Durable Complete Responses in Some Recurrent High Grade Glioma Patients Treated with Toca 511 & Toca FC


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Running title: Durable Responses with Toca 511 & Toca FC

T.C., J.L., S.B., B.C., C.C.C., J.B.E., S.N.K., S.K., A.L., I.Y.L., L.M.L., T.M., P.N., D.P., M.A.V. and T.W., ran the clinical trial at their respective sites, provided clinical samples, reviewed and provided insight to the manuscript. D.J.H., T.K., A.D., D.G., D.O., W.A., O.R.D., and, performed experiments and analyzed the data. H.E.G., D.J.J., A.D. and D.O. designed the study and supervised the overall project. A.D. and D.O. wrote the manuscript. N.K. developed the founding technology on which Toca 511 is based. All authors reviewed the final manuscript.
Abstract

Background: Vocimagene amiretrorepvec (Toca 511) is an investigational gamma-retroviral replicating vector encoding cytosine deaminase that, when used in combination with extended-release 5-fluorocytosine (Toca FC), results preclinically in local production of 5-fluorouracil, depletion of immune-suppressive myeloid cells, and subsequent induction of anti-tumor immunity. Recurrent high grade glioma (rHGG) patients have a high unmet need for effective therapies that produce durable responses lasting more than 6 months. In this setting, relapse is nearly universal and most responses are transient.

Methods: In this Toca 511 ascending-dose phase I trial (NCT01470794), HGG patients who recurred after standard of care underwent surgical resection, received Toca 511 injected into resection cavity wall followed by orally administered cycles of Toca FC.

Results: Among 56 patients, durable complete responses were observed. A subgroup was identified based on Toca 511 dose and entry requirements for the follow-up phase III study. In this subgroup, which included both IDH1-mutant and -wildtype tumors, the durable response rate is 21.7%. Median duration of follow-up for responders is 35.7+ months. As of August 25, 2017, all responders remain in response and are alive, 33.9+ to 52.2+ months after Toca 511 administration, suggesting a positive association of durable response with overall survival.

Conclusions: Multi-year durable responses have been observed in rHGG patients treated with Toca 511 & Toca FC in a phase I trial and the treatment will be further evaluated in a randomized phase III trial. Among IDH1 mutant patients treated at first recurrence, there may be an enrichment of complete responders.

Keywords: recurrent high grade glioma; immuno-oncology; gene therapy; immunotherapy; durable response rate
Importance of the study:

Patients with recurrent high grade glioma (rHGG) have a high unmet need for effective therapies. Response to current standard treatment is uncommon and durable responses even less so. Newer therapies that engage the immune system to break tumor tolerance likely require consideration of novel endpoints including durability of responses. We report on several multi-year complete responses in rHGG patients treated with Toca 511 & Toca FC, including 21.7% durable complete response rate in 23 patients who received maximum feasible doses of Toca 511. All responding patients are still alive with a median duration of follow up of > 35 months. Molecular profiling shows responding patients have tumors with low level of DNA mutations which differentiates this type of immunotherapy from others that require high mutagenic burden for response. The maturing phase I trial observations demonstrate that a replicating gene therapy vector combined with a prodrug may act as an anti-cancer immunotherapeutic in malignant glioma.
Vocimagene amiretrorepvec (Toca 511) & extended-release 5-fluorocytosine (Toca FC) are currently in development as a novel combination treatment for recurrent high grade glioma (rHGG), and clinical trials have shown anti-cancer activity and a favorable safety profile to date\(^1\). Since the initial published report on 45 patients, data on 11 additional patients, 2 years of additional safety and efficacy follow up on the 56 total patients, and new detailed molecular profiling are now reported. The durable objective responses and stable disease along with delayed onset of responses are consistent with an immunologic mechanism of action.

The 2017 estimated incidence and prevalence of adult glioblastoma (GBM; Grade 4 astrocytoma) and anaplastic astrocytoma (AA; Grade 3 astrocytoma), are approximately 16,081 and 49,407 respectively in the United States\(^2\) and approximately 36,104 and 110,922 respectively in Europe\(^3\). AA and GBM are collectively classified as high grade glioma. Following treatment in newly diagnosed surgery settings, radiation and chemotherapy with temozolomide, patients with GBM have a median survival of 14.5 months and patients with AA have a median survival of 3.9 years. These tumors inevitably relapse within approximately 7 months in patients with GBM and 21 months in patients with AA\(^4\,\,\,5\). Patients with rHGG have a high unmet need due to the limited efficacy of available treatments\(^6\). While surgical resection in newly diagnosed settings is thought to improve outcomes, prospective studies to demonstrate surgical resection benefit in the recurrent setting are lacking. However, analyses of patients enrolled in clinical studies indicate that surgery for recurrence is not associated with improved survival\(^7\,\,\,8\). Surgery is not curative for these highly infiltrative tumors, and patients with GBM and AA invariably recur after resection with measurable or non-measurable residual tumor\(^9\).

Among available therapies, temozolomide was granted accelerated approval for patients with recurrent AA (rAA), who experienced disease progression while on a nitrosourea and procarbazine, based on a response rate of 22% and median duration of response of 11.6 months. These patients were temozolomide naïve in the newly diagnosed setting, and the drug is now used with radiation and
surgery in first line treatment for GBM. However, after failure of first line temozolomide treatment, durable responses (meaning a partial or complete response (PR or CR) observed for 24 weeks or longer) with available therapies, is uncommon, with rates ranging from 0 to 2.15% in rGBM (Supplementary Table S1)\textsuperscript{10}. While objective responses require confirmation at least 4 weeks later, they are often transient and may not translate into overall survival benefit\textsuperscript{11}. In contrast, durable responses in the current study appear to indicate a lasting treatment effect with potential to translate into an improvement in overall survival\textsuperscript{12,13}.

Cancer immunotherapy presents challenges in the central nervous system (CNS) due to the unique regulation of immunological activity within the brain compared to most other tissues and the immune-suppression associated with high grade gliomas\textsuperscript{14}. The nervous system has historically been considered an immune privileged organ, with limited immunologic function as initially observed by the lack of graft rejection in the brain\textsuperscript{15,16}. Classically, this “privileged” site was described with selective blood brain barrier entry of immune cells from peripheral blood into the brain parenchyma\textsuperscript{17}, a lack of lymphatic vessels and lymph nodes within the CNS, and by low numbers of circulating T cells and human leukocyte antigen (HLA) expression\textsuperscript{18}. However, current understanding shows that the brain hosts a lymphatic system, several populations of cells with immune function, including microglia, which when activated can recruit other immune cells to sites of inflammation\textsuperscript{19-21}. Nevertheless, to date, immunotherapies have had poor to limited success in HGG clinical trials\textsuperscript{22,23}. The lack of success with immunotherapy strategies against tumors within the brain suggests that multimodal approaches that induce immune activation against tumor antigens and also diminish immune suppression are likely required to generate clinically meaningful durable responses. We suggest here that such a multimodal strategy, implemented by the treatment regime described here, leads to the durable responses observed in the reported study.

Toca 511, a gamma retroviral replicating vector encoding cytosine deaminase, when used in combination with 5-fluorocytosine (5-FC), results in local production of concentrated 5-fluorouracil (5-
FU) in the tumor without systemic 5-FU side-effects due to Toca 511 cancer selectivity and 5-FU’s short half-life. In preclinical models, local 5-FU selectively causes direct cancer cell death and depletion of immune-suppressive myeloid cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). The resultant tumor microenvironment is permissive to establishing a durable T cell mediated anti-tumor immune response and tumor shrinkage with durable systemic anti-tumor immunity, but without autoimmunity or surrounding healthy tissue toxicity. Based on both the clinical data, including durable objective responses, and preclinical mechanism of action, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation in rHGG indicating this new therapy may demonstrate substantial improvement over existing therapies. The potential for Toca 511 & Toca FC to provide relevant clinical benefit to patients is supported by the European Medicines Agency’s PRIME (PRIority MEdicines) designation in HGG.
Material and Methods

Resection-Injection Trial:

This phase I resection-injection trial (NCT01470794) was approved by institutional review boards at each site and complied with International Ethical Guidelines for Biomedical Research Involving Human Subjects, good clinical practice guidelines, Declaration of Helsinki, and local laws. All patients provided written informed consent. Between February 2011 and October 2015, HGG patients who recurred after initial treatment with at least subtotal resection, postoperative radiation, and temozolomide were enrolled. Ascending doses of Toca 511 were injected into resection cavity beds in patients with rHGG who were undergoing planned surgical resection of at least 80% of the enhancing tumor, followed by oral weekly Toca FC cycles initiated approximately 6 weeks after Toca 511 and repeated every six weeks.

Primary Endpoint

The primary end point of the study was to identify dose limiting toxicities of Toca 511 and Toca FC. Clinical benefit, measured by durable objective responses and stable disease, a safety database covering over 4 years for individual patients and extensive molecular profiling are reported here and build on previously presented data. Cohorts treated with Toca 511 & Toca FC plus bevacizumab or Toca 511 & Toca FC plus lomustine are also reported. In these cohorts, bevacizumab 10 mg/kg intravenously every two weeks or lomustine 110 mg/m² orally every six weeks was administered beginning with the first cycle of Toca FC.

Response Criteria

Objective responses are determined by independent radiology review taking neurologic status and corticosteroid use into account and using either modified Macdonald criteria for all except one cohort in which patients received Toca 511 & Toca FC and bevacizumab who were evaluated using modified Response Assessment in Neuro-oncology (RANO) criteria. For both criteria for response assessment,
Evaluable and measurable disease requires a lesion at least 1 cm in two dimensions, which can be assessed for a partial or complete response. The modification applied to evaluable non-measurable disease, which can only be assessed for a complete response. For objective response assessment, baseline for radiologic assessment for all patients is the MRI scan obtained approximately 6 weeks after surgical resection and Toca 511 administration and just prior to Toca FC administration.

Statistical analyses

Statistical analyses of phase I data are reported using summary tables, figures and data listings. Continuous variables are summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables are summarized by counts and by percentage of patients in corresponding categories. Association between durable response rate and overall survival was assessed using the Kaplan-Meier method.

For detailed material and methods including exome sequencing, immunophenotyping of blood, and RNA sequencing see Supplementary material.
Results

**Patient Characteristics and Treatment.** In this phase I dose escalation trial of Toca 511 & Toca FC in rHGG, patients in the newly diagnosed setting had undergone surgical resection, radiation therapy (RT) and chemotherapy with temozolomide. Results are presented for all 56 patients, including patients treated in combination cohorts with lomustine or bevacizumab, and for a subgroup of 23 patients that matches the recommended phase III Toca 511 dose and patient population (referred to as the phase III eligible subgroup). The phase III–eligible subgroup were identified as part of a post-hoc analysis based on selection of patients who received within a half log of the recommended Toca 511 phase III dose and who had the demographic profile of patients who appeared to derive the greatest benefit. This includes patients with glioblastoma or anaplastic astrocytoma who were at 1st or 2nd recurrence, had received no prior bevacizumab, and whose tumor size at the longest dimension was ≤5 cm³ (Supplementary Figure S1). Such inclusion criteria are commonly used in rHGG trials.

In supplementary Table S2, demographics and baseline characteristics for all patients and the phase III-eligible subgroup are reported.

**Complete Responses Observed by Radiographic Evaluation.** In this recurrent setting, the study entry criteria were designed to minimize pseudoprogression by enrolling rHGG patients who had an interval of at least 12 weeks after prior radiation for patients at first recurrence or, if less than 12 weeks, had histopathologic confirmation of recurrent tumor or new enhancement outside of the RT field. While enhancing tumor can be frequently resected, the non-enhancing deeply infiltrative tumor portion is typically not resected, in order to maintain neurologic function. Post resection, Toca 511 was injected into the walls of the resection cavity followed after approximately 6 weeks by cycles of oral Toca FC. In addition, the possibility of pseudo-responses was minimized by obtaining a baseline MRI brain scan at 6
weeks post-resection, a time when most post-surgical changes have typically resolved\textsuperscript{31}, and when therapeutic activity is not expected, as this starts with Toca FC administration and subsequent local conversion to 5-FU.

In the setting of rHGG, tumors are growing prior to surgical resection. Surgery is not a curative treatment for these highly infiltrative tumors, and patients invariably recur following re-resection. At the time of the baseline scan, all patients had evaluable disease, and a majority (55\%) had measurable disease. In Figure 1, an evaluable and measurable lesion 1 (041-LO1) grew in the area that was injected with Toca 511. Over time, the lesion regressed resulting in a durable complete response. Examples of responses with evaluable and either measurable or non-measurable disease at 6 weeks post resection and the durability of such responses are shown in supplementary figure S2. In addition, an evaluable and measurable lesion 1 (19-LO1) grew in the area that was injected with Toca 511, while a secondary lesion (19-LO2) was in an area that was not injected. Over a similar time, both lesions regressed resulting in a durable complete response.

**Objective and Durable Response Rates Observed in Patients treated with Toca 511 & Toca FC.** Among the 53 efficacy-evaluable patients, the rate of objective responses, which were all complete responses, was 11.3\% (6/53). In the 23 patient phase III-eligible subgroup, the percentage of patients with objective response was 21.7\%, with 5 complete responders, and the stable disease rate was 21.7\% for an overall clinical benefit rate of 43.5\% (Table 1). All responders met phase III-eligibility criteria and were treated at, or within a half-log of the recommended Toca 511 phase III dose. One additional complete responder was in the 5 patient bevacizumab combination treatment cohort and was treated with Toca FC in combination with bevacizumab for approximately 4.6 months and continued on bevacizumab for more than 16.2 months. No responders were observed in lower dose cohorts or in the temozolomide combination treatment cohort.
Tumors which responded were progressing prior to surgical resection and continued to grow after resection. Baseline MRI obtained prior to start of Toca FC showed all responders had either measurable disease of 1.7 to 2.8 cm$^2$ or non-measurable but evaluable tumor (Supplementary Table S3). In this trial, there was a delayed time to response (PR or CR) onset of more than 6 months and responses occurred gradually over time, such that they were not representative of a rapid decrease following surgery which would be indicative of resolution of post-operative changes or ischemia. A majority of patients were using ≤ 2mg/day systemic corticosteroids with dexamethasone at last follow up. Among patients with a response, only one patient was on corticosteroids at varying doses of dexamethasone of 1 to 4 mg (Supplementary Table S3 and Supplementary Table S4).

In the phase III-eligible subgroup, swim lanes (Fig. 2) show onset and durability of responses. Complete and partial responses begin about 6 to 19 months after Toca 511 administration consistent with an immunologic-based response (Supplementary Figure S2). Among the phase III-eligible subgroup, median time to initial response is 9.2 months and the median duration of response has not been reached after a median follow-up of 35.7+ months (range 14.1+ to 44.9+ months). All partial responders improved to complete responders and, as of August 25, 2017, all responders are in complete response and remain alive (range 33.9+ to 52.2+ months) after Toca 511 administration, suggesting a positive association of durable response with overall survival (Fig. 2). Typically in high grade glioma, the duration of each successive recurrence is usually shorter. In the phase III-eligible subgroup, the patients’ disease trajectory from initial diagnosis for newly diagnosed high grade glioma is summarized (Supplementary Figure S3) and supports that their disease course may be altered by Toca 511 & Toca FC. Median survival post-progression for the 23 patients was 9.1 months (95% CI 7.5, 11.4), suggesting many patients who did not have a response may have still received some benefit from treatment since overall survival in this setting is typically around 5 months (Supplementary Table S1)\(^2\).
**Overall Survival (OS) Improved with Toca 511 & Toca FC treatment.** In the phase III-eligible subgroup, median survival was 14.4 months; landmark survival shows durability of response with key landmarks at OS12 at 65.2% (15/23), OS24 at 34.8% (8/23), and, although the sample size is small, Kaplan-Meier estimate of the probability of survival at 3 years or beyond was 26.1% (6/23) (Table 2). Details regarding responding patients and a patient with durable stable response for more than 3 years are summarized (Supplementary Table S3). The safety profile is consistent with that previously reported\(^1\) with related treatment-emergent serious adverse events at 7.1% (Supplementary Table S5). With additional follow up since the previous report\(^1\) and with survival of up to 52.2 months, no secondary malignancies or lymphoproliferative disorders have been reported with this retroviral replicating vector treatment.

**Durable response rate and OS are Associated.** Durable response rate and OS outcomes are similar comparing patients with baseline evaluable and measurable disease to those with evaluable and non-measurable disease (Supplementary Table S6). The Kaplan-Meier curve suggests a clear relationship between durable response rate and overall survival (Supplementary Figure S4). Median survival for patients with a durable response has not been reached and for non-responders is 13.2 months (95%CI: 10.8, 14.6).

**Responding patients have low genomic mutational burden.** Response to checkpoint inhibitors correlates with tumor mutational burden, which is a proxy for the presence of “neoantigens” that can be recognized by tumor infiltrating lymphocytes\(^3\). As it appears that responses to Toca 511 treatment have an immunological basis, we tested whether mutational burden correlates with response, by “exome” sequencing all available patient tumors resected immediately prior to Toca 511 treatment. Consistent with previous characterization of HGG\(^4\), most patient tumors had relatively few total mutations (or nonsynononomous mutations) –of approximately 100 or about 2 per/Mb sequenced using blood DNA as baseline (Fig. 3). Two patients (011 and 030) displayed hallmarks of temozolomide-induced hypermutation with about 100-fold more mutations and a strong bias for CG to TA. Neither
patient responded and both patients had IDH1 R132H/S driver mutations. Patient 011 did not take Toca FC and patient 030 was on 5th recurrence. Neither patient lived longer than 7 months whereas most responding patients took 6 to 19 months to respond. All responding patients had few mutations and thus, responses observed were not associated with tumor mutation load determined by exome sequencing. No patients were reported to have 1p19q mutation.

HGG is a heterogeneous disease with diverse underlying driver mutations and consequent molecular profiles. We tested if response correlated with specific mutations, molecular subtype or expression of key immune cell markers. Responding patients did not show significant bias for molecular subtype (Supplementary Figure S5). mRNA levels of T cell genes, PD-L1, CD8A, IDO1, ICOS, OX40, and CTLA-4, did not differ between tumors from patients who lived more than 24 months compared to those who lived less than 24 months, suggesting that baseline resident T cells are not likely to be predictors of survival to this therapy (Supplementary Figure S6).

We performed longitudinal flow cytometric profiling of peripheral blood mononuclear cells from combination therapy cohorts. We observed a sustained treatment-associated increase in Ki-67 positive (proliferating) T lymphocytes (particularly the CD8+ cytotoxic T cell subset), in six patients who did not have disease progression compared to seven patients that progressed at time of analysis. (Supplementary Figure S7).

Discussion

Multi-year durable responses were observed in rHGG patients receiving Toca 511 & Toca FC. Responders were a diverse group across ages, KPS, and molecular subtypes. Whether patients had evaluable measurable tumors or evaluable non-measurable tumors, similar efficacy outcomes of durable response rate and overall survival was observed. While these data were obtained from uncontrolled non-randomized studies, durable responses lasting more than 24 weeks are rare in rGBM patients receiving approved treatments with durable response rates ranging from 0 to 2.15% for rGBM10,32. Also,
patients with rGBM and IDH1 mutation have the same objective response rate as patients with wild type phenotype. Treatment with Toca 511 & Toca FC compares favorably, demonstrating a durable response rate in rHGG of 21.7% and in rGBM of 15.8%. Among efficacy-evaluable patients (n=53), the estimated median duration of response for rHGG of at least 35.1+ months is substantially longer than the median duration of response observed for existing therapies, ranging from 2.79 to 11.6 months (Supplementary Table S1). In our dataset, there was positive association of durable response rate and overall survival. The delayed time to response, responses in some patients and prolonged duration of response is consistent with other immuno-oncology drugs. Common considerations for immuno-oncology drugs include objective response rates in a select subset of patients with prolonged duration of response, a delayed separation and a late plateau of survival curves as well as a median overall survival that may obscure the long-term benefits in the minority of patients with responses. Therefore durable response rate may represent a new and clinically meaningful surrogate endpoint for overall survival in brain cancer trials, to more accurately assess clinical benefit of novel immune-oncology drugs for the treatment of brain tumors. In post-surgical settings, appropriately timed baseline measurement provides confidence that outcomes of this novel treatment differentiate the treatment from standard of care. The reproducibility of the observed results, validity of durable response rate and relationship between durable response rate and overall survival will be further explored in the currently ongoing phase III trial in recurrent glioblastoma and recurrent anaplastic astrocytoma (NCT02414165).

In the study described here, tumor shrinkage was observed in areas that had not been directly injected with Toca 511, suggesting viral spread or abscopal anti-tumor immune effects (Fig. S2; patient 019). The impact of brain cancer on quality of life has been well documented in the literature. One component of quality of life is being able to resume one’s professional life. Historically, less than a third of patients with rHGG return to work, highlighting the pharmacoeconomic impact of this disease. Anecdotally, the majority of patients who responded in our study have been reported to return to work.
In newly diagnosed HGG, initial growth of IDH1 mt tumors may be slow and IDH1 mt is a significant prognostic marker of overall survival (OS)\(^35\). However, in the recurrent setting, particularly among patients with recurrent glioblastoma, the biology of IDH1 mt and wt tumors converge with neither conferring a survival advantage\(^35\). Additionally, IDH1 mt tumors do not spontaneously regress\(^35\). Objective response rates in patients with recurrent IDH1 mt tumors are similar to IDH1 wt tumors and IDH1 mutation does not correlate with objective response\(^35,39,40\). However, the observed data suggests an enrichment of durable complete responses in IDH1 mutant patients at first or second recurrence treated with Toca 511 & Toca FC.

In rHGG, complete responses are uncommon and typically occur in ≤1% of treated GBM patients\(^32,35\). We observed complete responses in patients with IDH1 mt and wt tumors, suggesting a benefit across the rHGG setting. Following treatment with Toca 511 & Toca FC, there were 6 complete responses (2 IDH1 mt and 3 IDH1 wt) and one also receiving bevacizumab (IDH1 wt). Interestingly, of 5 patients with IDH1 mutation, the 2 patients who entered the study at first recurrence had durable complete responses (Supplementary Table S3).

Patients with hypermutated tumors seem more likely to respond to immunotherapies\(^41\). Case reports of hypermutated glioblastomas have observed clinical responses to checkpoint inhibitors\(^42,43\). While high grade glioma tumors, especially those treated with temozolomide, are known to have higher mutational loads than low grade gliomas\(^44\), an increased tumor mutational burden in responding patients was not observed here. This observation held true for the responding IDH1 mutant tumor patients\(^1\) even though 50-60% of IDH1 mutant tumors have been reported to be hypermutated due to hypermethylation and inactivation of DNA repair genes\(^45\). Tumors with IDH1 mutations may be more susceptible to our immunotherapy for reasons other than hypermutation including increased sensitivity to 5-FU\(^46\). Also, as previously reported, MGMT methylation status does not appear to be a significant marker of survival in the recurrent setting\(^1\).
Given long lead times to achieve responses at 6 to 19 months and that responses occurred in patients at first and second recurrence in rHGG settings, newly diagnosed HGG patients who typically live longer and also may have a more intact immune system may derive benefit from treatment with Toca 511 & Toca FC. The newly diagnosed setting also provides an opportunity to leverage Toca 511 & Toca FC activity with radiation therapy and temozolomide as reported in preclinical models\textsuperscript{47,48}. The ability of Toca 511 & Toca FC therapy to alter immune-suppressive networks within the tumor microenvironment and cause cancer cell death may provide a mechanism for turning tumors with low immunogenic potential and immune activity into tumors actively destroyed by the immune system. Toca 511 & Toca FC likely breaks immune tolerance to the notoriously recalcitrant HGG by increasing both immunogenicity and immune activity within the tumor microenvironment. These data support further testing of Toca 511 & Toca FC in newly diagnosed HGG as well as a general modality for cancer immunotherapy in other indications.


39. Burnet NG, Jefferies SJ, Benson RJ, Hunt DP, Treasure FP. Years of life lost (YLL) from cancer is an important measure of population burden--and should be considered when allocating research funds. *British journal of cancer*. 2005; 92(2):241-245.


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Figure Legends

Figure 1. Top Panel- Timeline of Toca 511 delivery, Toca FC dosing, and MRI. Bottom Panel- Independent Radiology Review (IRR) determined radiographic response after Toca 511 & Toca FC therapy. The left temporal tumor is shown to be progressing prior to surgical resection. After surgical resection, residual tumor remains, which continues to grow post-operatively. Following Toca FC administration, there is gradual decrease of the tumor to a partial response and then to a complete response (Supplementary Figure S2 for complete series).

Figure 2. Swim Lane Demonstrating Responses are Durable (≥ 24 weeks) and Associated with Long Term Survival
Figure 3: Summary of RNA and DNA sequencing results from patient tumors
(left to right) The barplot shows the total number of high confidence mutations called by MUSE from exome sequencing data. The first three left columns summarize results from RNA sequencing: molecular subtype (mesenchymal – red, classical – black, neural – green, proneural – blue), and IDH1 R132H/S mutation (orange)). The next four columns show response (CR – green, SD – purple, PD – orange), clinical features, including eligibility for phase III trial (phase III-eligible subgroup – yellow), tumor grade at study entry as determined by clinical site pathologist (grade IV = grey, grade III = black), number of recurrences (1 or 2 – light brown, >2 – dark brown). Patients are ordered by duration of survival post-resection and Toca 511 treatment. Patients alive at last contact are indicated by light blue bars.
Table 1. Objective Response, Durable Response and Clinical Benefit Rates

<table>
<thead>
<tr>
<th>Response Category(^1)</th>
<th>All Patients(^2) n=53 (%)</th>
<th>Phase III-eligible subgroup n=23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>6 (11.3)(^3)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (18.9)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>37 (69.8)</td>
<td>13 (56.6)</td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>16 (30.2)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>(CR+PR+SD ≥ 6 weeks)</td>
<td></td>
<td></td>
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<tr>
<td>Durable response rate</td>
<td>6 (11.3)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>(PR or CR ≥ 24 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Duration of follow up</td>
<td>35.1+ (9.2 - 44.9)</td>
<td>35.7+ (14.1 – 44.9)</td>
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<tr>
<td>for responders (months)</td>
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\(^1\) Determined by independent radiology review (IRR) using modified Macdonald criteria for all patients, except for a cohort that received Toca 511 & Toca FC and bevacizumab that used modified RANO criteria, taking into account corticosteroid and clinical data.

\(^2\) Of 56 safety evaluable patients, 53 patients who received Toca 511 & Toca FC are efficacy-evaluable.
Table 2: Median and Landmark Survival as of August 15, 2017

<table>
<thead>
<tr>
<th></th>
<th>All Efficacy Evaluable Patients n=53</th>
<th>Phase III-eligible subgroup n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (months; 95% CI)</td>
<td>11.9 (10.7, 15.1)</td>
<td>14.4 (11.3, 28.1)</td>
</tr>
<tr>
<td>Landmark Survival* n (%)</td>
<td></td>
<td></td>
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<tr>
<td>OS 6-month</td>
<td>47 (88.7)</td>
<td>23 (100)</td>
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<td>OS 9-month</td>
<td>38 (71.7)</td>
<td>21 (91.3)</td>
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<tr>
<td>OS 12-month</td>
<td>26 (49.1)</td>
<td>15 (65.2)</td>
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<tr>
<td>OS 18-month</td>
<td>14 (26.4)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>OS 24-month</td>
<td>13 (24.5)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>OS 36-month</td>
<td>7 (13.4)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>OS 42-month</td>
<td>7 (13.4)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>OS 48-month</td>
<td>7 (13.4)</td>
<td>6 (26.1)</td>
</tr>
</tbody>
</table>

* Kaplan-Meier estimate of the probability of survival
Figure 1.

Toca 511 injection into the cavity wall after tumor resection

Study
Weeks

041-L01
Progression
Screening
1 day postop
Baseline
1/7/2009
1/7/2009
1/7/2009
1/7/2009

MRI
MRI
MRI
MRI

Downloaded from https://academic.oup.com/neuro-oncology/advance-article-abstract/doi/10.1093/neuonc/noy075/4995454 by University of Newcastle user on 15 May 2018
Figure 2.
Figure 3.