant status (variation vs wild type), Karnofsky Performance Status score (70-80 vs 90-100) and geographical region (United States vs Canada vs outside North America). Further methodologic details on randomization and masking are provided in the eMaterials and eMethods in Supplement 2.

Study Procedure

Patients in the Toca 511/FC group received 1 dose of approximately 4 mL of Toca 511 (10^8 TU/mL) injected into the resection cavity wall at the time of resection. Video training was provided for virus delivery as well as optional mentorship from experienced investigators from the similar phase 1 trial (NCT01470794). Approximately 6 weeks after resection, patients began the first cycle with a 7-day course of oral Toca FC dosed at 220 mg/kg/d, and repeated every 6 weeks. Toca FC was taken by patients as long as the drug was tolerated and the investigator believed patients were obtaining benefit. For the SOC group, patients began the first cycle approximately 6 weeks after resection, and the schedule was as follows: lomustine at 110 mg/m^2 repeated every 6 weeks; temozolomide either at 50 mg/m^2 once daily continuously or at 150 mg/m^2 once daily for 5 consecutive days per 28-day cycle that could be increased to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day cycles; or bevacizumab at 10 mg/kg by intravenous infusion every 2 weeks. The SOC group treatment was continued until confirmed progression or end of treatment.

Study End Points

The primary end point was overall survival (OS), and the secondary end points were safety, durable response rate (DRR), duration of durable response, durable clinical benefit rate, OS and DRR by *IDH1* variant status, and 12-month OS using modified Response Assessment in Neuro-Oncology criteria by independent radiologic review. Two additional secondary end points are not reported herein: patient reported outcome and quality of life and progression-free survival (see the trial protocol in Supplement 1). Further methodologic details on study end points are provided in eMaterials and eMethods in Supplement 2.

Exploratory Patient Molecular Profiling

Methodologic details of viral safety testing, peripheral blood monitoring, and tumor profiling are provided in eMaterials and eMethods in Supplement 2.

Statistical Analysis

The primary end point was OS, measured from randomization date to death due to any cause; the secondary end points were DRR, durable clinical benefit rate, duration of durable response, OS and DRR by *IDH1* variant status, and 12-month OS. The 257 events were needed to detect a hazard ratio (HR) of 0.685 at a 2-sided α of .05 and a power of 85%. The OS end point incorporated group sequential design with the O'Brien-Fleming boundaries as implemented by Lan-DeMets α spending method to avoid inflation of the type I error rate. For the secondary end points, the Holm procedure was planned to adjust for multiplicity. All efficacy analyses included the intent-to-treat population (ITT), and all safety analyses included all randomized patients who underwent resection. Further details on statistical analysis are provided in the eMaterials and eMethods in Supplement 2.

Results

A total of 403 patients (median [SD] age: 56 [11.46] years; 62.5% [252] men) underwent randomization from November 2015 to November 2018 (187 patients in the phase 2 and 216 patients in the phase 3) at 58 institutions in 4 countries, with an enrollment pause from February 2017 to October 2017 between the phase 2 and the phase 3 portion (Figure 1). The last-known follow-up date was May 2019. Patient demographic characteristics and neuro-oncology history were balanced between the two groups (Table 1), and were also balanced between the patients in phase 2 and the patients in phase 3 (eTable 1 in Supplement 2).

For the Toca 511/FC group, 199 patients (99%) received Toca 511 at the time of surgery, and 197 patients (98%) received both Toca 511 and at least one cycle of Toca FC. For the SOC group, 141 patients (70%) received at least one cycle of drug (Figure 1). At data cutoff, the median number of cycles of Toca FC taken by patients on the Toca 511/FC arm was 2 cycles. Maximal survival was achieved in patients who received up to 4 cycles of Toca FC (eFigure 1 in Supplement 2). For the SOC group, the median cycle of metronomic temozolomide was 3, of temozolomide was 3, of lomustine was 2, and of bevacizumab was 4 (eTable 2 in Supplement 2).

At final analysis, 271 deaths were observed, with 141 deaths in the Toca 511/FC group and 130 deaths in the SOC group. The median follow-up for all randomized patients was 22.8 months. A total of 29 patients (9.0% [18 of 201] on the Toca 511/FC arm and 5.4% [11 of 202] on the SOC arm) were continuing treatment at data cutoff. The mOS in the ITT population was 11.1 months for the Toca 511/FC arm and 12.22 months for the SOC arm (HR, 1.06; 95% CI, 0.83-1.35; P = .62) (Figure 2), which did not meet the statistical significance for the study's primary end point. The preplanned secondary end points also did not demonstrate statistically significant differences in outcomes (eTable 3 in Supplement 2).

In preplanned subgroup analyses, there was no statistically significant effect on mOS in the Toca 511/FC group among patients with *IDH1*-variant tumors and AA (HR, 0.64; 95% CI:, 0.33-1.24; P = .19; HR, 0.57; 95% CI, 0.28-1.14; P = .11, respectively) (Figures 3; eFigures 2a and 2b in Supplement 2). In the preplanned subgroup analysis of patients at second recurrence (n = 60), improvement in OS was observed, with an mOS of 21.8 months for the Toca 511/FC group (n = 28) and 11.1 months for the SOC group (n = 32) (HR, 0.43; 95% CI, 0.21-0.87; P = .02) (Figure 3; eFigure 2c in Supplement 2) although these numbers would not be statistically significant when adjusted for multiplicity. Demographic characteristics and neuro-oncology history in this subgroup were balanced between the 2 groups (eTable 4 in Supplement 2). In further exploratory post hoc subset analyses in the second recurrence subpopulation, while patient numbers were very small, there was an improvement in survival for patients with *IDH1*-variant tumors, with mOS not reached for the Toca 511/FC group (n = 8), and 10.9 months for the SOC group (n = 10) (HR, 0.14, 95% CI, 0.03-0.69; P < .001). Also with very small numbers, there was an improvement in survival for patients with AA, with mOS not reached for the Toca 511/FC group (n = 7) and 9.07 months for the SOC group (n = 6) (HRs were not estimated) (eFigure 3 in Supplement 2).

The safety population included 100% (201 of 201) of patients in the Toca 511/FC group and 99% (199 of 202) of patients in the SOC group. No treatment-associated adverse events resulted in deaths in either group, and the most common adverse events for both groups are reported in Table 2.

The presence of Toca 511 DNA and RNA was sampled longitudinally throughout the course of treatment.[14] Quantitative Toca 511 DNA was observed in 4.5% of patients at cycle 1 day 1 and no viral DNA signal was observed at cycle 4-day 1 or beyond in any patients out to 1.5 years (eTable 5 in Supplement 2). Most patients showed quantitative viral RNA signal postsurgery (70.9%) but had cleared signal before cycle 1 day 1 of Toca FC (eTable 5 in Supplement 2). Once a patient's viral RNA signal dropped below quantitative levels, no additional quantitative signal was detected thereafter. These results are consistent with prior experience under similar trial conditions (NCT01470794).[14]

Exploratory baseline molecular and immune profiling were performed to better understand the patient population and balance in this study (eFigures 4-32 in Supplement 2). Analyses of tumor obtained pretreatment during resection indicated that *IDH1*-variant tumors had a favorable immune cell composition for an immuno-oncology therapy compared with *IDH1*-wild type tumors (eFigure 26 in Supplement 2), including lower levels of M0 macrophages, higher levels of CD4 memory cells, resting NK cells, and resting dendritic cells than *IDH1*-wild type tumors. Immune cell composition was similar between the Toca 511/FC and SOC groups, including by ITT population, by subgroups such as histology, number of recurrences, and *IDH1* status (eFigure 22 in Supplement 2). Wild-type *IDH1* tumors preferentially expressed mRNAs encoding proteins involved in innate immune responses (eFigure 23 in Supplement 2), which could inhibit Toca 511 infection. Variant *IDH1* tumors exhibited higher lymphoid compartment cells in baseline peripheral blood mononuclear cells compared with wild-type *IDH1* tumors, suggesting that patients with a variant *IDH1* tumor have a more robust peripheral immune cell population (eFigure 29 in the Supplement 2).

Discussion

In a disease with an extremely high unmet need, recent trials such as CheckMate-143 with nivolumab,[15] INTELLANCE 2 with Depatux-M, GLOBE with VB-111 in combination with bevacizumab, have not shown efficacy benefits in recurrent HGG setting.[16,17] Similarly, TOCA 5 did not meet primary objective of improved OS or the secondary end points. Overall, there were no observed significant biases in demographic and specified stratification markers (Table 1), or known molecular prognostic markers (eFigure 4 in Supplement 2) between the groups. Toca 511 and Toca FC were well tolerated with safety comparable to the SOC group, similar to previously reported and as expected in this setting. All patients in the Toca 511/FC group either showed no detectable peripheral virus or had transient signal that was cleared before cycle 4. Baseline peripheral blood immune cell health was also comparable between groups. However, subgroups that appeared to do better on treatment group showed more robust baseline immune cells and reduced immune suppressive cells (eFigures 30 and 31 in Supplement 2). The median numbers of cycle for Toca FC and SOC were low and likely incompatible with the amount given to long-term survivors

or to the proposed mechanism of action of Toca 511/FC reported previously[11,12]; more cycles might be required to see a therapeutic effect. Suboptimal virus delivery was not practical to assess in this brain cancer setting and whether enough virus was delivered to patients remains unknown.

A preplanned subgroup analysis identified a subgroup with better outcomes. Patients with second recurrence appear to have better outcomes with Toca 511/FC treatment compared with SOC. These differences seem to be independent of other prognostic factors as the tumor molecular profiles between patients at first recurrence or second recurrence are generally similar and lack significant group imbalances between the two groups (eFigures 13, 14, and 28 in Supplement 2). Within the second recurrence population, while patient numbers were small, there was an improvement in survival for patients with *IDH1*-variant tumors and patients with AA. Patients with *IDH1* variants or AA histology have a notably better prognosis than those with *IDH1*-wildtype and GBM histology as evidenced by longer OS and higher rates of 5-year survival.[18,19,20] These slower growing, clinically less aggressive (indolent) HGG tumors may have more potential to respond to therapy that may stimulate a local immune response, such as Toca 511 and Toca FC, given the delayed nature of response to immune therapy noted by others in the field.[21]

Although the numbers analyzed were small, a consistent pattern of baseline immune potential was observed in treatment subgroups that demonstrated improvements in survival to Toca 511/FC treatment compared with SOC (eFigures 24, 26-31 in Supplement 2). The uniqueness of the potential mechanisms of action of Toca 511 and Toca FC may contribute to the efficacy advantage observed in these patients. In the phase 1 resection-injection trial (NCT01470794), a durable response rate of 21.7% was observed in patients who met the phase 2/3 trial entry criteria with a median duration of response follow-up of at least 35.7 months as of August 2017.[12,14] In these patients, responses were observed at approximately 6 to 19 months after Toca 511 administration, consistent with an immunologic-based response.

Limitations

This study has limitations. Study limitations include the small number of cycles of patients receiving treatment, the very small number of patients included in the subgroup analysis, insufficient number of blood and tissue samples collected for biomarker analysis, and variations of Toca 511 distribution in the resection cavity wall.

Conclusions

In this multicenter randomized clinical trial of patients who underwent tumor resection for first or second recurrence of glioblastoma or anaplastic astrocytoma, administration of Toca 511 and Toca FC, compared with SOC, did not improve overall survival or the secondary efficacy end points. In a small subgroup analysis, a treatment effect was seen in a few patients at second recurrence. The results of this study may help to inform future study designs including population selection and minimum number of Toca FC treatment cycles.

Notes

Supplement 1.

Trial Protocol

Supplement 2.

eMaterials and eMethods

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Figures and Tables

Figure 1.
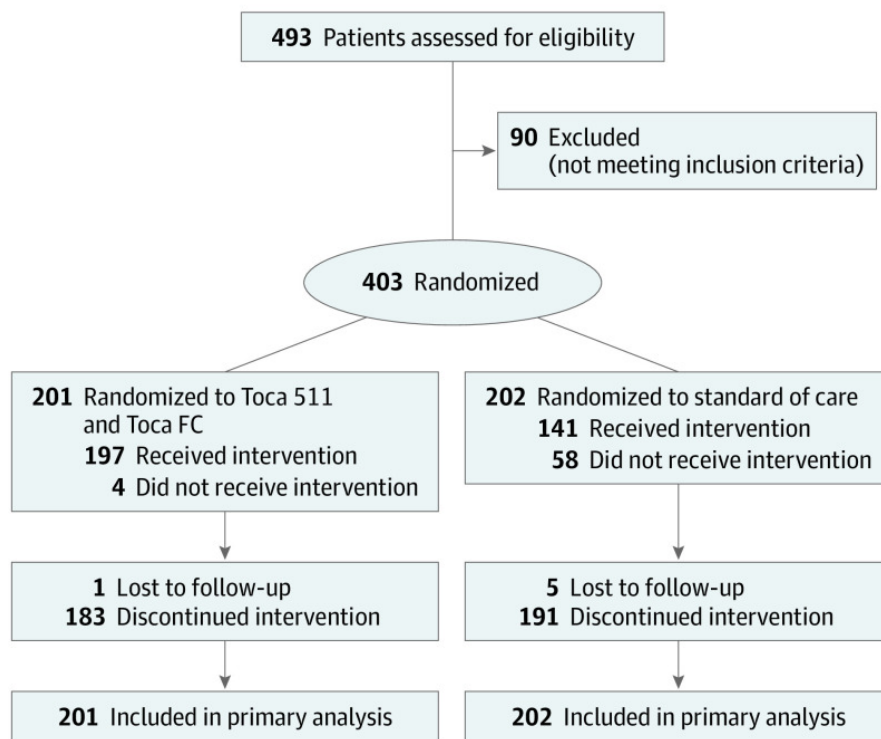
Patient Flow in the TOCA 5 Randomized Clinical Trial

Toca 511 indicates vocimagene amiretrorepvec; Toca FC, flucytosine.

Table 1.

Baseline Demographics and Neuro-Oncology History for Intent-to-Treat Population

Characteristic	No. (%)		
	Toca 511 and Toca FC (n = 201)	Standard of care (n = 202)	Total (N = 403)
Age, y			
Median	57.0	56.0	56.0
<65	155 (77.1)	164 (81.2)	319 (79.2)
≥65	46 (22.9)	38 (18.8)	84 (20.8)
Sex			
Male	125 (62.2)	127 (62.9)	252 (62.5)
Female	76 (37.8)	75 (37.1)	151 (37.5)
Race			
White	174 (86.6)	173 (85.6)	347 (86.1)
Karnofsky Performance Status score category			
70-80	64 (31.8)	66 (32.7)	130 (32.3)
90-100	137 (68.2)	136 (67.3)	273 (67.7)
Region			
US	156 (77.6)	158 (78.2)	314 (77.9)
Non US	45 (22.4)	44 (21.8)	89 (22.1)
Tumor histology at study entry from investigator			
Glioblastoma	171 (85.1)	183 (90.6)	354 (87.8)
Anaplastic Astrocytoma	30 (14.9)	19 (9.4)	49 (12.2)
IDH1 variant status			
Present (variant)	27 (13.4)	31 (15.3)	58 (14.4)
Absent (wild type)	174 (86.6)	171 (84.7)	345 (85.6)
No. of recurrences			
1	173 (86.1)	170 (84.2)	343 (85.1)
2	28 (13.9)	32 (15.8)	60 (14.9)

Abbreviations: HGGs, high-grade gliomas; Toca 511, vocimagene amiretrorepvec; Toca FC, flucytosine.

Figure 2.

No. at risk

	0	6	12	18	24	30	36	42
Toca	201	158	65	29	17	8	3	0
SOC	202	162	75	25	18	7	1	0
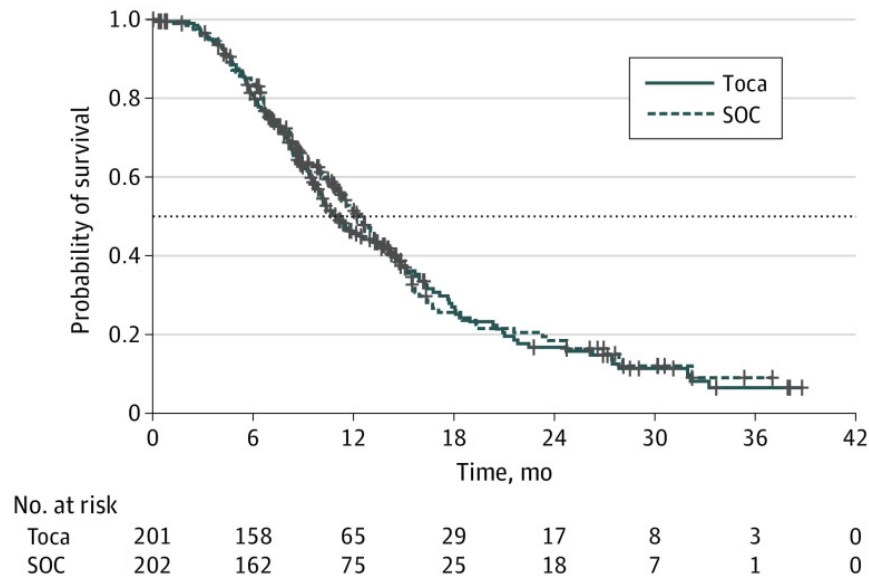
Kaplan-Meier Overall Survival Curves for Intent-to-Treat Population

Toca indicates vocimagene amiretrorepvec (Toca 511) followed by flucytosine (Toca FC), SOC, standard of care.

Figure 3.

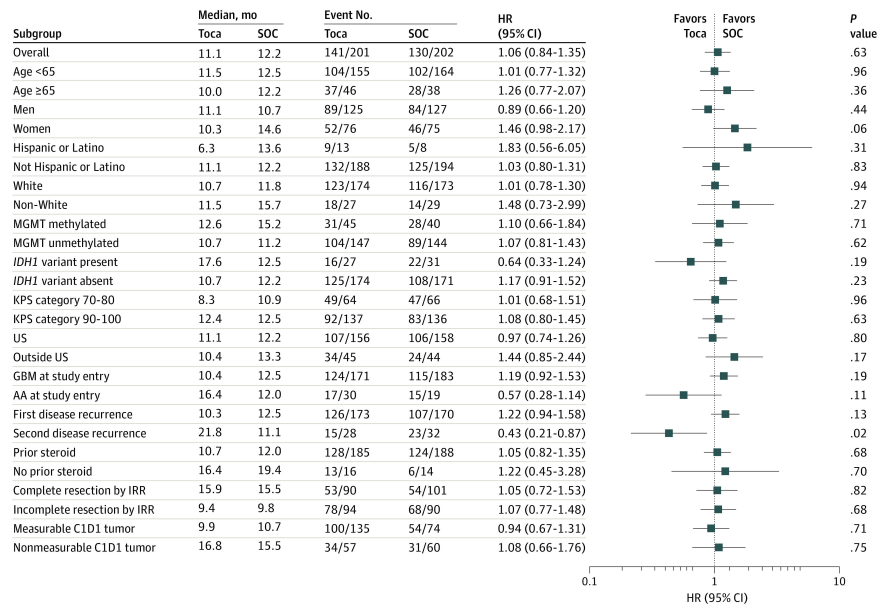| Subgroup	Median, mo Toca	SOC	Event No. Toca	SOC	HR (95% CI)	P value
Overall	11.1	12.2	141/201	130/202	1.06 (0.84-1.35)	.63
Age <65	11.5	12.5	104/155	102/164	1.01 (0.77-1.32)	.96
Age ≥65	10.0	12.2	37/46	28/38	1.26 (0.77-2.07)	.36
Men	11.1	10.7	89/125	84/127	0.89 (0.66-1.20)	.44
Women	10.3	14.6	52/76	46/75	1.46 (0.98-2.17)	.06
Hispanic or Latino	6.3	13.6	9/13	5/8	1.83 (0.56-6.05)	.31
Not Hispanic or Latino	11.1	12.2	132/188	125/194	1.03 (0.80-1.31)	.83
White	10.7	11.8	123/174	116/173	1.01 (0.78-1.30)	.94
Non-White	11.5	15.7	18/27	14/29	1.48 (0.73-2.99)	.27
MGMT methylated	12.6	15.2	31/45	28/40	1.10 (0.66-1.84)	.71
MGMT unmethylated	10.7	11.2	104/147	89/144	1.07 (0.81-1.43)	.62
IDH1 variant present	17.6	12.5	16/27	22/31	0.64 (0.33-1.24)	.19
IDH1 variant absent	10.7	12.2	125/174	108/171	1.17 (0.91-1.52)	.23
KPS category 70-80	8.3	10.9	49/64	47/66	1.01 (0.68-1.51)	.96
KPS category 90-100	12.4	12.5	92/137	83/136	1.08 (0.80-1.45)	.63
US	11.1	12.2	107/156	106/158	0.97 (0.74-1.26)	.80
Outside US	10.4	13.3	34/45	24/44	1.44 (0.85-2.44)	.17
GBM at study entry	10.4	12.5	124/171	115/183	1.19 (0.92-1.53)	.19
AA at study entry	16.4	12.0	17/30	15/19	0.57 (0.28-1.14)	.11
First disease recurrence	10.3	12.5	126/173	107/170	1.22 (0.94-1.58)	.13
Second disease recurrence	21.8	11.1	15/28	23/32	0.43 (0.21-0.87)	.02
Prior steroid	10.7	12.0	128/185	124/188	1.05 (0.82-1.35)	.68
No prior steroid	16.4	19.4	13/16	6/14	1.22 (0.45-3.28)	.70
Complete resection by IRR	15.9	15.5	53/90	54/101	1.05 (0.72-1.53)	.82
Incomplete resection by IRR	9.4	9.8	78/94	68/90	1.07 (0.77-1.48)	.68
Measurable C1D1 tumor	9.9	10.7	100/135	54/74	0.94 (0.67-1.31)	.71
Nonmeasurable C1D1 tumor	16.8	15.5	34/57	31/60	1.08 (0.66-1.76)	.75

Forest Plot of Preplanned Subgroup Analyses

AA indicates anaplastic astrocytoma; C1D1, cycle 1 day 1; GBM, glioblastoma multiforme; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; KPS, Karnofsky performance status; MGMT, O^6-methylgaunine-DNA-methyltransferase; SOC, standard of care; and Toca, vocimagene amiretrorepvec (Toca 511) followed by flucytosine (Toca FC).

Table 2.

Most Common (≥5%) Treatment-Emergent Adverse Events

Grade 3-4 TEAEs	No. (%)	
	Toca 511 and Toca FC (n = 201)	Standard of care (n = 199)
Aphasia	16 (8.0)	7 (3.5)
Hemiparesis	15 (7.5)	5 (2.5)
Headache	13 (6.5)	10 (5.0)
Seizure	8 (4.0)	11 (5.5)
White blood cell count decreased	0 (0)	10 (5.0)
TEAEs leading to treatment discontinuation	2 (1.0)	5 (2.5)
TEAEs leading to death	6 (3.0)	3 (1.5)

Abbreviations: TEAEs, treatment-emergent adverse events; Toca 511, vocimagene amiretrorepvec; Toca FC, flucytosine.