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EORTC protocol 1608-BTG

Study of TG02 in Elderly Newly Diagnosed or Adult Relapsed Patients with Anaplastic Astrocytoma or Glioblastoma: A Phase Ib Study

STEAM

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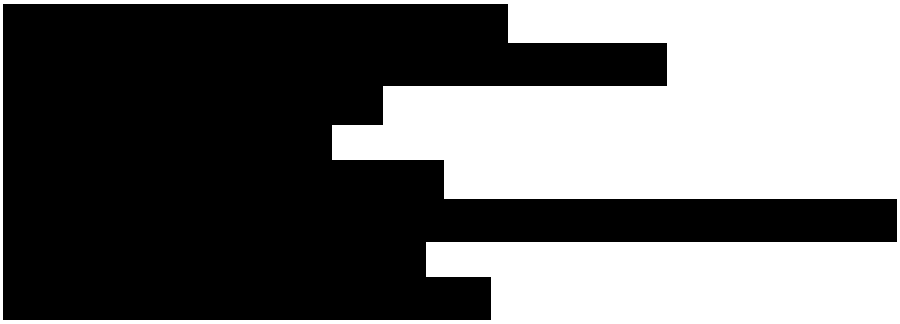

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Protocol summary

Title of the Study	**STEAM: Study of TG02 in Elderly Newly Diagnosed or Adult Relapsed Patients with Anaplastic Astrocytoma or Glioblastoma: A Phase Ib Study**
Objective(s)	**Primary objective** **Groups A and B: safety and tolerability** Group A: Establish the recommended phase II dose of TG02 in combination with radiotherapy (RT) to be used in further trials exploring the antitumor activity of TG02 in the elderly. Group B: Establish the recommended phase II dose of TG02 in combination with temozolomide (TMZ) to be used in further trials exploring the antitumor activity of TG02 in the elderly. **Group C: explore single agent activity** Investigate if single agent TG02 demonstrates sufficient antitumor activity in anaplastic astrocytoma or glioblastoma at first relapse after initial treatment with TMZ/RT-TMZ to justify further development. **Secondary objectives** • Investigate the efficacy, safety and tolerability of TG02 in all groups • Investigate quality of life in groups A and B • Correlate the frailty of elderly patients with safety, tolerability and outcome in groups A and B • Correlate the Neurologic Assessment in Neuro-Oncology (NANO) scale assessments with outcome assessed by RANO criteria and outcome in groups A and B • Correlate molecular markers with efficacy data in all groups • Evaluate Pharmacokinetics of TG02 in group C only
Methodology	This is a three parallel group (A, B & C), open-label, non-randomized, multicenter study. All three groups will enroll independently. Group A: will be composed of newly-diagnosed, elderly patients with $IDH1^{R132H}$-non mutant and MGMT promoter-unmethylated anaplastic astrocytoma or glioblastoma who will receive TG02 and radiation therapy. Group B will be composed of newly-diagnosed, elderly patients with $IDH1^{R132H}$-non mutant and MGMT promoter-methylated anaplastic astrocytoma or glioblastoma who will receive TG02 and temozolomide. For both Groups A and B, there will be a classical 3+3 dose escalation and an expansion phase with stopping rules in the study. Group C patients will be composed of patients initially diagnosed with $IDH1^{R132H}$-non-mutant anaplastic astrocytoma or glioblastoma at first relapse post TMZ/RT → TMZ therapy who will receive TG02. All patients will receive TG02 until disease progression, unacceptable toxicity or up to 12 cycles. [Upon completion of 12 cycles without disease progression

	or unacceptable toxicity, patients may continue on TG02 as determined by the Investigator.]
Number of patients Number planned (Statistical design) Number analyzed	**Groups A and B** This is an open-label, non-randomized, multi-center, phase Ib trial using the classical 3+3 design. Three patients will be enrolled at 100 mg TG02 twice weekly. Escalation or reduction decisions will be based on the monitoring for dose limiting toxicity (DLTs) during the first cycle of each dose level. • If no patient in the cohort of 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg twice weekly. • If 1 patient in the cohort of 3 patients experiences a DLT, 3 additional patients will be enrolled at 100 mg twice weekly. If none of the additional 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg twice weekly. • If the DLT criteria are not met (i.e., no patients with DLT out of 3 patients or ≤1 DLT out of 6 patients) at 150 mg twice weekly., no further dose escalation of TG02 will be done and 150 mg TG02 will be declared the maximum tolerated dose (MTD) for expansion. • If > 1 out of 3 patients or ≥ 2 out of 6 patients experiences a DLT at 150 mg, dose escalation will not proceed and 100 mg will be considered the maximum MTD. • If > 1 out of 3 patients or ≥2 out of 6 patients experiences a DLT at 100 mg, the arm will be closed. Within one dose level, patients may be entered simultaneously. The replacement of patients will be performed in case of patients that progress, die due to disease progression, or leave the study for any reason other than DLT prior to completion of the first cycle of therapy. After determination of the MTD, additional patients will be treated at this dose level for additional safety information: up to a total of 24 evaluable patients in Group A and up to a total of 12 evaluable patients in Group B (up to 36 evaluable patients for Groups A and B). Stopping rules for the expansion cohorts are described in the protocol. We consider groups A and B exploratory and independent from each other, with the prime goal of assessing feasibility (tolerability, safety). The difference in size in these two groups reflects the natural distribution of patients into those with tumors without (2/3, group A) and with (1/3, group B) MGMT promoter methylation. The elderly patient population is ideally suited to explore safety, tolerability and efficacy of TG02 with the two backbones of glioblastoma treatment, radiotherapy (group A) and temozolomide (group B), in isolation. Finally, there is a feasibility consideration: we anticipate that doctors and patients are more willing to omit temozolomide in group A than to omit radiotherapy in arm B although such a strategy is consistent with the EANO guideline updated in 2017.

	The MTD corresponds to the highest dose at which not more than 1 patient out of a maximum of 6 experiences a DLT. A dose intensity of 75% of either TG02 or RT (group A) and of either TG02 or TMZ (group B) is required to assess the toxicity. **Group C** Based on an A'Hern one-stage, 45 eligible patients who started treatment will be evaluated for PFS at 6 months. It is estimated that the total sample size should not be larger than 50 assuming a dropout of 10%. The following hypotheses apply: • P0 is the largest PFS rate at 6 months which, if true, implies that the therapeutic activity of TG02 is too low. In the present trial, P0 has been taken as 20%. • P1 is the lowest PFS rate at 6 months which, if true, implies that the therapeutic activity of TG02 is adequate. In the present trial, P1 has been taken as 40%. • α is the probability of accepting adequate activity of TG02 with a true PFS rate at 6 months equal to or lower than P0. In the present trial, α has been taken as 0.10. • β is the probability of rejecting adequate activity of a drug with a true PFS rate at 6 months rate at least equal to P1. In the present trial, β has been taken as 0.05. A decision rule for efficacy will be performed amongst the 45: • If < 13 patients are free of progression and alive at 6 months, the conclusion will be that TG02 should not be investigated. • If ≥ 13 patients are free of progression and alive at 6 months are observed, we will conclude that TG02 should be further investigated. In this case, the one-sided 90% confidence interval excludes P0.
Diagnosis and main criteria for inclusion	*REGISTRATION* *Patients must fulfill all of the following criteria to be eligible for registration in the study:* *Inclusion criteria:* *Specifics for groups A and B* *Patients may be registered at any time after surgery.* • Newly diagnosed glioblastoma or anaplastic astrocytoma, $IDH1^{R132H}$-non-mutant by immunohistochemistry locally assessed, with FFPE tissue available for central *MGMT* testing (treatment allocation will be performed based on centrally assessed *MGMT* result) • Tumor debulking surgery, including partial resection • Age > 65 and considered non-eligible for combination therapy (TMZ/RT→TMZ) in Investigator's opinion as outlined in in the protocol and in the current EANO guideline • Brain MRI within 14 days before the first dose of TG02

	Specifics for group C
	• $IDH1^{R132H}$-non-mutant glioblastoma or anaplastic astrocytoma at first relapse with tissue available from first surgery. [Per 2016 WHO classification, in patients older than 55 years of age at diagnosis with a histological diagnosis of glioblastoma, without a pre-existing lower grade glioma and with non-midline tumor location, immunohistochemical negativity for $IDH1^{R132H}$ suffices for classification as glioblastoma. In all other instances of diffuse gliomas, lack of $IDH1^{R132H}$ immunopositivity should be followed by IDH1 and IDH2 sequencing to detect or exclude other less common IDH mutations.]
	• Brain MRI at the time of progression and no more than 14 days before the first dose of TG02 and availability of last brain MRI done previously to the MRI done at progression and that was used to confirm/diagnose progression for upload to the EORTC Imaging Platform for post-hoc central review of progression
	• Diagnosis of recurrence more than 3 months after the end of RT for first-line treatment
	• Intention to be treated with standard RT/TMZ→TMZ for initial treatment (at least one dose of TMZ administered; RT alone or chemotherapy alone as initial treatment are not permitted)
	• Patient may have been operated for recurrence. If operated:
	  • surgery completed at least 2 weeks before initiation of TG02 and patients should have fully recovered as assessed by investigator. Criteria for full recovery include absence of active post-operative infection, recovery from medical complications (CTCAE grade 0 and 1 acceptable), and capacity for adequate fluid and food intake
	  • residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence
	  • a post-surgery MRI should be available within 72 hours; the post-surgery MRI can be used as baseline if performed within 2 weeks prior to first dose of TG02. If not, a baseline MRI has to be done within 2 weeks prior to first dose of TG02.
	• For non-operated patients: recurrent disease must be at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on a MRI scan done within 2 weeks prior to first dose of TG02.
	• Age ≥ 18 years
	• Negative serum or urine pregnancy test within 72 hours prior to the first dose for women of childbearing potential (WOCBP). Nursing must be discontinued at least 1 hour before 1st dose
	All groups
	• Karnofsky Performance Score (KPS) of 60-100
	• Recovered from effects of debulking surgery, postoperative infection and other complications of surgery (if any) (CTCAE grade 0 and 1 acceptable)

	• Adequate bone marrow, renal and hepatic function within the following ranges within 7 days before the first dose of TG02:
	  • WBC ≥ 3 x10^9/L
	  • ANC ≥ 1.5x10^9/L
	  • Platelet count of ≥ 100 x10^9/L independent of transfusion
	  • Hemoglobin ≥ 10 g/dl or ≥ 6.2 mmol/L
	  • Bilirubin ≤ 1.5 × ULN
	  • ALT and AST ≤ 2.5 × ULN
	  • Cockcroft–Gault calculated or measured creatinine clearance of ≥ 30 mL/min
	• life expectancy > 8 weeks
	• For men of reproductive potential and WOCBP, highly effective contraception must be used throughout the study and for 6 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly
	• Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments
	• Ability to take oral medication
	• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
	• Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.
	Groups A and B only
	• Central assessment of MGMT testing will be conducted after registration and before enrollment.
	Exclusion criteria:
	Specifics for groups A and B
	• Prior RT with overlap of radiation fields with the planned RT in this study (Group A).
	• Prior therapy for glioblastoma or anaplastic astrocytoma before surgery.
	Specifics for group C
	• Discontinuation of TMZ for toxicity during first-line treatment
	• RT or stereotactic radiosurgery is not allowed for the treatment of first recurrence prior to enrollment in this study
	All groups
	• Use of enzyme-inducing anti-epileptic drugs (EI-AED) within 7 days prior to the first dose of TG02

	• History of ventricular arrhythmia or symptomatic conduction abnormality in past 12 months prior to registration • Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to enrollment • 12-lead ECG with a prolonged QTc interval (males: > 450 ms; females: > 470 ms) as calculated by the Fridericia correction formula despite balancing of electrolytes at registration and/or discontinuing any drugs (for a time period corresponding to 5 half-lives) known to prolong QTc interval • Known contraindication to imaging tracer or any product of contrast media • MRI contraindications • Known hypersensitivity to the active substance or any of the excipients in the TG02 formulation, dacarbazin and TMZ • Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes, hypertension, coronary artery disease) that, in the opinion of the Investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study • Known human immunodeficiency virus infection or acquired immune deficiency syndrome • previous other malignancies, except for any previous malignancy which was treated with curative intent more than 3 years prior to enrollment, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix
Treatment Test product, dose and mode of administration Duration of treatment	**TG02 can be started on the day of enrollment.** **Group A:** Patients with MGMT promoter-unmethylated tumors will receive TG02 (initial dose of 100 mg) orally twice weekly (days 1, 4, 8, 11, 15 and 18) in combination with standard involved-field hypofractionated RT (40 Gy in 15 fractions of 2.66 Gy) for 3 weeks (days 1-21). TG02 should be taken approximately one hour prior to RT. Seven days after completing combination therapy, patients will receive maintenance cycles of single agent TG02 until disease progression, unacceptable toxicity or up to 12 months. TG02 will be administered on days 1, 4, 8, 11, 15, 18, 22 and 25 of each 28-day maintenance cycle. [Upon completion of 12 cycles without disease progression or unacceptable toxicity, patients may continue on TG02 as determined by the Investigator.] **Group B:** Patients with MGMT promoter-methylated tumors will receive TG02 (initial dose of 100 mg) orally twice weekly with temozolomide. TG02 will be taken on days -7, -4, 1, 4, 22 and 25 in cycle 1. As of cycle 2, TG02 is given on days 1, 4, 22 and 25 of a 28-day cycle. TMZ will be given in the standard 28-day cycle regimen (200 mg/m^2) for 5 days q 28 starting at Day 1. Combination therapy will continue until disease progression, unacceptable toxicity or up to 12 cycles. [Upon completion of 12 cycles without disease progression or

	unacceptable toxicity, patients may continue on TG02 and TMZ or single agent TG02 as determined by the Investigator.] **Group C:** Patients will receive single agent TG02 at 150 mg orally twice weekly. TG02 will be administered on days 1, 4, 8, 11, 15, 18, 22 and 25. The lowest permitted dose will be 100 mg BIW Single agent therapy will continue until disease progression, unacceptable toxicity or up to 12 cycles. [Upon completion of 12 cycles without disease progression or unacceptable toxicity, patients may continue on TG02 and TMZ or single agent TG02 as determined by the Investigator.]
Criteria for evaluation	• **Primary endpoint** **Groups A and B:** Primary endpoints in Groups A and B are the determination of the Maximum Tolerated Dose (MTD) and the recommended phase II combination dose. This part is a two-cohort study of the combination of TG02 with hypofractionated RT in patients with tumors with an unmethylated MGMT promoter, or with TMZ in patients with tumors with a methylated MGMT promoter. Up to two dose levels of TG02 will be explored in each group. **Group C:** Progression-free survival at 6 months (PFS-6) defined by RANO criteria. • **Secondary endpoints** **Groups A and B:** • progression-free survival at 6 months (PFS-6) • median progression-free survival (PFS) • median overall survival (OS) • OS at 9 months (OS-9) • for patients with measurable disease after debulking: best overall response distribution (BOR), objective (PR+CR) rate, complete response rate and duration of response (DOR) • quality of life (QOL) **Group C:** • median progression-free survival (PFS) • median overall survival (OS) • OS at 9 months (OS-9), 1 year (OS-12) • for non-surgical patients or patients with surgery for recurrence, but measurable disease thereafter: best overall response distribution (BOR), objective (PR+CR) rate, complete response rate and duration of response (DOR) • success rate defined as rate of patients achieving either confirmed CR or PR (> 4 weeks) or free of progression at 6 months

	• neurological progression-free survival (NPFS) based on the Neurologic Assessment in Neuro-Oncology (NANO): median NPFS and NPFS at 6 months (NPFS-6). • clinical deterioration free survival (CDFS). • safety profile (CTCAE) • Pharmacokinetics of TG02 (in group C only) at various timepoints. **Exploratory endpoints for all groups:** • Correlation of molecular markers including MYC, MCL-1, CDK9 and CDK5 protein levels, and potentially others, with measures of clinical benefit.
Statistical methods	**Group A and B** Primary endpoints are the determination of the Maximum Tolerated Dose (MTD) and the recommended phase II combination dose. All analyses will be performed in the safety population. Analyses will be descriptive only presented with tables and listings (i.e. no formal inference). Objective response rate will be reported with exact (binomial) 95% two-sided confidence interval. The PFS-6 and OS-9 and the medians will be extracted from their Kaplan-Meyer curves. The 95% two-sided confidence intervals will be computed based on the Greenwood's formula and based on the Reflected Method for the median. The best overall response will be presented in contingency table with numbers and percentages. The objective response (CR+PR) and complete response (CR) rates will be reported with exact (binomial) 95% two-sided confidence interval. Duration of objective response and complete response will be estimated using Kaplan-Meier methodology. Median duration of objective and complete response with corresponding 95% two-sided confidence interval provided by the Reflected Method will be displayed. Hematological and biochemistry parameters will be presented with clinical significance (CS vs NCS). **Group C** Number of patients free of progression at 6 months In the efficacy population: All patients will be observed during a minimum follow-up of 6 months. The number of patients free of progression and alive at 6 months will be computed and the above-mentioned decision rule applied. Patients lost to follow-up or who died before 6 months are considered as failures at the time of analysis. In case more than 45 eligible patients are recruited, the decision rule will be applied as such on the first 45 eligible patients. The proportion of patients free of progression at 6 months will be presented with 80% two-sided confidence intervals computed based on the Exact Binomial distribution.

Translational research	MYC and Mcl-1 over-expression have been reported in more than 80% and 46% of glioblastomas, respectively. TG02 is a potent inhibitor of cyclin-dependent kinase 9 and 5 (CDK9 and CDK5). We will determine the CDK9, MYC, Mcl-1 and CDK5 protein levels to assess the following: • preliminary correlation of CDK9, MYC, Mcl-1 and CDK5 over-expression prior to treatment with TG02 with efficacy endpoints • markers of TG02 activity in blood and tumor tissue Additionally, we will collect tumor tissue and blood from patients that underwent surgery after recurrence/progression while on TG02 to confirm that TG02 crosses the blood-brain barrier in humans and determine TG02 concentration in tumor tissue and peripheral blood. MYC, MCL-1, CDK9 and CDK5 (p35) protein levels will be determined in tumor tissue (surgical sample or biopsy) collected at any time. The tissues will be sent for analysis to Department of Neurology, University Hospital Zurich. Furthermore, we will collect blood samples at baseline, cycle 3 day 1 and end of study treatment for the potential determination of emerging peripheral biomarkers of TG02 sensitivity and correlate these with outcome. Plasma (10 mL) and cell pellet will be collected for collection of soluble and cellular DNA, respectively; serum (10 mL) will be collected for the determination of soluble biomarkers, e.g., cytokines or chemokines. Samples will be analyzed at the Department of Neurology, University Hospital Zurich.
Quality of Life	Since elderly patients are more prone to side-effects from treatments and since maintaining HRQoL is a major consideration in de-escalating treatments that provide little benefit, e.g., TMZ in patients with tumors without MGMT promoter methylation, this phase Ib trial will also capture data on HRQoL in Group A (addition of TG02 to postoperative RT in MGMT-unmethylated, $IDH1^{R132H}$-non-mutant WHO grade III and IV glioma) and B (addition of TG02 to postoperative TMZ chemotherapy in MGMT-methylated $IDH1^{R132H}$-non-mutant WHO grade III and IV glioma). The main objective of this study is to explore the impact of combined treatment on overall global health and HRQoL in this fragile, elderly (> 65 years) high-grade glioma patient population. A secondary objective is to evaluate the effect of the treatment on the self-reported symptom burden and functioning scales as treatment-related side-effects may have a (temporary) negative influence on the health related domains of HRQoL of these patients with a particular emphasis on fatigue, nausea/vomiting and diarrhea in the light of the expected side effects of TG02.

1 Background and Introduction

1.1 Background – current standards of care for patients with IDH wild-type glioblastoma and anaplastic astrocytoma

Glioblastoma is the most common and aggressive adult primary brain tumor. It has a survival rate at the population level of less than 40% of patients alive at 1 year, 10% at 3 years and 5% at 5 years despite standard of care treatment with surgery, radiotherapy and chemotherapy using concomitant and maintenance temozolomide (TMZ/RT→TMZ) (Ref. 22, Ref. 33, Ref. 35). The revised WHO classification places great emphasis on the absence or presence of isocitrate dehydrogenase (IDH) 1 or 2 mutations to improve the classification of diffuse gliomas (Ref. 16). Accordingly, glioblastomas are typically IDH wild-type tumors whereas the small proportion of approximately 5% of histological glioblastomas with IDH mutations are now considered a separate biological entity.

Conversely, most anaplastic gliomas are IDH mutant tumors and have better prognosis than glioblastomas. The minority of approximately 20% of anaplastic gliomas, notably anaplastic astrocytomas, without IDH mutations often share a less favorable prognosis similar to IDH wild-type glioblastoma, notably in the elderly (Ref. 6, Ref. 38).

For decades, neurosurgical resection and postoperative RT have been the cornerstones of treatment for patients with anaplastic astrocytoma (AA) and glioblastoma (GBM). Most chemotherapeutic agents showed little or no activity in patients affected by these tumors, with the possible exception of nitrosoureas. This changed with the introduction of TMZ, first shown to be active in recurrent disease (Ref. 40, Ref. 41) and later on in newly diagnosed GBM (Ref. 31, Ref. 32). The EORTC 26981-22981 NCIC CE.3 trial demonstrated an increase in median survival from 12.1 to 14.6 months and of the 2-year survival rate from 10% to 26% in patients receiving TMZ/RT-TMZ compared with RT alone. Notably patients with tumors exhibiting methylation of the promoter region of the O6-methylguanine DNA methyltransferase (MGMT) gene showed a benefit from TMZ (Ref. 7). Yet, inclusion in this trial was limited to patients up to the age of 70, and subgroup analyses demonstrated that younger patients were more likely to derive benefit from combined modality treatment than older patients.

TMZ is overall well tolerated. The most common adverse events are hematological. Neutropenia and thrombopenia may require dose adjustments. This hematological toxicity is usually reversible. Non-hematological toxicity includes nausea and vomiting that is readily controlled by antiemetics and occasionally hepatotoxicity that is rarely severe.

The value of RT on elderly GBM patients has been confirmed in a small randomized trial comparing best supportive care versus RT alone: median survival was 29 weeks with RT compared with 16.9 weeks with supportive care only (Ref. 9). Based on the overall shorter survival in elderly patients, hypofractionated RT has been explored and shown to be of equivalent activity in patients aged 60 years and more (Ref. 26). Building on the experience in younger patients and the emerging role of MGMT as a predictive biomarker in GBM, two directions of clinical research were explored: (i) asking whether TMZ alone was a therapeutic option in the elderly and (ii) determining whether or not elderly patients benefit from combined modality treatment.

Regarding the first question, results from two randomized trials were published in 2012, the German NOA-08 trial (Ref. 38) and the Nordic trial (Ref. 18). Both trials compared RT alone with TMZ alone in newly diagnosed GBM in elderly patients (> 65 years in the NOA-08 trial and > 60 years in the Nordic trial). In these trials where TMZ was tested as monotherapy, as also in WHO grade II gliomas (Ref. 56), TMZ is not given for 6 cycles as in the adjuvant setting, but longer, e.g., for 8 to 12 months. In the absence of RT, the starting dose is commonly 200 mg/m^2 at days 1 to 5 out of 28 days (= 1 cycle). Both

elderly trials confirmed MGMT promoter methylation as a predictive marker for the efficacy of TMZ chemotherapy in this study population. Further, the Nordic trial corroborated the equivalent activity of an accelerated RT protocol of 40 Gy administered in 15 fractions versus the standard fractionation of 30 x 2 Gy. Overall these results were practice-changing and called for MGMT promoter methylation analysis in elderly patients with newly diagnosed GBM as a clinical routine outside clinical trials (Ref. 35). For patients considered non-eligible for combined modality treatment, the therapeutic interventions should be planned based on MGMT promoter methylation analysis, i.e., elderly patients with MGMT promoter-methylated glioblastomas should receive TMZ chemotherapy, without or with RT (see below), and elderly patients with MGMT-unmethylated glioblastomas should receive RT without TMZ. A joint NCIC-EORTC trial addressed the question of combining RT and TMZ in the elderly: patients aged more than 65 years with an ECOG performance score of 0, 1 or 2 were randomized between TMZ combined with short-course RT (40 Gy in 15 fractions) versus short course RT alone (Ref. 24). A significant improvement of both PFS and OS was observed, with an improvement of 3.9 to 5.2 months for PFS (+1.4 months) and of 7.6 to 9.3 months for OS (+1.7 months). The survival gain with combined modality treatment was much more prominent in patients with tumors with as opposed to without MGMT promoter methylation. Moreover, MGMT data were lacking in almost 40% of patients who had an overall inferior outcome, and only patients considered eligible for combined modality treatment were enrolled.

Thus, for elderly patients aged more than 65-70, physicians have to answer the question whether they consider patients eligible for primary combined modality treatment or whether they prefer temozolomide alone for patients with MGMT promoter methylated tumors and radiotherapy alone for patients with MGMT promotor unmethylated tumors. Both options are supported by the updated guideline of the European Association for Neuro-oncology (EANO) (Ref. 35). The clinical practice may vary between sites, but the sites participating in this trial are among the sites that favor to place their treatment decision on MGMT promoter methylation testing as outlined in the EANO guideline. Typical selection criteria for temozolomide alone would be patients with MGMT promoter methylated tumors that would require large irradiation volumes or that have e.g. vascular comorbidities that would place them at increased risk of toxicity from radiotherapy. Here the primary intension would be to delay radiotherapy and thus toxicity from radiotherapy as long as possible. Moreover, there is concern among the sites opting to participate in this trial that the combination of radiotherapy with temozolomide in patients with tumors without MGMT promoter methylation adds little if any benefit relative to radiotherapy alone.

Therapeutic benefit has also to be weighed against general safety and tolerability which represent challenges in elderly patients (Ref. 14). Furthermore, there is debate whether increased hematological toxicity from combined modality treatment is acceptable with a view on limited benefit especially in patients with tumors lacking MGMT promoter methylation. For instance, there was increased grade 3 and 4 toxicity in the experimental versus standard arm of the NCIC EORTC trial of 27% versus 10% for lymphocytopenia, 9% versus 0% for neutropenia, and 11% versus 0% for thrombocytopenia (Ref. 24).

Standards of care for IDH wild-type AA remain controversial: many centers now propose to treat these tumors like glioblastomas and base this recommendation on their molecular similarity; moreover, clinical trial results obtained in patients with all anaplastic gliomas pooled are difficult to extrapolate to the subgroup of IDH wild-type tumors likely to have been in the range of 20%. The current consensus includes RT without or with TMZ, the latter often based on a methylated MGMT promoter status (Ref. 33).

The main systemic treatment options at progression of glioblastoma after TMZ/RT→TMZ in Europe are nitrosoureas, TMZ rechallenge, and bevacizumab depending on availability. CCNU is increasingly used, based on its activity as the control arm of several randomized trials (Ref. 3, Ref. 37, Ref. 39), with PFS

rates at 6 months in the range of 20%. Similar results have been reported with alternative dosing regimens of TMZ, but activity is probably limited to patients with tumors with MGMT promoter methylation (Ref. 34). Bevacizumab is not approved for recurrent glioblastoma in the European Union and its off-label use is likely to decline in Europe after the failure of the combination of lomustine and bevacizumab to prolong survival over lomustine alone in the EORTC 26101 trial (Ref. 39). The treatment options for recurrent IDH wild-type AA are similar to those for GBM and depend mainly on pretreatment, and, as with GBM, on overall patterns of recurrence.

Altogether and considering the poor efficacy of the current approaches, these clinical data justify:

- The exploration of new, TMZ-free first-line treatment strategies in MGMT promoter-unmethylated GBM of elderly patients.
- The development of new treatment options in combination with TMZ for patients with MGMT promoter-methylated GBM who are not considered candidates for RT or who opt against RT as a first-line treatment.

These considerations apply also to patients with IDH wild-type AA who share a similarly poor outcome in the elderly population.

- The development of novel treatment approaches for patients who have failed first-line RT in combination with alkylating agent chemotherapy

Hence, the STEAM study will investigate the safety and tolerability of TG02 in combination with RT (Group A) or in combination with TMZ (Group B) in elderly patients (>65 years) with newly diagnosed IDH^{R132H}-non-mutant GBM or AA, as well as the efficacy of TG02 in the setting of first recurrence of an IDH^{R132H}-non-mutant GBM or AA (Group C).

1.2 Development of CDK inhibitors in cancer treatment

The first generation of CDK inhibitors were non- selective, pan CDK blocking agents that showed lack of anti-tumor activity, coupled with excessive toxicity due the narrow therapeutic window (Ref. 28). Further clinical development of both alvocidib and seliciclib was abandoned as high rates of treatment induced neutropenia coupled with modest antitumor activity was observed in the conducted phase II trials (Ref. 17, Ref. 13). However several second generation CDK inhibitors (mainly those blocking CDK 4/6) have been successfully tested in metastatic breast cancer rendering again these agents eligible for further clinical development in oncology (Ref. 21).

1.3 Investigational product: zotiraciclib (TG02)

1.3.1 Mechanism and Rationale

TG02, also known as zotiraciclib, is an oral multi-kinase inhibitor that potently inhibits cyclin-dependent kinase (CDK) 9 but also other CDK such as 1, 2, 5 and 7 and other tyrosine kinases. Through the inhibition of CDK9, its main target, TG02 blocks the activity of RNA polymerase II, leading to a depletion of gene products with short half-lives, such as the C-MYC oncoprotein as well as MCL-1, a survival protein of the BCL-2 family, with the potential consequence of apoptosis induction in glioma cells.

Both MYC and MCL-1 overexpression are associated with poorer survival in ovarian and probably hepatocellular cancer, although no such data are available for GBM yet. MYC overexpression has been reported in more than 80% of GBMs (Ref. 5, Ref. 8), and MCL-1 overexpression is present in 46% (Ref. 30). The roles of MYC and MCL-1 have been explored in glial tumors only recently. MYC inhibition has been validated as a therapeutic approach in experimental glioma models in vitro and in vivo by reduced proliferation, increased apoptosis and ineffective mitosis (Ref. 1).

CDK5 is also overexpressed in a large number of GBMs (Ref. 4, Ref. 42). CDK5 is an atypical CDK, which suppresses the cell cycle without the use of its kinase activity (Ref. 43). CDK5 also regulates the phosphatidylinositol 3 (PI3)-kinase enhancer (PIKE)-A-Akt pathway and promotes GBM cell migration and invasion by phosphorylation of phosphatidylinositol 3-kinase enhancer-A GTPase (Ref. 15).

Other main CDK targets of TG02, such as CDK1 and CDK2 directly promote cell cycle progression (Ref. 44). CDK7, which represents a minor target of TG02, is also involved in the regulation of transcription (Ref. 44).

Preclinical studies of TG02 in patient-derived glioma cell lines as well as standard glioma cell lines have demonstrated broad anti-tumor activity with IC_{50} values in the range of 25-70 nM. In addition, TG02 has demonstrated activity in cell lines without MGMT promoter methylation as well as glioma stem cell lines overexpressing the MYC oncogene (see TG02 investigator brochure).

1.3.2 Clinical experience with TG02

To date, 112 patients have been treated with single agent TG02:

- TG02 was administered to 55 patients with acute leukemia at doses from 10 mg to 150 mg. The most frequently-reported TEAEs (≥ 20%) were nausea, vomiting, fatigue, abdominal pain, decreased appetite, and diarrhea.
- TG02 was administered to 18 patients with multiple myeloma at doses from 50 mg to 200 mg. The most frequently-reported TEAEs (≥ 20%) were diarrhea, fatigue, nausea, constipation, vomiting, hypophosphatemia, decreased appetite, and hypokalemia.
- TG02 was administered to 16 patients with chronic lymphocytic leukemia at doses from 70 mg to 150 mg. The most frequently-reported TEAEs (≥20%) were nausea, diarrhea, vomiting, constipation, fatigue, dyspnea, cough, hyperglycemia, hypertension, anemia, decreased platelet count, dizziness, myalgia, and peripheral edema.
- TG02 was administered to 17 patients with GBM or AA at a dose of 200 mg. The most frequently reported AEs (≥20%) were increased ALT, diarrhea, nausea, decreased neutrophil count, decreased WBC count, fatigue, vomiting, and constipation.
- TG02 was administered to 6 patients with GBM/ AA at a dose of 250 mg. The most frequently reported AEs (≥20%) were diarrhea, fatigue, increased ALT, vomiting, decreased neutrophil count, decreased platelet count, and decreased WBC count

To date, 69 patients have been treated with TG02 in combination:

- TG02 was administered in combination with carfilzomib to 26 patients with multiple myeloma at doses from 150 mg to 300 mg. The most frequently-reported TEAEs (≥20%) were diarrhea, nausea, vomiting, fatigue, anemia, increased ALT, decreased appetite, neutropenia, and thrombocytopenia.
- TG02 was administered in combination with dose dense TMZ to 19 patients with GBM or AA at doses from 200 mg to 300 mg. The most frequently reported TEAEs (≥20%) were decreased lymphocyte count, decreased neutrophil count, decreased WBC count, and increased ALT.
- TG02 was administered in combination with metronomic TMZ to 21 patients with GBM or AA at doses from 200 to 250 mg. The most frequently reported TEAEs (≥20%) were decreased lymphocyte count, decreased neutrophil count, decreased WBC count, and hypophosphatemia.
- TG02 was administered in combination with radiation therapy to 3 patients with GBM or AA at a dose of 200 mg. The most frequently reported AEs (≥20%) were decreased lymphocyte count, urinary tract infection, increased ALT, decreased lymphocyte count, decreased neutrophil count, decreased WBC count, increased alanine aminotransferase, and hyperglycemia.

Please see the Investigator's Brochure for additional information

1.3.3 Dose and schedule rationale

1.3.3.1 Rationale for Bi-weekly Dosing of TG02

Single agent TG02 has been orally administered to 89 hematological patients at doses ranging from 10 mg to 200 mg on daily and intermittent schedules as described below. All schedules were conducted in a 28-day cycle.

1) daily for 28 days
2) 5 days on/ 2 days off for 2 weeks
3) Three times a week (TIW) for 3 weeks (Days 1, 3, 5, 8, 10, 12, 15, 17, 19)
4) Twice a week (BIW) for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22 and 25)
5) Twice a week for 3 weeks (Days 1, 4, 8, 11, 15 and 18)

Pharmacokinetic (PK) data in patients demonstrated that T_{max} for TG02 is around 1-4 hours and $t_{½}$ is between 10 and 15 hours. This PK profile was not predicted by the 28-day repeat dose toxicity studies in mice and dogs. The long half-life in patients led to accumulation when TG02 was taken on multiple consecutive days (on Schedules 1 and 2, above). A TIW schedule (Schedule 3 above) reduced but did not alleviate accumulation; therefore, BIW Schedules 4 and 5 were evaluated. The PK data demonstrated that the BIW dosing schedules alleviated accumulation.

Preclinical in vitro and in vivo studies have demonstrated that daily administration is not required for the therapeutic effect. In vitro pharmacodynamics demonstrated that a single dose of TG02 resulted in significant inhibition of downstream targets for at least 24 hours with apoptosis still increasing at 24 hours (Figure 1).

Figure 1: TG02 Depletes Survival Proteins

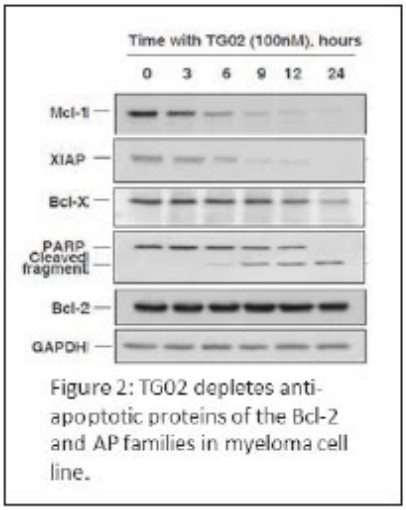
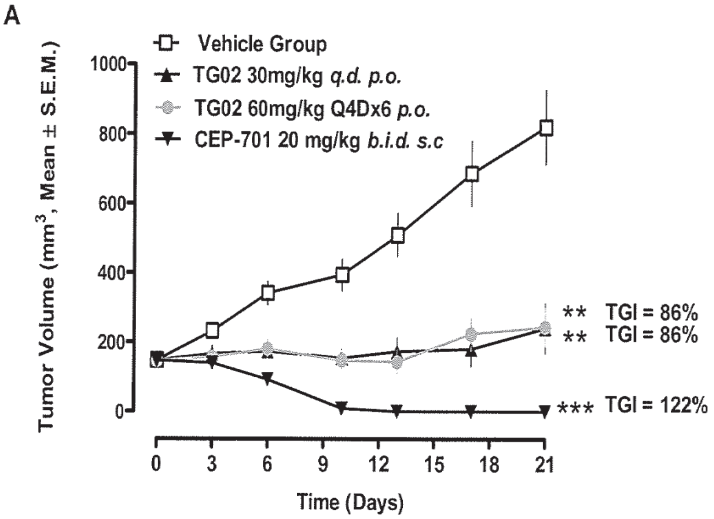


Figure 2: TG02 depletes anti-apoptotic proteins of the Bcl-2 and AP families in myeloma cell line.

An in vivo efficacy study was performed to determine the effects of two dosing schedules on efficacy using the MV4-11 xenograft model. Mice were dosed with TG02 either at 30 mg/kg daily for 3 weeks (for a total weekly dose of 210 mg/kg) or 60 mg/kg every 4 days for 6 doses (for a total weekly dose of 120 mg/kg). Figure 2 demonstrates that the twice weekly schedule had equivalent efficacy to the daily schedule even with a lower overall dose per week. When these schedules were compared in other tumor models, equivalent or superior efficacy was also demonstrated on the twice weekly schedule. While both

schedules were active, twice weekly dosing was generally better tolerated and therapeutically superior in several models. Therefore, this dosing regimen was used going forward and is currently used in clinical studies.

Figure 2: Efficacy of TG02 in MV4-11 tumor xenografts



1.3.3.2 Rationale for Schedule and Dose by Group

Group A

Schedule: to maximize synergy with RT, TG02 will be taken twice a week during the 3-week RT treatment. A 7-day break will be given from both TG02 and RT prior to starting maintenance therapy with TG02. During maintenance therapy, TG02 will be dosed twice weekly for 4 weeks of a 28-day schedule.

Original starting dose: In a previous Multiple Myeloma study, single agent TG02 was dosed at 150 mg and 200 mg on the BIW schedule. At the highest dose evaluated, 200 mg, no dose limiting toxicities occurred and TG02 was well tolerated. Additionally, TG02 was dosed at 150 mg to 300 mg in combination with carfilzomib in multiple myeloma patients. The protocol-defined MTD of TG02 in combination with carfilzomib was 250 mg. RT is a new combination agent with TG02, therefore the original starting dose for TG02 in 1608-BTG study in combination with RT was 200 mg.

Adjusted starting dose: In the current study, in Group C, 24 patients were enrolled and treated with single agent TG02 (6 pts at 250 mg and 18 pts at 200 mg). The frequency of some AEs, specifically Grade 3 or 4 neutropnia and Grade 3 or 4 liver enzyme elevations, was higher than previously observed in the previous multiple myeloma studies with TG02. An Independent Data Monitoring Committee (IDMC) reviewed the data for the first 24 patients of Group C. The IDMC made a recommendation to change the dosing cohorts for Group A. We agreed with the recommendation and incorporated these in the amendment to protocol version 4.0.

Therefore, a new dosing cohort of 100 mg TG02 is being added for Group A. Patients being enrolled to this study will start in this cohort. If the safety profile in that cohort is acceptable (i.e., meets the criteria described in Section 5.2.1, the dose will be escalated to the next cohort, 150 mg TG02.

Group B

Schedule: preclinical data demonstrated that TG02 reduces the expression of anti-apoptotic proteins and synergizes with TMZ. Additionally, better anti-glioma effects were observed with pretreatment of TG02 followed by combination treatment with TG02 and TMZ. Therefore, two doses of TG02 (one week of

dosing) will be taken prior to combination with TMZ in each cycle, with the rationale of depleting anti-apoptotic proteins in human tumors in vivo, too. Because TG02 and TMZ may have overlapping toxicities, TG02 will not be dosed on weeks 2 and 3 of each cycle to allow patients a recovery period prior to the next course of treatment.

Original starting dose: as described above, the MTD of TG02 in combination with carfilzomib was 250 mg. TMZ is a new combination agent with TG02. Therefore, the original starting dose for TG02 in combination with TMZ was 200 mg, one dose level below the MTD from the Multiple Myeloma study combining TG02 with carfilzomib.

Adjusted starting dose: As described above, an IDMC reviewed the data for the first 24 patients of Group C. The IDMC made a recommendation to change the dosing cohorts for Group B. We agreed with the recommendation and incorporated these in the amendment to protocol version 4.0.

Therefore, a new dosing cohort of 100 mg TG02 is being added for Group B. Patients being enrolled to this study will start in this cohort. If the safety profile in that cohort is acceptable (i.e., meets the criteria described in Section 5.2.1, the dose will be escalated to the next cohort, 150 mg TG02.

Group C

Schedule: TG02 will be dosed twice a week for 4 weeks of a 28-day schedule.

Original starting dose: as described above, the MTD of TG02 in combination with carfilzomib was 250 mg. Therefore, single agent TG02 was initially dosed at 250 mg in this group.

Adjusted starting dose: In Group C, 24 patients were enrolled and treated with single agent TG02. The frequency and severity of neutropenia in the first 6 patients was higher than expected and the starting dose was reduced to 200 mg. Eighteen (18) patients were enrolled and treated at 200 mg. The frequency of some AEs, specifically Grade 3 or 4 neutroepnia and Grade 3 or 4 liver enzyme elevations, was still higher than previously observed in the multiple myeloma studies with TG02. An Independent Data Monitoring Committee (IDMC) reviewed the data for the first 24 patients of Group C. The IDMC made a recommendation to change the starting dose for patients in Group C. We agree with the recommendation and are incorporating it in this amendment to protocol v 4.0.

Therefore, the new starting dose for TG02 in Group C is 150 mg.

Standard supportive care measures to be employed in this study are outlined in section 5.6. A detailed grid is provided to aid physicians in the management of potential toxicities of TG02 (see section 5.5.3).

1.3.3.3 Rationale for Pharmacokinetics (Group C only)

Pharmacokinetics for TG02 have been assessed in acute leukemia and multiple myeloma patients in studies conducted in the United States. In these acute leukemia and multiple myeloma studies, PK analysis was conducted on a total of 12 patients (6 from each study) who were administered single agent TG02 at a dose of 150 mg on a twice weekly schedule. Moderate variability was observed in that data; this may be due to the small number of patients. PK analysis on an additional 12 patients will add to the database and provide a more robust assessment of the PK parameters.

We are adding PK sampling on an additional 12 patients, treated with single agent TG02 at a dose of 150 mg on a twice weekly schedule, to this protocol for GBM patients to compare the PK parameters for TG02 across different patient groups.

The following pharmacokinetic parameters will be calculated:

Maximum plasma concentration (Cmax)

Time to maximum plasma concentration (Tmax) and T1/2

Area under the plasma concentration time curve to the last measurable concentration (AUC0-t)

This data will be used to monitor plasma concentrations of TG02 and correlate to toxicity, clinical response and pharmacodynamic endpoints.

PK analysis will only be performed on the first 12 patients in group C that consent for the PK portion of the study. This sampling will be optional to the patients enrolled in group C and documented in the informed consent.

1.3.3.4 Risk/benefit assessment of COVID-19

The risk/benefit assessment related to the COVID-19 is included in the Appendix L.

2 Objectives of the trial

2.1 General objectives

2.1.1 Main objective

Groups A and B: safety and tolerability

Group A: Establish the recommended phase II dose of TG02 in combination with radiotherapy (RT) to be used in further trials exploring the antitumor activity of TG02 in elderly patients with IDH1^{R132H}-non-mutant anaplastic astrocytoma or IDH1^{R132H}-non-mutant glioblastoma and unmethylated MGMT promoter.

Group B: Establish the recommended phase II dose of TG02 in combination with temozolomide (TMZ) to be used in further trials exploring the antitumor activity of TG02 in elderly patients with IDH1^{R132H}-non-mutant anaplastic astrocytoma or IDH1^{R132H}-non-mutant glioblastoma and methylated MGMT promoter.

Group C: explore single agent activity

Investigate if single agent TG02 demonstrates sufficient antitumor activity in IDH1^{R132H}-non-mutant anaplastic astrocytoma or IDH1^{R132H}-non-mutant glioblastoma at first relapse after initial treatment with TMZ/RT - TMZ to justify further development.

2.1.2 Secondary objectives

Groups A and B:

- Investigate quality of life
- Correlate the frailty of elderly patients with safety, tolerability and outcome

Group C:

- Evaluate Pharmakokinetic studies.

In all groups:

- Investigate the efficacy, safety and tolerability of TG02
- Correlate the Neurologic Assessment in Neuro-Oncology (NANO) scale assessments with outcome assessed by RANO criteria
- Correlate molecular markers with efficacy data

2.2 Endpoints

2.2.1 Primary endpoints

Groups A and B:

Primary endpoints in Groups A and B are the determination of the Maximum Tolerated Dose (MTD) and the recommended phase II combination dose. This part is a two-cohort study of the combination of TG02 with hypofractionated RT in patients with tumors with an unmethylated MGMT promoter, or with TMZ in patients with tumors with a methylated MGMT promoter. Up to two dose levels of TG02 will be explored in each group.

Group C:

Progression-free survival at 6 months (PFS-6) defined by RANO criteria.

2.2.2 Secondary endpoints

Groups A and B:

- progression-free survival at 6 months (PFS-6)
- median progression-free survival (PFS)
- median overall survival (OS)
- OS at 9 months (OS-9)
- for patients with measurable disease after debulking: best overall response distribution (BOR), objective response rate (PR+CR), complete response rate and duration of response (DOR)
- quality of life (QOL)

Group C:

- median progression-free survival (PFS)
- median overall survival (OS)
- OS at 9 months (OS-9), 1 year (OS-12)
- for non-surgical patients or patients with surgery for recurrence, but measurable disease thereafter: best overall response distribution (BOR), objective (PR+CR) rate, complete response rate and duration of response (DOR)
- success rate defined as rate of patients achieving either confirmed CR or PR (> 4 weeks) or free of progression at 6 months
- neurological progression-free survival (NPFS) based on the Neurologic Assessment in Neuro-Oncology (NANO): median NPFS and NPFS at 6 months (NPFS-6).
- clinical deterioration free survival (CDFS).
- safety profile (CTCAE)
  pharmacokinetic profile of TG02: pre-dose, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours after the intake of TG02

In all groups:

- Correlation of molecular markers including MYC, MCL-1, CDK9 and CDK5 protein levels, and potentially others, with measures of clinical benefit.

3 Patient selection criteria

Patients must fulfill all of the following criteria to be eligible for registration in the study:

3.1 Inclusion criteria

Specifics for groups A and B

Patients may be registered at any time after surgery.

- Newly diagnosed glioblastoma or anaplastic astrocytoma, IDH1^{R132H}-non-mutant by immunohistochemistry locally assessed, with FFPE tissue available for central *MGMT* testing and optional biomarker studies (treatment allocation will be performed based on centrally assessed *MGMT* result)
- Tumor debulking surgery, including partial resection
- Age > 65 and considered non-eligible for combination therapy (TMZ/RT→TMZ) in Investigator's opinion as outlined in chapter 1 and in the current EANO guideline (Ref. 35)
- Brain MRI within 14 days before the first dose of TG02

Specifics for group C

- IDH1^{R132H}-non-mutant glioblastoma or anaplastic astrocytoma at first relapse with tissue available from first surgery. [Per 2016 WHO classification, in patients older than 55 years of age at diagnosis with a histological diagnosis of glioblastoma, without a pre-existing lower grade glioma and with non-midline tumor location, immunohistochemical negativity for IDH1^{R132H} suffices for classification as glioblastoma. In all other instances of diffuse gliomas, lack of IDH1^{R132H} immunopositivity should be followed by IDH1 and IDH2 sequencing to detect or exclude other less common IDH mutations (Ref. 16, Ref. 35).]
- Brain MRI at the time of progression and not more than 14 days before the first dose of TG02 and availability of last brain MRI done previously to the MRI done at progression and that was used to confirm/diagnose progression for upload to the EORTC Imaging Platform for post-hoc central review of progression
- Diagnosis of recurrence more than 3 months after the end of RT for initial treatment
- Intention to be treated with standard TMZ/RT→TMZ for initial treatment (at least one dose of TMZ administered; RT alone or chemotherapy alone as initial treatment are not permitted)
- Patient may have been operated for recurrence. If operated:
    - surgery completed at least 2 weeks before initiation of TG02 and patients should have fully recovered as assessed by investigator. Criteria for full recovery include absence of active post-operative infection, recovery from medical complications (CTCAE grade 0 and 1 acceptable), and capacity for adequate fluid and food intake
    - residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence
    - a post-surgery MRI should be available within 72 hours; the post-surgery MRI can be used as baseline if performed within 2 weeks prior to first dose of TG02. If not, a baseline MRI has to be done within 2 weeks prior to first dose of TG02.
- For non-operated patients: recurrent disease must be at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on a MRI scan done within 2 weeks prior to first dose of TG02.
- Age ≥ 18 years
- Negative serum or urine pregnancy test within 72 hours prior to the first dose for women of childbearing potential (WOCBP). Nursing must be discontinued at least 1 hour before first dose.

All groups

- Karnofsky Performance Score (KPS) of 60-100
- Recovered from effects of debulking surgery, postoperative infection and other complications of surgery (if any) (CTCAE grade 0 and 1 acceptable)
- Adequate bone marrow, renal and hepatic function within the following ranges within 7 days before the first dose of TG02:
  - WBC ≥ 3 $x10^9$/L
  - ANC ≥ 1.5$x10^9$/L
  - Platelet count of ≥ 100 $x10^9$/L independent of transfusion
  - Hemoglobin ≥ 10 g/dl or ≥ 6.2 mmol/L
  - Bilirubin ≤ 1.5 × ULN
  - ALT and AST ≤ 2.5 × ULN
  - Cockcroft–Gault calculated or measured creatinine clearance of ≥ 30 mL/min
- Life expectancy > 8 weeks
- For men of reproductive potential and WOCBP (refer to Appendix K for definition), highly effective contraception must be used throughout the study and for 6 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly (see Appendix K).
- Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments
- Ability to take oral medication
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Groups A and B only

- Central assessment of MGMT testing will be conducted after registration and before enrollment. Please see sections 7.1.9 and 13.1.2 for further information.

3.2 Exclusion criteria

Specifics for groups A and B

- Prior RT with overlap of radiation fields with the planned RT in this study (Group A)
- Prior therapy for glioblastoma or anaplastic astrocytoma before surgery

S*pecifics for group C*

- Discontinuation of TMZ for toxicity during first-line treatment
- RT or stereotactic radiosurgery is not allowed for the treatment of first recurrence prior to enrollment in this study

All groups

- Use of enzyme-inducing anti-epileptic drugs (EI-AED) within 7 days prior to the first dose of TG02
- History of ventricular arrhythmia or symptomatic conduction abnormality in past 12 months prior to registration

- Congestive heart failure (New York Heart Association Class III to IV, see Appendix C), symptomatic ischemia, uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to enrollment
- 12-lead ECG with a prolonged QTc interval (males: > 450 ms; females: > 470 ms) as calculated by the Fridericia correction formula despite balancing of electrolytes at registration and/or discontinuing any drugs (for a time period corresponding to 5 half-lives) known to prolong QTc interval
- Known contraindication to imaging tracer or any product of contrast media
- MRI contraindications
- Known hypersensitivity to the active substance or any of the excipients in the TG02 formulation, dacarbazin and TMZ
- Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes, hypertension, coronary artery disease) that, in the opinion of the Investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study
- Known human immunodeficiency virus infection or acquired immune deficiency syndrome
- Previous other malignancies, except for any previous malignancy which was treated with curative intent more than 3 years prior to enrollment, or adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix

4 Trial Design

This is a three parallel group Phase Ib, open-labeled, non-randomized, multicenter study. Each group is described below and outlined in the diagram. All three groups will enroll independently.

4.1 Group A

Newly-diagnosed, elderly patients with $IDH1^{R132H}$-non mutant and MGMT promoter-unmethylated anaplastic astrocytoma or glioblastoma will receive TG02 orally twice weekly in combination with radiation therapy (RT). Elderly patients are ≥ 65 years AND non-eligible for TMZ/RT → TMZ therapy.

TG02 will be administered on days 1, 4, 8, 11, 15 and 18 of the first 28-day cycle (Appendix H). Standard involved-field hypofractionated RT will be administered at 40 Gy in 15 fractions of 2.66 Gy for 3 weeks (days 1-21).

After completing combination therapy, patients will receive maintenance cycles of single agent TG02 until disease progression or for up to 12 cycles. TG02 will be administered on days 1, 4, 8, 11, 15, 18, 22 and 25 of each 28-day maintenance cycle. Upon completion of 12 cycles without disease progression or unacceptable toxicity, patients may continue on TG02 as determined by the Investigator.

For Group A, there will be a dose escalation (see section 5.2.1) and an expansion phase in the study. Additional patients will be enrolled at MTD up to a total of 24 evaluable patients in Group A.

Dose escalation for group A will proceed independently from the dose escalation in group B.

4.2 Group B

Newly-diagnosed, elderly patients (see section above for age specification) with $IDH1^{R132H}$-non mutant and MGMT promoter-methylated tumors will receive TG02 orally twice weekly with temozolomide (TMZ). TG02 will be taken on days -7, -4, 1, 4, 22 and 25 in cycle 1. As of cycle 2, TG02 is given on days 1, 4, 22 and 25 of a 28-day cycle (Appendix H). TMZ will be given in the standard 28-day cycle regimen (200 mg/m^2) for 5 days q 28 starting at Day 1. Combination therapy will continue until disease progression or

for up to 12 cycles. Upon completion of 12 cycles without disease progression or unacceptable toxicity, patients may continue on TG02 and TMZ or single agent TG02 as determined by the Investigator.

For Group B, there will be a dose escalation (see section 5.2.1) and an expansion phase in the study. Additional patients will be enrolled at MTD up to a total of 12 evaluable patients in Group B.

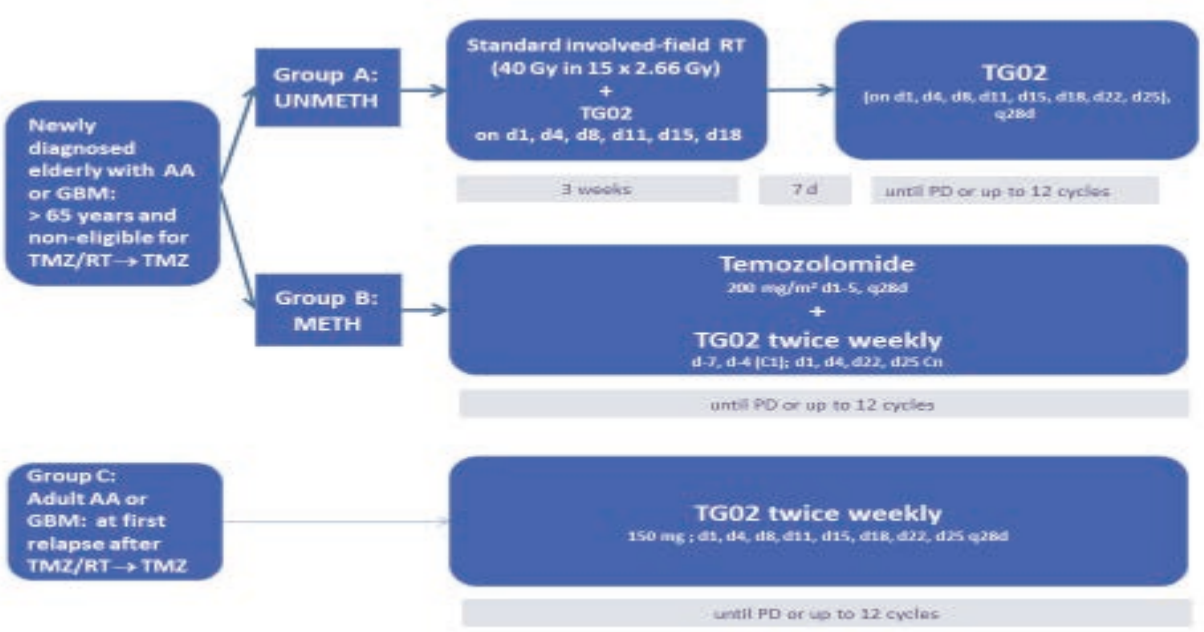
Dose escalation for group B will proceed independently from the dose escalation in group A.

4.3 Group C

AA and GBM patients at first relapse after TMZ/RT → TMZ therapy will receive single agent TG02 at 150 mg orally twice weekly. TG02 will be administered on days 1, 4, 8, 11, 15, 18, 22 and 25 of each 28-day cycle (Appendix H). Single agent therapy will continue until disease progression or for up to 12 cycles. Upon completion of 12 cycles without disease progression or unacceptable toxicity, patients may continue on TG02 as determined by the Investigator.

The lowest permitted dose will be 100 mg TG02 twice weekly.

An A'Hern one-stage design will be applied. Forty-five (45) eligible patients who started treatment will be evaluated for PFS at 6 months.



AA-Anaplastic Astrocytoma	d-Days
GBM-Glioblastoma	Q28q-cycle of 28 days
TMZ-Temozolomide	PD-progressive disease
RT-Radiation Therapy	

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Drug information

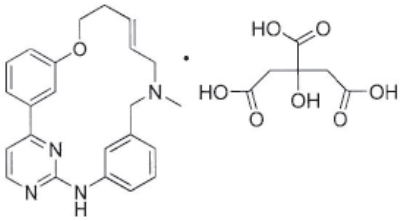
5.1.1 General information

5.1.1.1 Study Treatment

Description of TG02 Citrate

The chemical name for TG02 citrate is (16E)-14-Methyl-20-oxa-5,7,14,26-tetraaza-tetracyclol[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene − citric acid. The molecular formula of TG02 citrate is $C_{23}H_{24}N_4O$. $C_6H_8O_7$ and it has a molecular weight of 564.58 (TG02 citrate salt) and 372.46 (TG02 base).

The structure is as follows:



Description of TG02 citrate capsules

Trade name	Not applicable
Manufacturer	Adastra Pharmaceuticals, Inc.
Strength (mg)	50, 150
Dosing instructions	Take appropriate number of capsules with approximately 250 mL water while fasting (i.e., at least 1 hour before or 2 hours after a meal). Capsules should not be crushed or broken for administration. For groups A and B, capsules should be taken approximately 1 hour before administration of TMZ or RT.
Route	Oral
Dosage form	Capsule

TG02 citrate capsules

TG02 citrate capsules will be provided as immediate release capsules for oral administration. Capsule strengths are expressed as mg. The capsule strength is based on the free-base equivalents of TG02 (e.g., TG02-100 citrate capsules contain 151.5 mg of TG02 citrate equivalent to 100 mg of TG02). The product strength are distinguished by capsule size and color (TG02-50 is orange and TG02-150 is light blue).

TG02 is formulated as a powder blend with silicified microcrystalline cellulose (NF), hypromellose 2910 (USP), crospovidone (NF) and magnesium stearate (NF) and filled into hard gelatin capsules. TG02 has been shown to be compatible with these excipients. The excipients are routinely used in oral drug products.

5.1.2 Drug supply

Drug supplies and re-supplies will be provided free of charge by Tragara as long as patients are on protocol treatment. Guidelines for drug resupply will be provided in a separate document.

5.1.3 Packaging, dispensing and storage

TG02 citrate capsules are provided in HDPE bottles as follows:

	Strength (mg)	
	50 mg (TG02-50)	**150 mg (TG02-150)**
Capsules per Bottle	8	4

For instructions regarding drug inventory, handling, storage, accountability and disposal, please refer to the IMP management guidelines (provided as a separate document) for TG02.

TG02 will be labeled according to the current regulatory requirements.

5.1.4 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC Headquarters.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.2 Initial dose and schedule

5.2.1 Study Drug Administration

Patients are registered to the study when they sign the PISIC. For groups A and B, patients must have a central assessment of MGMT testing after registration. Once MGMT status is confirmed, the site is informed by a notification e-mail, and proceeds to the next step to enroll the patient into either group A or group B. Please see section 13.1.2 for detailed information.

Dosing calendars can be found in Appendix H.

5.2.1.1 Group A

Patients with MGMT promoter-unmethylated AA or GBM will receive TG02 orally twice weekly in combination with radiation therapy (RT).

TG02 and RT can start on the day of enrollment but no more than 7 days after enrollment. TG02 will be administered on days 1, 4, 8, 11, 15 and 18. Standard involved-field hypofractionated RT will be administered at 39.9 Gy in 15 fractions of 2.66 Gy for 3 weeks (days 1-21).

Seven days after completing combination therapy, patients will receive maintenance cycles of single agent TG02. TG02 will be administered on days 1, 4, 8, 11, 15, 18, 22 and 25 of each 28-day maintenance cycle.

DOSE ESCALATION

The dose escalation scheme for TG02 is provided below. Three patients will be enrolled at 100 mg.

- If no patient in this cohort of 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg.
- If 1 patient in the cohort of 3 patients experiences a DLT, 3 additional patients will be enrolled at 100 mg. If none of the additional 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg.
- If the DLT criteria are not met (i.e., no patients with DLT out of 3 patients or ≤1 DLT out of 6 patients) at 150 mg, then, 150 mg TG02 will be declared the MTD for expansion.
- If > 1 out of 3 patients or ≥ 2 out of 6 patients experiences a DLT at 150 mg, dose escalation will not proceed and 100 mg will be considered the maximum MTD.
- If > 1 out of 3 patients or ≥ 2 out of 6 patients experiences a DLT at 100 mg, the arm will be closed

Patients who have not experienced any DLTs at the end of their first cycle will continue at the same TG02 dose for the subsequent cycles, unless they experience a severe side effect needing a dose reduction or delay (see section 5.5 for specific instructions).

TG02 Citrate Capsules Dose Escalation Scheme

Dose Level (Cohort)	**Dose (mg)**	**# Units/ Capsule Strength (mg)**	
		50	**150**
0	100	2	0
1	150	0	1

The Dose-Limiting Toxicity (DLT) for group A will be defined as any of the following adverse events occurring during cycle 1 that are considered clinically significant and there is a reasonable possibility that the AE is related to the combination treatment by the clinical investigator:

- Any non-hematological grade III–IV toxicity according to CTCAE, Version 5.0 with the exclusion of alopecia and asymptomatic or reversible laboratory abnormalities which can be rapidly controlled with appropriate measures. This acute toxicity must be declared as possibly related by the clinical investigator in order to be taken into account in the decision rule.
- An absolute neutrophil count < $0.5x10^9$/L lasting for ≥ 7 days
- Febrile neutropenia defined as an absolute neutrophil count < $0.5x10^9$/L and fever of at least 38.5°C
- Thrombocytopenia grade III with bleeding or any grade IV according to CTCAE, Version 5.0

- Nausea, vomiting or diarrhea grade III-IV not controlled after 48 h of maximal antiemetic or antidiarrheal treatment
- Any toxicity not qualifying for DLT but which does not allow intake of 75% of intended dose intensity of TG02 or of RT

EXPANSION

After dose escalation is completed, additional patients will be enrolled at MTD up to a total of 24 evaluable patients in Group A. Expansion at the predetermined MTD will be stopped if 2 or more of the first 6 patients, or 33% or more of the patients thereafter, experience a DLT. The expansion cohort will be fully enrolled at the next lower dose level. If there are again 2 DLT in the first 6 patients, expansion will be stopped in that arm.

5.2.1.2 Group B

Patients with MGMT promoter-methylated AA or GBM will receive TG02 orally twice weekly in combination TMZ.

TG02 can start on the day of enrollment but no more than 7 days after enrollment. TG02 will be taken on days -7, -4, 1, 4, 22 and 25 of a 28-day schedule. TMZ will be given in the standard 28-day cycle regimen (200 mg/m^2) for 5 days q 28d.

DOSE ESCALATION

The dose escalation scheme for TG02 is provided below.

Three patients will be enrolled at 100 mg.

- If no patient in this cohort of 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg.
- If 1 patient in the cohort of 3 patients experiences a DLT, 3 additional patients will be enrolled at 100 mg. If none of the additional 3 patients experiences a DLT, the dose will be escalated and 3 patients enrolled at 150 mg.
- If the DLT criteria are not met (i.e., no patients with DLT out of 3 patients or ≤1 DLT out of 6 patients) at 150 mg, then, the data for the 100mg and 150 mg will be reviewed by an IDMC.
- If > 1 out of 3 patients or ≥ 2 out of 6 patients experiences a DLT at 150 mg, dose escalation will not proceed and 100 mg will be considered the maximum MTD.
- If > 1 out of 3 patients or ≥ 2 out of 6 patients experiences a DLT at 100 mg, the arm will be closed

Patients who have not experienced any DLTs at the end of their first cycle will continue at the same TG02 dose for the subsequent cycles, unless they experience a severe side effect needing a dose reduction or delay (see section 5.5 for specific instructions).

- TG02 Citrate Capsules Dose Escalation Scheme

Dose Level (Cohort)	**Dose (mg)**	**# Units/ Capsule Strength (mg)**	
		50	**150**
0	100	2	0
1	150	0	1

The Dose-Limiting Toxicity (DLT) for group B will be defined as any of the following adverse events occurring during cycle 1 that are considered clinically significant and there is a reasonable possibility that the AE is related to the combination treatment by the clinical investigator:

- Any non-hematological grade III–IV toxicity according to CTCAE, Version 5.0 with the exclusion of alopecia and asymptomatic or reversible laboratory abnormalities which can be rapidly controlled with appropriate measures. This acute toxicity must be declared as possibly related by the clinical investigator in order to be taken into account in the decision rule.
- An absolute neutrophil count < $0.5x10^9$/L lasting for ≥ 7 days
- Febrile neutropenia defined as an absolute neutrophil count < $0.5x10^9$/L and fever of at least 38.5°C
- Thrombocytopenia grade III with bleeding or any grade IV according to CTCAE, Version 5.0
- Nausea, vomiting or diarrhea grade III-IV not controlled after 48 h of maximal antiemetic or antidiarrheal treatment
- Any toxicity not qualifying for DLT but which does not allow intake of 75% of intended dose intensity of TG02 or of TMZ

EXPANSION

After dose escalation is completed, additional patients will be enrolled at MTD up to a total of 12 evaluable patients in Group B. Expansion at the predetermined MTD will be stopped if 2 or more of the first 6 patients, or 33% or more of the patients thereafter, experience a DLT. The expansion cohort will be fully enrolled at the next lower dose level. If there are again 2 DLT in the first 6 patients, expansion will be stopped in that arm.

EXPECTED TOXICITIES OF THE COMBINATION

Expected overlapping toxicities for TG02 and TMZ are gastrointestinal, hematological and hepatotoxicity. TG02 is being evaluated in combination with TMZ in a dose escalation study being conducted by the National Cancer Institute. In this study, TG02 has been dosed at either 200 or 250 mg on Day -3 prior to Cycle 1 and on Days 1, 12, 15, and 26 of each cycle. TMZ is dosed at 125 mg/m^2 7 days on and 7 days off (dosing days 1-7 and 15-21). Twelve (12) patients have been treated to date. The adverse events occurring in >15% of patients are provided in the following table (Ref. 57).

Description of AE	Adverse Events N (%)	
	All grades	Grades 3 and 4
ALT elevation	10 (83)	4 (33)
Leukopenia	10 (83)	4 (33)
Diarrhea	9 (75)	1 (8)
Lymphopenia	9 (75)	6 (50)
Fatigue	8 (67)	
Nausea	7 (58)	
AST elevation	6 (50)	
Neutropenia	6 (50)	5 (41)
Thrombocytopenia	6 (50)	
Vomiting	4 (33)	1 (8)

Description of AE	Adverse Events N (%)	
	All grades	Grades 3 and 4
Constipation	3 (25)	
Anemia	3 (25)	
Headache	2 (17)	

5.2.1.3 Group C

Patients will receive TG02 orally twice weekly at 150 mg on days 1, 4, 8, 11, 15, 18, 22 and 25. TG02 can start up to 7 days after registration/enrollment of the patient. The decision process for dose reductions is outlined in detail in section 5.5.3. The starting dose of TG02 will be reduced to 100 mg if 2 of the first 6 patients or 33% or more of the patients thereafter come off study treatment for any reason other than progression during the first three months. There will be no dose reduction below 100 mg and enrolment in arm C will be stopped.

5.2.1.4 Instructions for Study Drug Administration

TG02:

For all groups, TG02 will be taken as follows:

- TG02 citrate capsules should be swallowed whole with approximately 250 mL (one glass) of water while fasting, i.e., at least 1 hour before or 2 hours after a meal.
- TG02 should be taken approximately at the same time on each dosing day. For groups A and B, capsules should be taken approximately 1 hour before administration of TMZ or RT.
- A patient diary card for TG02 and TMZ should be given to and completed by patients
- Missed doses of TG02 and TMZ will be noted in the patient diary card and will not be replaced.
- Patients who vomit may be redosed with TG02 only if the TG02 capsules are still intact and visible in the vomitus and after appropriate antiemetic therapy has begun.
- Treatment compliance will be verified at each monthly visit using the study drug diary completed by patients and by a capsule count.

PROPHYLAXIS:

Nausea, vomiting and diarrhea are very commonly associated with TG02. Prophylaxis for nausea, vomiting and diarrhea are required. Please see section 5.6.2 for prophylaxis instructions.

PHOTOTOXICITY:

At present it is not yet established whether TG02 alone or in combination with other drugs might cause phototoxicity.

Nevertheless, patients should be advised to minimize UV light exposure for the duration of the TG02 use and to use sun protecting creams.

RT: For group A, see Section 5.7 for RT administration.

TMZ: For group B, TMZ will be administered at 200 mg/m² once daily for 5 days followed by 23 days without treatment.

Method of administration: as per local practice.

- Temozolomide hard capsules should be administered in the fasting state.
- The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

- Nausea and vomiting are very commonly associated with TMZ. Anti-emetic therapy should be administered as per local practice.
- If vomiting occurs after the dose is administered, a second dose should not be administered that day.

Detailed guidelines for the management of toxicity are provided in the protocol in section 5.5 for TG02 and RT and section 5.7.8 for RT.

5.3 Treatment duration

Group A: combination treatment (TG02 and RT) will continue for 3 weeks. Maintenance cycles (TG02 single agent) will continue until disease progression or until the patient completes 12 cycles therapy.

Group B: combination treatment (TG02 and TMZ) will continue until disease progression or until the patient completes 12 cycles of therapy.

Group C: TG02 treatment will continue until disease progression or until the patients completes 12 cycles of therapy.

Treatment with TG02 may be continued beyond 12 cycles if there is no relevant toxicity, no progressive disease, and if the treating physician considers this to be of clinical benefit. The disease status will be regularly assessed according to the protocol during this period to evaluate the duration of response.

5.4 Withdrawal criteria

Patients discontinuing study therapy including RT in Group A and TMZ in Group B in the absence of progression should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient.

After progression, treatment will be left to the discretion of the treating physician. Any further anti-cancer therapy will not be considered as part of the protocol treatment.

The principal investigator should discontinue study treatment for a patient in the event of:

- Progressive disease
- Intercurrent illness
- Unacceptable toxicity
- Protocol violation, loss to follow-up, patient significant non-compliance
- Pregnancy
- Study treatment interruptions, **i.e., more than 28 days delay of TG02**
- Administrative or other reasons

An end of study visit should be performed, and follow-up for survival collected, whenever feasible.

Patients have the right to withdraw from the study at any time for any reason

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Please note that upon patient withdrawal from the study for any reason other than withdrawal of consent, end of study visit should still be performed, and follow-up for survival collected, whenever feasible.

Data collection and follow-up of patients after withdrawal of consent for study treatment

In the case that the patient decides to prematurely discontinue study treatment, the patient must be followed for disease assessments and survival follow-up, unless the patient decides to withdraw consent for the collection of these data. In the case that the patient withdraws consent, the patient must be asked if can still be contacted for survival follow-up only. The outcome of these discussions should be documented in both the medical records and in the eCRF.

5.5 Dose modifications following adverse events

5.5.1 RT Delays

RT-related toxicities should be managed as per local practice. RT dose modifications are not allowed per se, but information on managing delays is given in the radiotherapy section (section 5.7.8). In case of any AEs leading to RT interruption or delays not considered related to TG02, TG02 should continue as scheduled if medical condition allows it.

During dose escalation, an interruption of RT for >25% of the planned total dose in Cycle 1 will be considered a DLT (see section 5.2.1).

5.5.2 TMZ

TMZ-related toxicities should be managed as per local practice. Dose modifications for TMZ are allowed and should follow the standard of care at the institution except as instructed in sections 5.5.3.2, 5.5.3.3 and 5.5.3.4 below. In case of any AEs leading to TMZ interruption or delays not considered related to TG02, TG02 should continue as scheduled if medical condition allows it. If TMZ is interrupted due to toxicity, upon its resolution, TMZ should be restarted only at the next cycle.

During dose escalation, an interruption of TMZ for >25% of the planned total dose in Cycle 1 will be considered a DLT (see section 5.2.1).

5.5.3 TG02

5.5.3.1 For all groups

The following dose levels of TG02 will/can be used:

- 150 mg (groups A,B,C)
- 100 mg (groups A,B, C)

TG02 dose should not be reduced below 100 mg. If a patient's initial or current dose is 100 mg and the patient experiences a toxicity requiring TG02 dose reduction as described in the tables below, the patient should be discontinued from study treatment.

TG02 should not be skipped for more than 28 days. If TG02 cannot be re-introduced within 28 days, the patient should be discontinued from the study treatment.

In case of uncertainty regarding dose modifications described in the tables below, please contact the Sponsor.

In all cases, appropriate symptomatic treatment should be considered to manage the AE.

5.5.3.2 Group A

5.5.3.2.1 Dose escalation phase

Cycle 1: no TG02 dose reductions are allowed in Cycle 1, except if a patient experiences a DLT.

Skipped doses for TG02 are allowed. A “skipped dose” for TG02 when RT is not interrupted means that one or more single doses will be omitted and not replaced, in order not to change the temporal relationship with RT.

For example, if TG02 is planned on days 1, 4, 8 but day 4 has to be omitted, TG02 can be restarted on day 8 if the AE is sufficiently resolved: TG02 is always restarted on a scheduled dose day. Skipping TG02 for >25% of the planned total dose in Cycle 1 will be considered a DLT (see section 5.2.1).

Toxicities possibly related to TG02 should be managed as outlined in the tables below.

Cycles 2+: TG02 dose reductions and skipped dose(s) can be made for adverse events as described in the tables below.

5.5.3.2.2 Expansion phase

TG02 dose reductions and skipped dose(s) are allowed in any cycle. A “skipped dose” for TG02 means that one or more single doses will be omitted and not replaced, in order not to change the temporal relationship.

For example, if TG02 is planned on days 1, 4, 8 but day 4 has to be omitted, TG02 can be restarted on day 8 if the AE is sufficiently resolved: TG02 is always restarted on a scheduled dose day.

Toxicities possibly related to TG02 should be managed as outlined in the tables below.

NOTE: * in below tables: There will be no dose reductions below 100 mg TG02 BIW

Group A: TG02-related Hematological Adverse Events

Adverse Event	Action to be taken with TG02
Thrombocytopenia	
First occurrence of grade 3 without bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at initial dose.
Recurrence of the same grade 3 event without bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose*If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose *If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
First occurrence of grade 3 with bleeding or grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *
Recurrence of the same grade 3 event with bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose * If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.

Adverse Event	Action to be taken with TG02
Recurrence of the same grade 4 event	Discontinue TG02.
Anemia	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at initial dose.
Recurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Recurrence of the same grade 4 event	Discontinue TG02.
Neutropenia	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *
Recurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose * If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose * . If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
Grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *.
Recurrence of the same grade 4 event	Discontinue TG02.
Febrile Neutropenia	
Grade 3 or 4 event	Skip one or more doses of TG02 until fever is resolved and neutropenia is improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *

Adverse Event	Action to be taken with TG02
Recurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose *. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Recurrence of the same grade 4 event	Discontinue TG02.

Group A: TG02-related Non-hematologic Adverse Events

Adverse Event	Action to be taken with TG02
Nausea/ Vomiting	
Grade 1 or 2 event	Manage with moderate anti-emetic treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 nausea/ vomiting that do not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced *
Grade 3 nausea Grade 3 or 4 vomiting	Skip one or more doses of TG02 until improved to grade ≤ 1. If improved to grade ≤1 in <48 hours, re-introduce TG02 at the initial dose. If not improved to grade ≤1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose *. Continue prophylaxis and management with at least moderate anti-emetic treatment (see Section 5.6.2).
Diarrhea	
Grade 1 or 2 event	Manage with anti-diarrheal treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 diarrhea that does not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced *. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2).

Adverse Event	Action to be taken with TG02
Grade 3 or 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Physician should instruct patient regarding hydration. If improved to grade ≤1 in <48 hours, re-introduce TG02 at the initial dose. If not improved to grade ≤1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose *. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2)
Other non-hematologic events except alopecia and asymptomatic or reversible laboratory abnormalities	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at initial dose.
Second occurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at a reduced dose *. If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose *. If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
First occurrence of the same grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at a reduced dose*.
Second occurrence of the same grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.

5.5.3.3 Group B

5.5.3.3.1 Dose escalation phase

Cycle 1: no TG02 or TMZ dose reductions are allowed in Cycle 1 except if a patient experiences a DLT.

Skipped doses of TG02 are allowed. A "skipped dose" for TG02 when TMZ is not interrupted means that one or more single doses will be omitted and not replaced, in order not to change the temporal relationship with TMZ.

For example, if TG02 is planned on days 1, 4 and 22, but day 4 has to be omitted, TG02 can be restarted on day 22 if the AE is sufficiently resolved: TG02 is always restarted on a scheduled dose day.

Interruptions of TMZ are allowed.

Skipping TG02 or interrupting TMZ for >25% of the planned total dose in Cycle 1 will be considered a DLT (see section 5.5.1).

Toxicities possibly related to TG02 should be managed as outlined in the tables below. Toxicities of TMZ should be managed as outlined in the table below and per local practice, where noted.

Cycles 2+: TG02 dose reductions and skipped dose(s) can be made for adverse events as described in the tables below. TMZ dose reductions and interruptions can be made for adverse events as described in section 5.5.2 and the tables below.

5.5.3.3.2 Expansion phase

TG02 dose reductions and skipped dose(s) are allowed in any cycle as described in the tables below. A "skipped dose" for TG02 when TMZ is not interrupted means that one or more single doses will be omitted and not replaced, in order not to change the temporal relationship with TMZ.

For example, if TG02 is planned on days 1, 4 and 22, but day 4 has to be omitted, TG02 can be restarted on day 22 if the AE is sufficiently resolved: TG02 is always restarted on a scheduled dose day.

Toxicities possibly related to TG02 should be managed as outlined in the tables below. Toxicities of TMZ should be managed as outlined in the table below and per local practice, where noted.

In the absence of progressive disease, either TMZ or TG02 may be interrupted/ skipped or discontinued permanently while treatment with the other agent is continued. In all cases where TMZ has to be discontinued, patient can continue with TG02. Otherwise patient is considered off study and treating physician can consider other treatment such as RT.

5.5.3.3.3 TG02 or TMZ Hematological Adverse Events

The actions to be taken with TG02 or TMZ for hematological AEs in this study are based on these adverse event profiles. Hematological AEs should be managed as outlined in the table below and per local practice, where noted.

NOTE: * in below tables: There will be no dose reductions below 100 mg BIW

Group B: TG02-related Hematological Adverse Events

Adverse Event	Action to be taken with TG02/ TMZ
Thrombocytopenia	
Administration of TMZ or TG02 may induce thrombocytopenia. The profile of thrombocytopenia is different between TMZ and TG02. For TMZ, a nadir occurs around day 21. In a Phase 1b study of TG02 in combination with carfilzomib in multiple myeloma patients, 21% of patients administered TG02 at 250 mg bi-weekly experienced grade 3 or 4 thrombocytopenia. Onset was typically within the first week of administration and resolved within 72 hours after TG02 interruption. Attributing hematological and biochemical toxicity to TMZ versus TG02 may be challenging, This remains to be judged by the investigator, but guidance will be provided by the study chairs and Sponsor on an individual case-by-case basis.	
First occurrence of grade 3 event without bleeding	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤1. Re-introduce TG02 and TMZ at initial dose.

Adverse Event	Action to be taken with TG02/ TMZ
Recurrence of the same grade 3 event without bleeding	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤1. Re-introduce TG02 at a reduced dose * and TMZ at a reduced dose. If TG02/TMZ have been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02 or TMZ: • Discontinue TMZ. Continue TG02 at the same or a reduced dose * bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule. • Alternatively, discontinue TG02 and continue TMZ at a reduced dose If TG02 or TMZ has been re-introduced after a third event and the event recurs, discontinue TG02 and TMZ.
First occurrence of grade 3 with bleeding or grade 4 event occurring on Day -7 to Day -1 prior to Cycle 1 Day 1	Skip one or more doses of TG02 until improved to grade ≤ 1. If improved to grade ≤ 1 by Cycle 1 Day 1, initiate TMZ at initial dose and re-introduce TG02 at a reduced dose *.
Second occurrence of grade 3 event with bleeding or grade 4 event occurring on Day -7 to Day -1 of cycle	Skip one or more doses of TG02 until improved to grade ≤1. If improved to grade ≤ 1 by Cycle 1 Day 1, initiate TMZ at initial dose. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose *. If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
First occurrence of grade 3 event with bleeding or grade 4 event occurring on Day 1 to Day 7 of cycle	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TMZ: • If TMZ is re-introduced, re-introduce TMZ and TG02 at a reduced dose *. • If TMZ is discontinued, continue TG02 at the same or a reduced dose *bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule.
Second occurrence of grade 3 event with bleeding or grade 4 event occurring on day 1 to Day 7 of cycle	Skip one or more doses of TG02 and interrupt TMZ (if TMZ was re-introduced after the first event) until improved to grade ≤1. Re-introduce TG02 at a reduced dose*. Discontinue TMZ. If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose *. If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.

Adverse Event	Action to be taken with TG02/ TMZ
Grade 3 or 4 event occurring on Day 21 – Day 28 of cycle	Skip one or more doses of TG02 and TMZ until improved to grade ≤ 1. Re-introduce TG02 at initial dose and re-introduce TMZ at a reduced dose.
Recurrent grade 4 event occurring on Day 21 – Day 28 of cycle	Discontinue TMZ. Consider the individual benefit versus the risk of continuing TG02. If TG02 is continued, continue TG02 at the same or a reduced dose * bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule. Alternatively, discontinue TG02 and rechallenge with TMZ at lower dose.
Grade 3 or 4 event that does not improve to grade ≤ 2 within 28 days	Discontinue patient from study.
Anemia (TMZ decision as per local practice)	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at initial dose.
Recurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at reduced dose *. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02 at reduced dose *. If TG02 is re-introduced, re-introduce at a reduced dose *.
Recurrence of the same grade 4 event	Discontinue TG02.
Neutropenia	
First occurrence of grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *and TMZ at initial dose.

Adverse Event	Action to be taken with TG02/ TMZ
Recurrence of the same grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Re-introduce TG02 * and/ or TMZ at a reduced dose. If TG02 and TMZ have been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02 or TMZ: • Discontinue TMZ. Continue TG02 at the same or a reduced dose *bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule. • Alternatively, discontinue TG02 and continue TMZ at a reduced dose. If TG02 or TMZ has been re-introduced after a second event and the event recurs, discontinue TG02 and TMZ.
Grade 4 event	Skip one or more doses of TG02 and TMZ until improved to grade ≤ 1. Re-introduce TG02 * and TMZ at a reduced dose.
Recurrence of the same grade 4 event	Discontinue TG02. TMZ dosing as per local practice.
Febrile Neutropenia	
Grade 3 or 4 event	Skip one or more doses of TG02 and interrupt TMZ until fever is resolved and neutropenia is improved to grade ≤ 1. Re-introduce TG02 * and TMZ at a reduced dose.
Recurrence of the same grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until fever is resolved and neutropenia is improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02 or TMZ: • Discontinue TMZ. Continue TG02 at the same or a reduced dose * bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule. • Alternatively, discontinue TG02 and continue TMZ at a reduced dose. If TG02 or TMZ has been re-introduced after a second event and the event recurs, discontinue TG02 and TMZ.
Recurrence of the same grade 4 event	Discontinue TG02 and TMZ.

Group B: TG02-related Non-hematologic Adverse Events

Adverse Event	Action to be taken with TG02
Nausea / Vomiting (TMZ decision as per local practice)	
Grade 1 or 2 event	Manage with moderate anti-emetic treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 nausea/ vomiting that do not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced *.
Grade 3 nausea Grade 3 or 4 vomiting	Skip one or more doses of TG02 until improved to grade ≤1. If improved to grade ≤1 in <48 hours, re-introduce TG02 at the initial dose. If not improved to grade ≤ 1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose *. Continue prophylaxis and management with at least moderate anti-emetic treatment (see Section 5.6.2).
Diarrhea (TMZ decision as per local practice)	
Grade 1 or 2 event	Manage with anti-diarrheal treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 diarrhea that does not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced *. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2).
Grade 3 or 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Physician should instruct patient regarding hydration. If improved to grade ≤ 1 in < 48 hours, re-introduce TG02 at initial dose. If not improved to grade ≤ 1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose *. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2).
Cardiotoxicity	
Grade 3 event	Discontinue TMZ. Consider the individual benefit versus risk of continuing TG02. If TG02 is continued, continue TG02 at the same or a reduced dose * bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule.

Adverse Event	Action to be taken with TG02
Hepatotoxicity	
First occurrence of grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *. Consider the individual benefit versus the risk of continuing TMZ. If TMZ is re-introduced, re-introduce at a reduced dose.
Recurrence of the same grade 3 event	If TMZ was re-introduced after the first event, discontinue TMZ. Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose *. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
First occurrence of grade 4 event	Discontinue TMZ. Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02 at reduced dose *. If TG02 is re-introduced, re-introduce at a reduced dose *.
Recurrence of the same grade 4 event	Discontinue TG02.
Other non-hematologic events except alopecia and asymptomatic or reversible laboratory abnormalities	
First occurrence of grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 and TMZ at initial dose.
Second occurrence of the same grade 3 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 * and TMZ at a reduced dose. If TG02 and TMZ have been re-introduced after a second event and the event recurs, discontinue TG02 and/ or TMZ.
First occurrence of the same grade 4 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 * and TMZ at a reduced dose.
Second occurrence of the same grade 4 event	Skip one or more doses of TG02 and interrupt TMZ until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Consider the individual benefit versus the risk of continuing TG02 and TMZ: • Discontinue TMZ. Continue TG02 at the same or a reduced dose * bi-weekly (on Days 1, 4, 8, 11, 15, 18, 22, 25) of a 28-day schedule. • Alternatively, discontinue TG02 and continue TMZ at a reduced dose.

5.5.3.4 Group C

TG02 dose reductions and skipped dose(s) are allowed in any cycle as described in the tables below. A "skipped dose" for TG02 means that one or more single doses will be omitted and not replaced.

For example, if TG02 is planned on days 1, 4 and 8, but day 4 has to be omitted, TG02 can be restarted on day 8 if the AE is sufficiently resolved: TG02 is always restarted on a scheduled dose day.

Toxicities possibly related to TG02 should be managed as outlined in the tables below.

NOTE: * in below tables: There will be no dose reductions of TG02 below 100 mg BIW

Group C: TG02-related Hematological Adverse Events

Adverse Event	Action to be taken with TG02
Thrombocytopenia	
First occurrence of grade 3 without bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at initial dose.
Recurrence of the same grade 3 event without bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose. * If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose. * If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
First occurrence of grade 3 with bleeding or grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *.
Recurrence of the same grade 3 event with bleeding	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Recurrence of the same grade 4 event	Discontinue TG02.
Anemia	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at initial dose.
Recurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 2. Re-introduce TG02 at a reduced dose *. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.

Adverse Event	Action to be taken with TG02
Grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.
Recurrence of the same grade 4 event	Discontinue TG02.
Neutropenia	
Occurrence grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *.
Grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Re-introduce TG02 at a reduced dose*.
Febrile Neutropenia	
Grade 3 or 4 event	Skip one or more doses of TG02 until fever is resolved and neutropenia is improved to grade ≤ 1. Re-introduce TG02 at a reduced dose *.
Recurrence of the same grade 4 event	Discontinue TG02.

Group C: TG02-related Non-hematologic Adverse Events

Adverse Event	Action to be taken with TG02
Nausea/ Vomiting	
Grade 1 or 2 event	Manage with moderate anti-emetic treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 nausea/ vomiting that do not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced*.
Grade 3 nausea Grade 3 or 4 vomiting	Skip one or more doses of TG02 until improved to grade ≤ 1. If improved to grade ≤1 in <48 hours, re-introduce TG02 at the initial dose. If not improved to grade ≤1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose *. Continue prophylaxis and management with at least moderate anti-emetic treatment (see Section 5.6.2).

Adverse Event	Action to be taken with TG02
Diarrhea	
Grade 1 or 2 event	Manage with anti-diarrheal treatment until improved to grade ≤ 1. Prophylaxis should be given before TG02 dosing (see Section 5.6.2). If a patient experiences persistent or recurrent grade 2 diarrhea that does not improve to grade ≤ 1 with maximal supportive measures within 3 days, then TG02 dosing should be skipped until improved to grade ≤ 1. The dose of TG02 may be reduced*. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2).
Grade 3 or 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Physician should instruct patient regarding hydration. If improved to grade ≤1 in <48 hours, re-introduce TG02 at the initial dose. If not improved to grade ≤1 with maximal supportive measures within 48 hours, re-introduce TG02 at a reduced dose*. Continue prophylaxis and management with anti-diarrheal treatment (see Section 5.6.2)
Other non-hematologic events except alopecia and asymptomatic or reversible laboratory abnormalities	
First occurrence of grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at initial dose.
Second occurrence of the same grade 3 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose*. If TG02 has been re-introduced after a third event and the event recurs, discontinue TG02.
First occurrence of the same grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Re-introduce TG02 at a reduced dose *.
Second occurrence of the same grade 4 event	Skip one or more doses of TG02 until improved to grade ≤ 1. Provide appropriate symptomatic treatment. Consider the individual benefit versus the risk of continuing TG02. If TG02 is re-introduced, re-introduce TG02 at a reduced dose*. If TG02 has been re-introduced after a second event and the event recurs, discontinue TG02.

5.6 Concomitant treatments

All concomitant and/or rescue treatment(s) have to be recorded on the eCRF. For corticosteroids, dose, frequency, dates of administration, and route of administration must be recorded in the dedicated eCRF.

Administration of a COVID-19 vaccine will be the treating physician decision after evaluation of benefit-risk ratio and depending on local vaccine availability and in compliance with local regulatory guidelines.

The administration of a SARS-CoV-2 vaccine including the name of the vaccine (e.g. Moderna, Pfizer BioNTech, AstraZeneca Oxford, …) shall be added in the concomitant medication form in the eCRF and noted in the patient's Medical file. Any possible vaccine related AE should be captured in the AE forms in the eCRFs, specifying the potential relationship to the vaccine.

Any diagnostic, therapeutic or surgical procedure for other cancers or conditions performed during the study treatment period must be recorded with corresponding dates, description and any clinical findings.

5.6.1 Treatment of AA or GBM

The following treatments are **NOT** permitted during the study treatment:

- Treatment with other systemic anti-cancer agents before disease progression (chemotherapy, hormonal therapy, immunotherapy, anti-tumor vaccines, targeted agents, or other treatments not part of protocol-specified anti-cancer therapy)
- Concurrent investigational agents of any type before disease progression
- Craniotomy, intra-tumoral interstitial therapy, any surgical procedures under investigation or any form of radiosurgery

Any of the above will lead to patient's discontinuation from study treatment.

Alternative therapies are discouraged and must be discussed with the local investigator.

5.6.2 Prophylaxis for TG02-related Gastro-intestinal Adverse Events

5.6.2.1 Nausea/Vomiting

Nausea and vomiting are very commonly associated with TG02. Prophylaxis with anti-emetic treatment **IS REQUIRED** prior to taking TG02 on dosing days.

Prophylaxis with a moderate anti-emetic has been more effective at preventing and managing TG02-related nausea and vomiting than lightly anti-emetogenic treatments (e.g., prochlorperazine).

Some recommended prophylaxis regimens include:

- 5-HT3 antagonist (e.g. ondansetron, granisetron, palonosetron, etc.) These medications are known to increase QTc intervals. Please refer to Section 5.6.4.3 for directions regarding drugs that prolong QTc intervals.
- 2.5 mg olanzapine daily
- Other moderate or highly anti-emetic regimens tailored to the individual patient at the Investigator's discretion

If the patient experiences nausea or vomiting on the dosing day, manage according to tables in Section 5.5. Additionally please refer to ESMO and ASCO guidelines (Ref. 27, Ref. 2). If a patient experiences recurrent nausea/ vomiting on dosing days, anti-emetic prophylaxis is highly recommended the day prior to giving TG02 in addition to the day TG02 is given.

5.6.2.2 Diarrhea

Diarrhea is very commonly associated with TG02. Prophylaxis with anti-diarrheal treatment **IS REQUIRED** prior to taking TG02 on dosing days. Recommended prophylaxis regimen is loperamide or equivalent.

If the patient experiences diarrhea on the dosing day, manage according to the tables in Section 5.5. If a patient experiences recurrent diarrhea on dosing days, anti-diarrheal prophylaxis is highly recommended the day prior to giving TG02 in addition to the day TG02 is given.

5.6.3 Other concomitant therapies

The following treatments are **to be used with caution:**

- Therapeutic dose of oral anticoagulants because of risks of thrombocytopenia by TMZ /TG02.

The following treatments **ARE PERMITTED** for other diseases or conditions:

- Anticoagulants (low-molecular weight heparin [LMWH], Vitamin K antagonists) for thromboembolic events or continued as prophylaxis for past thromboembolic events.
- Up to 325 mg aspirin daily.
- Non enzyme inducing anti-epileptic drugs.
- Hematopoietic growth factors may be administered for therapeutic purposes in accordance with American Society of Clinical Oncology (ASCO) guidelines (Ref. 29, Ref. 25).
- Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and should be reduced and/or discontinued if possible.

5.6.4 Concomitant therapies to use with caution

5.6.4.1 NSAID

The use of NSAIDs is not recommended as it may interfere with platelet activity. These drugs should be carefully considered and given only if in the best interest of the patient.

5.6.4.2 Myelosuppressive agents

Use of myelosuppressive agents in combination with TG02 or TMZ may increase the likelihood of myelosuppression. Use of any of these drugs should be carefully considered.

5.6.4.3 Therapies that prolong QTc

In vitro, TG02 citrate inhibits the hERG channel, a risk factor for torsade de pointes (QT prolongation). In a clinical study, 73 acute leukemia and multiple myeloma patients were given TG02 and ECGs conducted. The conclusions from this cardiac assessment were

- No clinically meaningful changes from baseline in resting 12-lead QTc intervals were observed following administration of TG02 at 10 to 200 mg doses.
- No clinically meaningful changes from baseline in resting 12-lead QTc intervals were observed following multiple doses of TG02 at 10 to 200 mg doses through Cycle 1, regardless of schedule.

Interpretation of the QTc interval results is confounded by the small sample size, lack of a placebo or active control, and variable lead placement across time points in a number of subjects.

Therefore, the use of medications that prolong QTc should be carefully considered and given only if the best interest of the patient. The investigator should consider if alternative medication(s) that do not prolong QTc can be used, particularly those for anti-emesis and anti-seizure activity.

These medications include but are not limited to: azithromycin, clarithromycin, erythromycin, roxithromycin, metronidazole (with alcohol), moxifloxacin, fluconazole (in cirrhosis), ketoconazole,

nelfinavir, chloroquine, mefloquine, halothane, disopyramide, procainamide, quinidine, amiodarone, sotalol, amitriptyline, clomipramine, imipramine, dothiepin, doxepin, risperidone, fluphenazine, haloperidol, clozapine, thioridiazine, ziprasidone, pimozide, droperidol, terfenadine, astemizole, probucol, dolasetron mesylate and cisapride.

If a patient requires one or more of these medications every effort should be made to maintain a normal electrolyte balance with special attention to K^+ and Mg^{++} levels. A 12-lead ECG in triplicate should be obtained after beginning such a medication to determine any change to the QTc duration based on the average QTc of triplicate ECGs.

In the event of Grade 1 or Grade 2 QT/QTc prolongation, electrolytes should be corrected to keep the potassium and magnesium within normal limits and the ECG in triplicate should be repeated. If the 12-lead ECG (in triplicate and 2-5 minutes apart) obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position shows a QT/ QTc > 500 ms, this result should be confirmed with 2 additional 12-lead ECGs obtained over a brief period (e.g., 30 minutes). If the measurement is confirmed, scope the patient until QT/ QTc returns to an acceptable value (≤ 480 ms) and seek the advice of a cardiologist before discharging the patient.

TG02 doses may be skipped until QT/ QTc improves to grade ≤ 1. Patients may be monitored on telemetry at the investigator's discretion.

5.6.4.4 CYP450 Drug Interactions (Related to Metabolism)

TG02 is a substrate of CYP3A4 and CYP1A2. Strong inhibitors and inducers of CYP3A4 and CYP1A2 should be used with caution in this study as they may impact the exposure of TG02.

- Known inhibitors of CYP1A2 include ciprofloxacinand fluvoxamine
- Known inhibitors of CYP3A4 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin, known inducers of CYP1A2 include omeprazole, insulin, and cigarette smoking
- Known inducers of CYP3A4 include rifampin and carbamazepine

TG02 is an inhibitor of CYP2D6 and inducer of CYP1A2. Drugs that are known substrates for CYP1A2 and CYP2D6 with a narrow therapeutic index should be used with caution in this study.

- Sensitive CYP1A2 substrates with narrow therapeutic indices include theophylline and tizanidine
- Sensitive CYP2D6 substrates with narrow therapeutic indices include thioridiazine and tamoxifen

5.7 Radiotherapy

Radiotherapy should commence within 6 weeks of neurosurgery and on the same day as the first dose of TG02. The prescribed dose is 39.9 Gy delivered in a once daily schedule of 2.66 Gy per fraction, five days per week for a total of 15 fractions.

5.7.1 Facility and Equipment

Institutions must comply with the Quality Assurance of Radiotherapy requirements and procedures described in detail in the Quality Assurance in Radiotherapy chapter.

Treatment must be delivered with a linear accelerator. The volume should be treated using Intensity-Modulated Radiotherapy (IMRT) with either fixed fields or arcs.

5.7.2 Patient position and data acquisition

Patients can be planned and treated either supine or prone depending on the site of the lesion, in a custom-made immobilization shell (any fixation system with relocation accuracy <5 mm).

The use of a planning CT is mandatory. The use of intravenous contrast medium is recommended unless there is a specific medical contra-indication. The planning CT should extend from top of head (beyond skull) to foramen magnum using a CT slice thickness of 3 mm or less.

Acquisition of an MRI scan for contouring purposes is mandatory up to 2 weeks prior to RT start. Immediate MRI scan should not be used for this purpose. Image fusion of planning CT and MRI will be performed for all patients; fusion protocols as per local institutional protocol.

5.7.3 Volume definition

Treatment planning should conform to ICRU reports #50, #62 and #83 rules for coverage of GTV, CTV and PTV (Ref. 10, Ref. 11, Ref. 12), and wherever possible should follow the ESTRO-ACROP guideline “target delineation of glioblastomas” (Ref. 20).

5.7.3.1 GTV

The Gross Target Volume (GTV) is defined as the entire contrast-enhanced tumor by CT and fused MRI obtained post-operatively. If the tumor has been completely resected, the GTV will be the surgical defect plus any contrast-enhanced abnormality surrounding the surgical defect. In case of postoperative bleeding and/or tumor bed shifting, the definition of volume is left to the best judgment of local investigators making reference to the pre-operative CT or MRI.

5.7.3.2 CTV

The Clinical Target Volume (CTV) is generated by adding a margin of 20 mm to the GTV in all dimensions to account for microscopic spread. This margin should be edited to take into account natural boundaries (e.g. falx cerebri, tentorium, cranium, brain stem, and optic chiasm) and/or areas of high T2/FLAIR signal and may be reduced or increased accordingly at the clinician’s discretion.

5.7.3.3 PTV

The Planning Target Volume (PTV) results from adding margin to the CTV in all directions. The magnitude of this margin will reflect the known geometric accuracy of the institution’s immobilization system (usually 3 – 5 mm).

5.7.3.4 Organs at Risk

The following organs at risk (OAR) should be delineated in all patients: optic chiasm, optic nerves (L, R), ocular globes (L, R), lenses (L, R), and brain stem.

5.7.4 Dose

The prescribed dose is 39.9 Gy to the median PTV dose (D50%), delivered in a once daily schedule of 2.66 Gy per fraction, 5 days per week for a total of 15 fractions. In order to optimize dose uniformity, not more than 2% of the PTV should receive more than 107% of the prescription dose (i.e. D2% < 42.7Gy) or less than 95% of the prescription dose (i.e. D95% > 37.9Gy), presuming normal tissue constraints are met.

Dose prescription will be to the median dose to the PTV (D50%) as recommended by ICRU report #83, which approximates to the dose at the center of the target volume (ICRU 2010).

For calculation of dose constraints for this hypofractionated schedule, α/β ratio values were taken as 2.0 except for ocular globe (3.0) and lens (1.2). Where maximum tolerated doses exceed 40 Gy, 40 Gy has been cited as the maximum dose to avoid hotspots outside the PTV. The following dose constraints are required for OAR:

Dose limits for OAR	Constraint	Maximum Dose (Gy)
Optic chiasm	D1%	40
Right and left optic nerves	D1%	40
Right and left ocular globes	D1%	26.5
Right and left lenses	D1%	4.9
Brain stem	D5%	40

	Dose limits
Dose limits for PTV	D2% < 42.7 Gy D95% > 37.9 Gy

5.7.5 Treatment planning

The volume should be treated using Intensity-Modulated Radiotherapy (IMRT) with either fixed fields or arcs. The treatment plan to be used for each patient is based on an analysis of volumetric doses including the dose volume histogram (DVH) for the PTV and PRVs.

Tissue inhomogeneity correction for bone and soft tissue density variation will be applied according to standard international practice.

Centers who are unable to prescribe to the median dose due to their planning system capabilities can alternatively prescribe to the mean dose. The median and mean doses should both be reported on the CRF and are expected to be within 1% of each other. Centers with any issues regarding median/mean dose prescription should contact the RTQA team.

5.7.6 Treatment verification and accuracy

The minimum protocol for on-treatment verification comprises imaging the initial three fractions with megavoltage or kilovoltage portal imaging. Further verification should comprise weekly imaging using the same technique.

The decision rules for patient setup corrections will be based on the institution's procedures for setup verification. These should be established and recorded as part of RTQA.

5.7.7 Complications

Expected adverse events for radiotherapy are listed below:

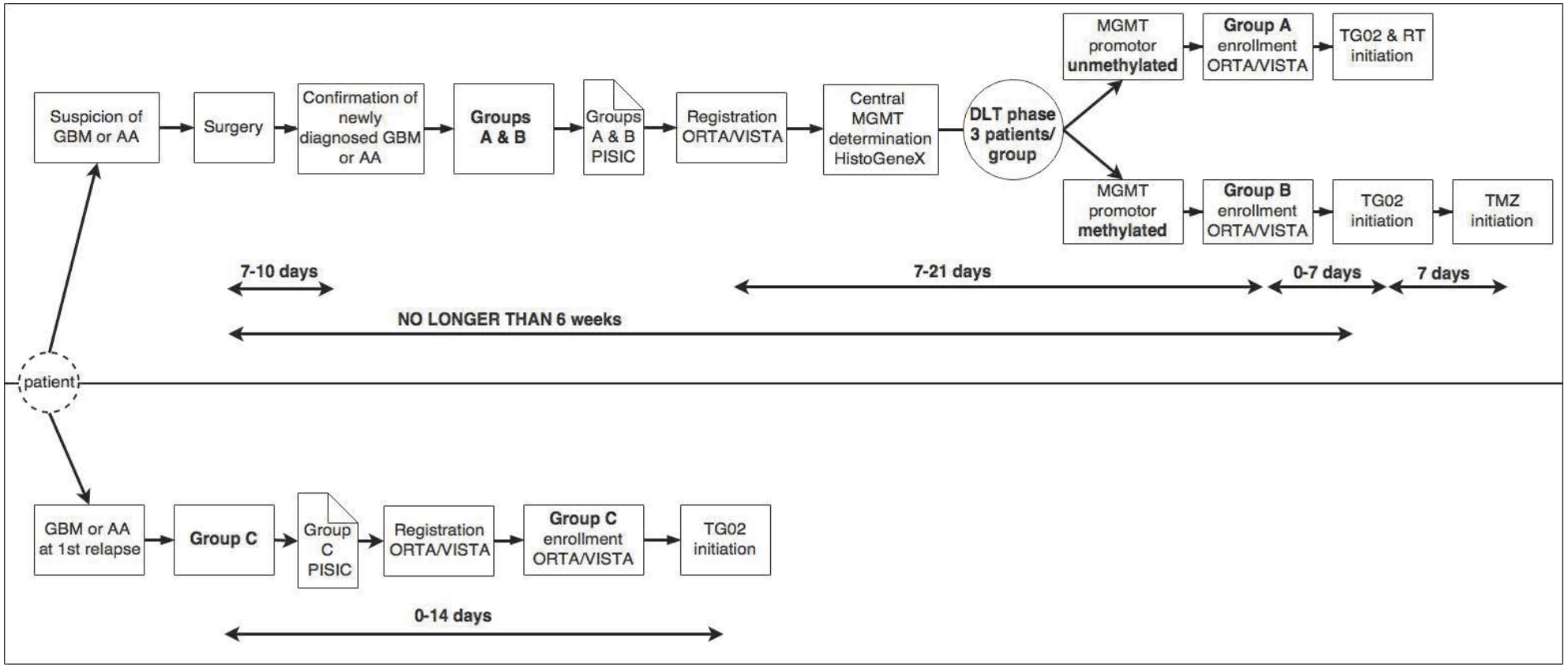
- Constitutional: fatigue / lethargy
- Dermatology / skin: alopecia, scalp erythema
- Gastrointestinal: nausea, vomiting
- Musculoskeletal: muscle weakness
- Neurology: cerebral edema, cognitive disturbance, concentration impairment, depressed level of consciousness, dysphasia, memory impairment, reduced sensation, seizure, somnolence
- Ocular: visual field defect, blurred vision, papilledema
- Pain: headache

5.7.8 Treatment interruptions / modifications

Delays of up to 7 days are permitted once the patient has started radiotherapy. This includes breaks in treatment caused by public holidays, transport failures, machine breakdown, intercurrent illness and other factors. In the case of delays, dose compensation is not required for ANY associated increase in overall treatment time.

In case of any AEs leading to RT interruption or delays not considered related to TG02, TG02 should continue as scheduled if medical condition allows it.

6 Clinical evaluation, laboratory tests and follow-up



6.1 Before treatment start

6.1.1 Registration

6.1.1.1 Groups A and B

These assessments must be completed within 28 days prior to enrollment

- Histological diagnosis of glioblastoma or anaplastic astrocytoma
- Informed consent for phase 1b
- FFPE block or 25 unstained slides. The slides or the block MUST be sent to [redacted] for MGMT analysis as soon as the patient has signed the consent form. Results are needed before enrollment onto the study for these two groups (for more information see sections 7.1.9, 13.1.2 and HBM guidelines provided as separate document).
- Evaluation of inclusion and exclusion criteria
- Medical history, including prior cancer

These assessments must be completed within 14 days of enrollment

- Complete physical examination, including any ongoing clinical symptoms. For female patients, menopausal status should be documented.
- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight, height
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- Coagulation: PT, PTT and INR
- Complete neurological examination (NANO, see section 7.2.4)
- Quality of life assessment (modified EORTC QLQ C30/BN20) (see Chapter 10 and Appendix F)
- Geriatric evaluation (G8) (see Appendix G)
- 12-Lead ECG

This assessment must be scheduled within 14 days of first dose of TG02

- Brain gadolinium (Gd)-MRI. If a 72-h post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated. See Section 7.2.5 and Appendix J for detailed MRI sequences. Additional information can be found in the study specific imaging guidelines.

6.1.1.2 Group C

These assessments must be completed within 14 days of first dose of TG02

- Histological diagnosis of glioblastoma or anaplastic astrocytoma
- Informed consent
- Online registration of FFPE block or 25 unstained slides from the surgery at glioblastoma diagnosis (for more information see section 14.3 and HBM guidelines provided as separate document)
- Evaluation of inclusion and exclusion criteria

- Medical history, including prior cancer
- Complete physical examination, including any ongoing clinical symptoms. For female patients, menopausal status should be documented.
- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight, height
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- Coagulation: PT, PTT and INR
- 12-Lead ECG
- Brain gadolinium (Gd)-MRI: baseline must be completed within 14 days of first dose of TG02. For patients with surgery for recurrence, if a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated. See Appendix J for detailed MRI sequences. Additional information can be found in the study specific imaging guidelines. The last brain MRI before disease progression diagnosis should also be available.
- Complete neurological examination (NANO, see section 7.2.4)

This assessment must be completed within 72 hours of first dose of TG02

- For WOCBP, serum or urine pregnancy test within 72 hours prior to the first dose of TG02

6.1.2 Enrollment

Enrollment of patients to Group A or B will be done after central determination of the MGMT promoter methylation status and if the general and neurological status of the patient remains stable.

Group A: patients with MGMT promoter-unmethylated AA or GBM will be enrolled.

Group B: patients with MGMT promoter-methylated AA or GBM will be enrolled.

Group C: registration and enrollment occur at the same time, when the patient signs the informed consent form.

6.1.3 Initiation of Study Treatment

6.1.3.1 Group A

The first dose of TG02 and first treatment of RT can be started as soon as the patient is enrolled. A maximum of 7 days is allowed between enrollment and initiation of study treatment. Every effort should be made to reduce the time between enrollment and first dose of study treatment.

On days when both TG02 and RT are scheduled, TG02 will be taken approximately 1 hour before RT treatment.

A patient card and a patient diary will be given to each enrolled patient in order to record AE and treatment intake.

6.1.3.2 Group B

The first dose of TG02 (Day -7) can be started as soon as the patient is enrolled. A maximum of 7 days is allowed between enrollment and first dose of TG02. Every effort should be made to reduce the time between enrollment and first dose.

On days when both TG02 and TMZ are scheduled, TG02 will be taken approximately 1 hour before TMZ treatment.

A patient card and a patient diary will be given to each enrolled patient in order to record AE and treatment intake.

6.1.3.3 Group C

A maximum of 7 days is allowed between registration and first dose of TG02.

A patient card and a patient diary will be given to each enrolled patient in order to record AE and treatment intake.

6.2 Study treatment phase

6.2.1 Cycle 1 for Group A

All cycles are 28 days. Cycle 1 is 21 days of RT and a 7-day break. Cycle 2 will begin after completion of combination TG02 and RT treatment, including the 7 day break.

6.2.1.1 Day 1 (prior to first dose of TG02)

- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count. If the registration hematology panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate. If the registration biochemistry panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Coagulation: PT, PTT and INR. If the registration coagulation panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Optional translational research: 20 mL blood for soluble biomarker assessment
- **Prescription:** TG02 prescription (+ prophylaxis, see section 5.6.2)

6.2.1.2 Every week (Days 8 and 15)

- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count

- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- Adverse events assessment (see section 7.3.1)
- TG02 compliance

6.2.2 Cycle 1 for Group B

Cycle 1 is 35 days including a Day -7 and -4 dose of TG02. All subsequent cycles (Cycle 2+) are 28 days.

6.2.2.1 Day -7 (prior to first dose of TG02)

- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count. If the registration hematology panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate. If the registration biochemistry panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Coagulation: PT, PTT and INR. If the registration coagulation panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Adverse event assessment (see section 7.3.1)
- Optional translational research: 20 mL blood for soluble biomarker assessment
- **Prescription:** TG02 prescription (+ prophylaxis, see section 5.6.2) and TMZ prescription (+ prophylaxis)

6.2.2.2 Every week (Days 1, 8, 15 and 22)

- Concomitant medications assessment
- Steroid dose
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Adverse event assessment
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- TG02 compliance
- TMZ compliance

6.2.3 Cycle 1 for Group C

All cycles are 28 days.

6.2.3.1 Day 1: prior to first dose of TG02

- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count. If the registration hematology panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate. If the registration biochemistry panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Coagulation: PT, PTT and INR. If the registration coagulation panel has been done within 72 h prior to first dose of TG02, it does not need to be repeated.
- Adverse events assessment (see section 7.3.1)
- Optional translational research: 20 mL blood for soluble biomarker assessment
- **Prescription:** TG02 prescription (+ prophylaxis, see section 5.6.2)
- Blood sample for Pharmacokinetics (6 mL blood) for patients consented to the PK study just prior to TG02 administration.

6.2.3.2 Every week (Days 8, 15 and 22)

If no SAEs are reported by the patient or ongoing on Day 8, the safety evaluations on Days 15 and 22 can be omitted.

- Concomitant medications assessment
- Steroid dose
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: includes hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- Adverse events assessment
- TG02 compliance
- Cycle 1 D 15 only: blood samples for Pharmacokinetics (6 mL blood each sample) for patients consented to the PK study: pre-dosing, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours after dosing.

Following table will serve as an example:

PK Sampling Time Point	Window	Activity	
		Breakfast	
Prior to dosing	Prior to dosing	Pre-dose blood draw (6mL)	
	N/A	Dose TG02	
30 min	+/- 5 min	Blood draw (6 mL)	
1 hr	+/- 10 min	Blood draw (6 mL)	
2 hr	+/- 10 min	Blood draw (6 mL)	
4 hr	+/- 30 min	Blood draw (6 mL)	
	N/A	Lunch	
8 hr	+/- 1 hr	Blood draw (6 mL)	
24 hr	+/- 1 hr	Blood draw (6 mL)	

6.2.4 Cycle 2+ until withdrawal criteria are met (for all groups)

After Cycle 1, all cycles are 28 days for all groups. Visits should be performed at D1 of each cycle every 28 days (± 3 days). See section 5.4 for withdrawal criteria.

6.2.4.1 Every 28 days (± 3 days)

- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: hemoglobin, hematocrit, total WBC count with differential -neutrophils and lymphocytes-, and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate will be measured
- **Group C, WOBCP only:** urine or serum pregnancy test
- Adverse events assessment
- 12-lead ECG, if clinically indicated
- TG02 compliance
- **Cycle 2 only, Group A: RT compliance; Cycle 2+, Group B**: TMZ compliance
- **Prescription:** TG02, TMZ (+ prophylaxis, see Section 5.6 for TG02 prophylaxis)

6.2.4.2 Every 2 cycles (± 8 days) until 6 cycles, then every 3 cycles (± 8 days)

- Brain Gd-MRI. See Appendix J for detailed MRI sequences. Additional information can be found in the study specific imaging guidelines
- Complete neurological examination (NANO scale, see section 7.2.4)
- **Group A and B ONLY:** Quality of life assessment (modified EORTC QLQ C30/BN20, see Chapter 10 and Appendix F) at start of cycles 3, 5, 7, 10, 13, etc. (every 3 cycles) until disease progression (to coincide with scheduled visit)

6.2.4.3 Optional translational research biology

Optional translational research biology at C3 D1 2 months after TG02 initiation (20 mL blood for biomarkers analysis)

6.3 At study treatment discontinuation (for all groups)

6.3.1 End of study visit for all groups

End of study evaluation should take place within 30 days (± 5 days) after the last dose of TG02

- Complete physical examination
- Concomitant medications assessment
- Steroid dose. For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
- Vital signs: blood pressure, pulse, temperature, weight
- Karnofsky Performance Status (KPS) (see Appendix E)
- Hematology: hemoglobin, hematocrit, total WBC count with differential -neutrophils and lymphocytes-, and platelet count
- Biochemistry: sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate
- Coagulation: PT, PTT and INR
- **Group C, WOBCP only:** urine or serum pregnancy test
- Adverse event assessment. When the patient discontinues study treatment, suspected adverse reactions (AEs for which there is a reasonable possibility that the drug caused the AE) that started while on study treatment should be followed for 30 days from the date of the last dose of study drug or until considered chronic/ stable (as judged by the Investigator), whichever comes first. SAEs and serious suspected adverse reactions that are reported after the last dose of study drug but before 30 days after the last dose of study drug should be followed until resolved or considered stable/ chronic (as judged by the Investigator).
- TG02 compliance. All patient diaries should be collected if not done previously
- **Group B ONLY**: TMZ compliance
- Brain Gd-MRI. See Appendix J for detailed MRI sequences. Additional information can be found in the study specific imaging guidelines
- Complete neurological examination (NANO, see section 7.2.4)
- **Groups A and B ONLY:** Quality of life assessment (modified EORTC QLQ C30/BN20, see Chapter 10 and Appendix F)
- Optional translational research: 20 mL blood for biomarkers analysis

6.3.2 Discontinuation due to progressive disease

If study treatment is discontinued because of progressive disease AND a surgical procedure is planned for recurrent or progressive tumor, TG02 should be maintained until the surgery and tissue should be collected, online registered and sent to Department of Neurology, University Hospital Zurich (refer to sections 11.2.1, 14.3 and HBM guidelines provided as a separate document). If possible, a 10-mL plasma sample should be obtained close to the time of surgery

If a surgical procedure is NOT planned, patients with progressive disease will terminate the study treatment (see “end of study visit” below). The therapeutic strategy at progression will be determined by the treating physician at the participating center. Patients will remain in survival follow-up (see section 6.3.3) unless they refuse further data collection.

6.3.3 Follow-up every 3 months (± 14 days)

For all groups:

- Survival, irrespective of type of treatment administered or any progression event. (Follow-up can be done by regular visits or phone calls.)
- If progression has not occurred,
    - Brain Gd-MRI (Appendix J)
    - Quality of life assessment (modified EORTC QLQ C30/BN20) Group A & B only

6.3.3.1 After progression, until death every 3 months (± 14 days)

- Survival. (Follow-up can be done by regular visits or phone calls.)
- Quality of life assessment (modified EORTC QLQ C30/BN20) Group A & B only
- Any antitumoral therapy follow-up (Group C only)

6.4 Summary tables

6.4.1 Summary table for Group A

All cycles are 28 days. Cycle 2 will begin 7 days after completion of combination treatment.

GROUP A	**Registration**		**Enrollment**	**Cycle 1, Day 1 pre-dose**	**Cycle 1, Days 8, 15**	**Study Treatment[2] Phase**		**End of treatment[20]**	**Follow Up**
	Within 28 days of enrollment[2]	**Within 14 days of enrollment**		**Within 7 days of enrollment**		**Safety / Prescription[18]**	**Efficacy [19]**		
Histological diagnosis of glioblastoma or AA	X								
Signed informed consent	X								
FFPE block or 25 unstained slides sent to [redacted]	X								
Medical history, including prior cancer	X								
Determination of MGMT promoter-methylation status			X						
Complete physical examination[3]		X						X	
Concomitant medications assessment		X		X	X	X		X	
Steroid dose[4]		X		X	X	X		X	
Vital signs[5]		X		X	X	X		X	
Karnofsky Performance Status (KPS)[6]		X		X	X	X		X	
Hematology[7]		X		X	X	X		X	
Biochemistry[8]		X		X	X	X		X	
Coagulation[9]		X		X		X		X	
Adverse events evaluation[10]				X	X	X		X	

GROUP A (continued)	Registration		Enrollment	Cycle 1, Day 1	Cycle 1, Days 8, 15	Study Treatment Phase		End of treatment[20]	Follow Up
	Within 28 days of enrollment[2]	Within 14 days of enrollment		Within 7 days of enrollment		Safety / Prescription[18]	Efficacy [19]		
TG02 prescription (+prophylaxis)[11]				X		X			
TG02 compliance evaluation[11]					X	X		X	
Radiotherapy [12]				X	X				
12-Lead ECG[13]		X							
Brain Gd-MRI [14]		X[2]					X	X	X[14]
Neurological examination (NANO) [15]		X					X	X	
Quality of life assessment (modified EORTC QLQ C30/BN20) [16]		X					X	X	X[22]
Geriatric evaluation[17]		X							
Optional translational research [21]		X				X		X	
Survival follow-up[22]									X

[1] Tissue must be sent to [redacted] for MGMT analysis as soon as the patient has signed the consent form. Results are needed before enrollment onto the study for Group A.
[2] Brain Gd-MRI must be completed within 14 days of first dose of TG02. If a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.
[3] Complete physical examination will be done at registration and end of study visit. The examination should include any ongoing clinical symptoms. For female patients, menopausal status should be documented.
[4] For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
[5] Blood pressure, pulse, temperature, weight and height will be collected at registration. At all other times, blood pressure, pulse, temperature and weight will be collected.
[6] See Appendix E.
[7] Hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8 and 15, on Day 1 of subsequent cycles, and at the end of study visit. If the registration hematology panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[8] Sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8 and 15, on Day 1 of subsequent cycles, and at the end of study visit. If the registration chemistry panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[9] PT, PTT, and INR will be measured at registration, Cycle 1 Day 1 pre-dose and at the end of study visit. If the registration coagulation panel has been done within 72 hours of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[10] Adverse events grading according to CTCAE 5.0

[11] TG02 and RT can start on the day of enrollment but no more than 7 days after enrollment. TG02 is given on Days 1, 4, 8, 11, 15 and 18 of the first cycle in combination with RT. Skipped doses of TG02 will be noted in the patient study drug diary. On days when both TG02 and RT are scheduled, TG02 will be taken approximately 1 hour before RT treatment. TG02 is given on Days 1, 4, 8, 11, 15, 18, 22 and 25 of maintenance cycles. See section 5.2.1.1.
[12] TG02 and RT can start on the day of enrollment but no more than 7 days after enrollment. Standard involved-field radiotherapy (40 Gy in 15 fractions of 2.66 Gy for 3 weeks). See Section 5.7.
[13] ECG should be repeated if medically indicated.
[14] Brain Gd-MRI will be done every 2 cycles (± 8 days) until 6 cycles, then every 3 cycles (± 8 days). If treatment is stopped before progression is observed, brain Gd-MRI should be done every 3 months (± 14 days). See Appendix J for detailed MRI sequences. Additional details can be found in the study specific imaging guideline.
[15] NANO scale (see section 7.2.4).
[16] QOL evaluation: QLQ C30 and BN20 will be filled out within 2 weeks before enrollment, every 2 cycles until cycle 6 (X 3), every 3 cycles, and at the end of study visit. See Chapter 10 and Appendix F.
[17] G8 screening tool will be completed at registration. See Appendix G.
[18] Safety evaluations in Cycles 2+ should be performed at D1 of each cycle (± 3 days)
[19] Efficacy evaluations should be performed every 2 cycles (±8 days) until 6 cycles and then every 3 cycles (± 8 days)
[20] End of study visit should be performed within 30 days (± 5 days) after the last dose of TG02
[21] Optional collection of 20 mL blood samples for future analysis (baseline, C3D1, progression or end of study)
[22] Follow-up for survival and QOL administration every 3 months (± 14 days) until death. Follow up can be done by regular visits or phone calls.

6.4.2 Summary table for Group B

Cycle 1 is 35 days including a Day -7 and -4 administration of TG02. All cycles 2+ are 28 days.

GROUP B	**Registration**		**Enrollment**	**Cycle 1, Day -7**	**Cycle 1, Days 1, 8, 15, 22**	**Study Treatment Phase**		**End of treatment**[20]	**Follow Up**
	Within 28 days of enrollment[2]	**Within 14 days of enrollment**		**Within 7 days of enrollment**		**Safety / Prescription**[18]	**Efficacy**[19]		
Histological diagnosis of glioblastoma or AA	X								
Signed informed consent	X								
FFPE block or 25 unstained slides sent to [redacted]	X								
Medical history, including prior cancer	X								
Determination of MGMT promoter-methylation status			X						
Complete physical examination[3]		X						X	
Concomitant medications assessment		X		X	X	X		X	
Steroid dose[4]		X		X	X	X		X	
Vital signs[5]		X		X	X	X		X	
Karnofsky Performance Status (KPS)[6]		X		X	X	X		X	
Hematology[7]		X		X	X	X		X	
Biochemistry[8]		X		X	X	X		X	
Coagulation[9]		X		X		X		X	

GROUP B (continued)	**Registration**		**Enrollment**	**Cycle 1, Day -7**	**Cycle 1, Days 1, 8, 15, 22**	**Study Treatment Phase**		**End of treatment**[20]	**Follow Up**
	Within 28 days of enrollment[2]	**Within 14 days of enrollment**		**Within 7 days of enrollment**		**Safety / Prescription**[18]	**Efficacy**[19]		
Adverse events evaluation[10]				X	X	X		X	
TG02 prescription (+prophylaxis)[11]				X		X			
TG02 compliance evaluation[11]					X	X		X	
TMZ prescription (+ prophylaxis)[12]				X					
TMZ compliance evaluation[12]					X	X		X	
12-Lead ECG[13]		X							
Brain Gd-MRI[14]		X[2]					X	X	X[14]
Neurological examination (NANO) [15]		X					X	X	
Quality of life assessment (modified EORTC QLQ C30/BN20) [16]		X					X	X	X[22]
Geriatric evaluation[17]		X							
Optional translational research [21]		X				X		X	
Survival follow-up [22]									X

[1] Tissue must be sent to [redacted] for MGMT analysis as soon as the patient has signed the consent form. Results are needed before enrollment onto the study for Group B.
[2] Brain Gd-MRI must be completed within 14 days of first dose of TG02. If a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.
[3] Complete physical examination will be done at registration and end of study visit. The examination should include any ongoing clinical symptoms. For female patients, menopausal status should be documented.
[4] For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
[5] Blood pressure, pulse, temperature, weight and height will be collected at registration. At all other times, blood pressure, pulse, temperature and weight will be collected.
[6] See Appendix E.
[7] Hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8 and 15, on Day 1 of subsequent cycles, and at the end of study visit. If the registration hematology panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.

[8] Sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8 and 15, on Day 1 of subsequent cycles, and at the end of study visit. If the registration chemistry panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[9] PT, PTT, and INR will be measured at registration, Cycle 1 Day 1 pre-dose and at the end of study visit. If the registration coagulation panel has been done within 72 hours of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[10] Adverse events grading according to CTCAE 5.0
[11] TG02 (Day -7) can start on the day of enrollment but no more than 7 days after enrollment. TG02 is given on Days -7 and -4 prior to the first cycle. TG02 is given on Days 1, 4, 22 and 25 of each cycle.
[12] TMZ prescription: d1 to d5 of every cycle (max 12 cycles). On days when both TG02 and TMZ are administered, TG02 will be administered first, 1 hour before TMZ.
[13] ECG should be repeated if medically indicated.
[14] Brain Gd-MRI will be done every 2 cycles (± 8 days) until 6 cycles, then every 3 cycles (± 8 days). If treatment is stopped before progression is observed, brain Gd-MRI should be done every 3 months (± 14 days). See Appendix J for detailed MRI sequences. Additional details can be found in the study specific imaging guideline.
[15] NANO scale (see section 7.2.4).
[16] QOL evaluation: QLQ C30 and BN20 will be filled out within 2 weeks before enrollment, every 2 cycles until cycle 6 (X 3), every 3 cycles, and at the end of study visit. See Chapter 10 and Appendix F.
[17] G8 screening tool will be completed at registration. See Appendix G.
[18] Safety evaluations in Cycles 2+ should be performed at D1 of each cycle (± 3 days)
[19] Efficacy evaluations should be performed every 2 cycles (±8 days) until 6 cycles and then every 3 cycles (± 8 days)
[20] End of study visit should be performed within 30 days (± 5 days) after the last dose of TG02
[21] Optional collection of 20 mL blood samples for future analysis (baseline, C3D1, progression or end of study)
[22] Follow-up for survival and QOL administration every 3 months (± 14 days) until death. Follow up can be done by regular visits or phone calls.

6.4.3 Summary table for Group C

All cycles are 28 days.

GROUP C	Registration	Cycle 1, Day 1	Cycle 1, Days 8, 15, 22 [9]	Study Treatment Phase		End of treatment[15]	Follow Up
	Within 14 days of first dose of TG02			Safety / Prescription[13]	Efficacy[14]		
Histological diagnosis of glioblastoma or AA	X						
Online registration FFPE block or 25 unstained slides from surgery at diagnosis of GBM/AA to be sent to Department of Neurology, University Hospital Zurich	X						
Signed informed consent	X						
Medical history, including prior cancer	X						
Complete physical examination [1]	X					X	
Concomitant medications assessment	X	X	X	X		X	
Steroid dose [2]	X	X	X	X		X	
Vital signs [3]	X	X	X	X		X	
Karnofsky Performance Status (KPS) [4]	X	X	X	X		X	
Hematology [5]	X	X	X			X	
Biochemistry [6]	X	X	X			X	
Coagulation [7]	X	X		X		X	
Serum or urine pregnancy test [8]	X			X		X	
Adverse events evaluation[10]		X	X	X		X	

GROUP C (continued)	Registration	Cycle 1, Day 1	Cycle 1, Days 8, 15, 22 [9]	Study Treatment Phase		End of treatment[17]	Follow Up
	Within 14 days of first dose of TG02			Safety / Prescription[15]	Efficacy[16]		
TG02 prescription (+prophylaxis)[11]		X		X			
TG02 compliance evaluation[11]			X	X		X	
12-Lead ECG[12]	X						
Brain Gd-MRI[13]	X				X	X	X[13]
Neurological examination (NANO) [14]	X				X	X	
Optional translational research [18]	X			X		X	
Survival follow-up [19]							X
Optional TG02 PK sampling		X[20]	X[21]				

[1] Complete physical examination will be done at registration and end of study visit. Examination should include any ongoing clinical symptoms. For female patients, menopausal status should be documented.
[2] For corticosteroids, dose, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF.
[3] Blood pressure, pulse, temperature, weight and height will be collected at registration. At all other times, blood pressure, pulse, temperature and weight will be collected.
[4] See Appendix E.
[5] Hemoglobin, hematocrit, total WBC count with differential (neutrophils and lymphocytes), and platelet count will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8, 15 and 22, on Day 1 of subsequent cycles, and at the end of study visit. If the registration hematology panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[6] Sodium, potassium, chloride, BUN, creatinine, total protein, albumin, AST and/or ALT, total bilirubin, alkaline phosphatase, calcium, magnesium, LDH, glucose, creatinine kinase and phosphate will be measured at registration, Cycle 1 Day 1 pre-dose, Cycle 1 Days 8, 15 and 22, on Day 1 of subsequent cycles, and at the end of study visit. If the registration chemistry panel is done within 72 h of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[7] PT, PTT, and INR will be measured at registration, Cycle 1 Day 1 pre-dose and at the end of study visit. If the registration coagulation panel has been done within 72 hours of pre-dose on Cycle 1 Day 1, it does not need to be repeated.
[8] For WOCBP, serum or urine pregnancy test will be conducted within 72 hours prior to the first dose of TG02, D1 of every cycle and at end of study visit.
[9] If no SAEs are reported by the patient or ongoing on Day 8, the safety evaluations on Days 15 and 22 can be omitted.
[10] Adverse events grading according to CTCAE 5.0
[11] TG02 should start within 7 days of registration. TG02 will be taken on days 1, 4, 8, 11, 15, 18, 22 and 25 in all cycles. Skipped doses of TG02 will be noted in the patient study drug diary. See section 5.2.1.3.
[12] ECG should be repeated if medically indicated.
[13] Baseline brain Gd-MRI must be completed within 14 days of first dose of TG02. For patients with surgery for recurrence, if a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated. Brain Gd-MRI will also be every 2 cycles (± 8 days) until 6 cycles, then every 3 cycles (± 8 days). If treatment is stopped

before progression is observed, brain Gd-MRI should be done every 3 months (± 14 days). See Appendix J for detailed MRI sequences. Additional details can be found in the study specific imaging guideline.

[14] See section 7.2.4.

[15] Safety evaluations in Cycles 2+ should be performed at D1 of each cycle (± 3 days)

[16] Efficacy evaluations should be performed every 2 cycles (±8 days) until 6 cycles and then every 3 cycles (± 8 days)

[17] End of study visit should be performed within 30 days (± 5 days) after the last dose of TG02

[18] Optional collection of 20 mL blood samples for future analysis (baseline, C3D1, progression or end of study)

[19] Follow-up for survival every 3 months (± 14 days) and new anti-tumoral therapy information until death. Follow up can be done by regular visits or phone calls.

[20] TG02 PK sample will be collected at Cycle1D1 pre-dosing only.

[21] TG02 blood samples will be collected at Cycle 1 day 15 only: pre- dose and 30 min, 1 hr, 2hrs, 4 hrs, 8 hrs and 24 hrs post-dose of TG02.

[22]

7 Criteria of evaluation

7.1 Study procedures

7.1.1 Compliance evaluation

TG02 (all groups) and TMZ (group B) compliance will be verified by:

(1) a patient diary. Treatment intake, dose modifications, skipped doses of TG02 and delays/ interruptions of TMZ will be recorded in the patient diary and reported on the CRF.

(2) capsule counts at each visit, with the number of capsules taken relative to the number expected to be taken summarized for each cycle. The patient must take ≥ 75% of the planned doses of TG02 in a cycle to be deemed compliant. Planned dose interruptions may occur and will not result in a patient being considered as noncompliant. A patient will be considered noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken ≥ 125% of the planned doses of TG02 in a cycle.

Patients will be instructed to bring all unused capsules and their medication diary to each study visit for assessment of compliance.

7.1.2 Physical examination

Physical examination will be performed as per local standard practice.

7.1.3 Neurological examination

Neurological examination will be performed using the NANO scale (section 7.2.4, Appendix I). A conclusion on the evaluation of neurological status (improved, stable, and deteriorated) by the treating physician is required at each evaluation.

At any time, in case of suspicion of progression, a brain MRI should be done.

7.1.4 Karnofsky Performance Score

Karnofsky Performance Status will be determined according to the scale provided in Appendix E.

7.1.5 Quality of life assessment

A modified version of the QLQ C30 and BN20 questionnaires will be used to assess the quality of life. (See chapter 10 and Appendix F).

7.1.6 Geriatric assessment

See section 7.4 and Appendix G.

7.1.7 Blood analysis

Blood analysis can be done as per local standard practice, at the hospital laboratory during a hospitalization or at the local laboratory. Laboratory reference range values have to be provided for all the laboratories used by the patients.

7.1.8 Magnetic resonance imaging (MRI)

The basic MRI protocol is mandatory for all participating centers for baseline and follow-up MRI examinations. The order of the prescribed sequences particularly after contrast administration should be respected across all visits for each patient during the treatment. The duration of MRI data acquisition is 30 minutes. According to the preferences of the respective centers, further sequences can be added to the protocol. Only 1.5T and 3T MR scanners should be used. All scans should be sent to EORTC HQ for central review. Details on how to do this can be found in the study specific imaging guidelines.

Detailed acquisition parameters are provided in the study specific guidelines.

If progression is not clear (e.g. pseudo progression), it is recommended to continue study treatment and confirm the diagnosis of progression with a new MRI, including perfusion sequences, no earlier than 28 days later.

Table 1: Overview of the required study time points

	Baseline	**During treatment**	**End of study**
Group A	Within 14 days of first dose of TG02 [1]	Every 2 cycles (± 8 days) until 6 cycles (X 3 times) then every 3 cycles (± 8 days)	Within 30 days (+/- 5 days) of last dose of TG02
Group B	Within 14 days of first dose of TG02 [1]	Every 2 cycles (± 8 days) until 6 cycles (X 3 times) then every 3 cycles (± 8 days)	Within 30 days (+/- 5 days) of last dose of TG02
Group C	Within 14 days prior to first dose of study treatment [2]	Every 2 cycles (± 8 days) until 6 cycles (X 3 times) then every 3 cycles (± 8 days)	Within 30 days (+/- 5 days) of last dose of TG02

[1] If a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.
[2] For non-surgical patients, baseline brain Gd-MRI must be completed within 14 days of first dose of TG02. For patients with surgery for recurrence, if a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.

7.1.9 MGMT promoter methylation (for Groups A and B)

MGMT promoter methylation status will be centrally assessed in groups A and B by methylation-specific PCR at [redacted].

Tissue samples in groups A and B must be sent to [redacted] as soon as the patient has signed the consent form to avoid any delay in the treatment. Guidelines for human biological management will be provided in a separate document.

[redacted]

7.1.10 IDHR132H mutation

IDH^{R132H} mutation will be determined locally by immunohistochemistry.

In patients older than 55 years of age at diagnosis with a histologically typical glioblastoma, without a pre-existing lower grade glioma and with non-midline tumor location, immunohistochemical negativity for $IDH1^{R132H}$ suffices for classification as glioblastoma, IDH-wild-type (Ref. 16, Ref. 35).

In all other instances of diffuse gliomas, lack of $IDH1^{R132H}$ immunopositivity should be followed by IDH1 and IDH2 sequencing to detect or exclude other less common IDH mutations.

7.1.11 Other pathological and molecular examinations in anaplastic astrocytoma

IDH mutation and loss of nuclear ATRX expression suffice for classification as IDH-mutant astrocytic gliomas.

ATRX expression should be explored by immunohistochemistry.

IDH-wild-type diffuse astrocytic gliomas with loss of nuclear ATRX expression may be additionally tested for histone 3 mutations (immunostaining for histone 3 K27M (H3-K27M) mutation) according to EANO guidelines (Ref. 35).

7.2 Criteria of Evaluation

7.2.1 Safety

See section 7.3 evaluation of safety.

7.2.2 Efficacy

To ensure a homogeneous radiological evaluation, all MRI images will be retrospectively centrally reviewed.

The following criteria will be used to determine the efficacy of study treatment.

Progression Free Survival (PFS): PFS is defined as the number of days from consent to the date of earliest disease progression based on Response Assessment in Neuro Oncology (RANO) criteria (as determined by the Investigator) or to the date of death, if disease progression does not occur. In group C, patients for whom neither death nor progression have been documented will be censored on the date of the last radiological assessment if they have no post anti-cancer therapy. If a patient has other post anti-cancer therapy prior to progression or death, the data will be censored at the date of last radiological assessment prior to or on the start date of post anti-cancer therapy. In group A and B, post anti-cancer therapy is not collected. The data will be censored at the date of the last radiological assessment. In all groups, if a patient with no post-baseline radiological assessment did not experience progression nor died, then the data will be censored at the date of enrollment.

PFS at 6 months (PFS-6) is the PFS rate at 6 months extracted from the PFS Kaplan Meier distribution based on RANO criteria (as determined by the Investigator)

Overall Survival (OS)*:* OS is defined as the number of days from consent to the date of death due to any cause. If a patient has not died, the data will be censored at the last date documented to be alive.

OS at 9 months (OS-9) is the OS rate at 9 months extracted from the OS Kaplan Meier distribution.

Objective (ORR) and complete (CR) response rates are the proportions of patients with best overall response PR+CR or CR (see below) respectively.

Duration of objective (complete) response (DOR): DOR is determined as the number of days from the time point where the overall response PR or CR (CR) was first seen to the earliest date of detection of disease progression based on RANO criteria (as determined by the Investigator) or to the date of death, if disease progression does not occur. The same censoring rules defined above for PFS are applicable.

A success is defined as a patient achieving either confirmed CR or PR (> 4 week) or free of progression at 6 months.

Neurologic progression free survival (NPFS): NPFS is defined as the number of days from patient enrollment in trial until the date of first neurologic progression or the date of patient's death whichever occurs first, regardless of whether radiological progression has occurred or not. If a patient neither experienced neurologic progression nor died, then the data will be censored at the last date of post-baseline neurologic assessment. If a patient with no post-baseline neurologic assessment did not experience neurologic progression nor died, then the data will be censored at the date of enrollment.

Clinical deterioration free survival (CDFS): CDFS is defined as the number of days from patient enrollment in trial until the date of first clinical deterioration or the date of patient's death whichever occurs first, regardless of whether clinical deterioration has occurred or not. If a patient neither experienced clinical deterioration nor died, then the data will be censored at the last date of post-baseline Karnofsky performance score assessment. If a patient with no post-baseline Karnofsky performance score assessment did not experience clinical deterioration nor died, then the data will be censored at the date of enrollment.

See definitions below.

7.2.3 Definition of Response and progression

PFS6 is the primary endpoint for Group C. Additionally; several secondary endpoints are based on neuroimaging as assessed by MRI: the response rate, median progression-free survival, and the progression-free survival at defined time points. The sites should base their estimate of response according to the RANO criteria (Ref. 36) which would also be state of the art outside a clinical trial. The subsequent MRIs will be compared to the baseline MRI as defined in Section 7.2.5. In brief, the following definitions apply:

- **Complete Response (CR)**: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
- **Partial Response (PR)**: 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
- **Stable disease (SD)**: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- **Progression (PD)**: 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy; any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication

adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

The measures previously proposed by RANO (Ref. 36) to measure the clinical deterioration will also be completed and a comparison of both clinical and radiological evaluation will be made.

RANO clinical evaluation will be based on KPS evaluation. Clinical progression is defined as the presence of the following conditions

- a decline in KPS from 100 or 90 to 70 or less, or
- a decline in KPS of at least 20 from 80 or less, or
- a decline in KPS from any baseline to 50 or less, for at least 7 days,

will be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose.

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑
New lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	Not applicable*
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirements for response	All	All	All	Any

*increase in steroids alone does not qualify for PD

For this trial, the primary measure of response and progression will be determined by the locally assessed response according to the RANO criteria. All treatment decisions should be based on the RANO criteria.

7.2.4 Neurological evaluation

Neurological evaluation will be performed using NANO scale.

The NANO criteria will be determined as follows (Ref. 19):

- *Neurologic response* is defined as a ≥2 level improvement in at least one domain without worsening in other domains from baseline or best level of function that is not attributable to change in concurrent medications or recovery from a comorbid event.
- *Neurologic stability* indicates a score of neurologic function that does not meet criteria for neurologic response, neurologic progression, non-evaluable, or not assessed.
- *Neurologic progression* is defined as a ≥2 level worsening from baseline or best level of function within ≥1 domain or worsening to the highest score within ≥1 domain that is felt to be related to underlying tumor progression and not attributable to a comorbid event or change in concurrent

medication. Of note, an assessment of neurologic progression does not require evaluation of a minimum number of domains of the NANO scale if any of these conditions is met.

- *Non-evaluable* should be selected if it is more likely than not that a factor other than underlying tumor activity contributed to an observed change in neurologic function. Such factors may include changes in a concurrent medication, such as corticosteroids, sedatives, narcotics, or anti-epileptic agents; acute or chronic adverse events related to therapeutic interventions; or a comorbid event such as a toxic-metabolic encephalopathy, post-ictal state, stroke, etc. Non-evaluable could also be selected if measurement of a given domain is not feasible due to an alteration of another domain. For example, assessment of upper extremity ataxia may not be possible if weakness of the extremity limits mobility. In this case, the strength domain should be assigned a numeric score but the upper extremity ataxia domain would be scored as non-evaluable.
- *Not assessed* should be scored if the clinician omits evaluation of that particular domain during his/her examination. If a particular domain is marked not assessed at baseline, then that domain cannot thereafter be considered for progression or response. In general, assessment and scoring of all domains is encouraged.

Neurologic Assessment in Neuro-Oncology will be based on NANO scale.

7.2.5 MRI evaluation

Follow up assessments will be done using modified RANO (while considering T2/FLAIR).

- Only contrast-enhancing MRI lesions with two perpendicular diameters of 10 mm or more visible on 2 or more axial slices which are not more than 5 mm apart are eligible as target lesions.
- In most patients, only one lesion will be present. In case of multifocal measurable disease, a minimum of 2 and maximum of 5 largest enlarging lesions will be chosen as target lesions and the sum of the products of the perpendicular diameters will be determined.
- All other lesions that do not meet the criteria for target lesions are defined as non-target lesions and are assessed according to the same schedule. They are only taken into account in two situations:
  - if one of them clearly progresses, the overall response to therapy will be evaluated as "progression", independent of the response of target lesions.
  - all lesions must have completely disappeared to report a "complete response".
- Adequate investigations must be carried out at each evaluation of the disease to detect new lesions. If any new lesion is found, the response will be evaluated as "progression". Regardless of the status of enhancing lesions, if progressive lesions are observed on T2-weighted images or FLAIR images, the patient will be considered radiologically progressive, but treatment may continue if this is considered to be in the best interest of the patient and there are no signs or symptoms of clinical progression.
- Postoperative changes on contrast-enhanced neuro-imaging may interfere with disease evaluation. Within the first three days after surgery on MR imaging a thin linear enhancement may develop around the resection cavity, thereafter this enhancement may become thick and nodular. Enhancement of dural and meninges may be more pronounced, even within the first days. The postoperative linear enhancement may persist up to 3-6 months, dural and meningeal enhancement may last much longer. If MRI obtained within 72 hours after surgery shows enhancing lesions with a nodular or mass-like appearance in areas showing tumor on the pre-operative scans this is highly suggestive of residual tumor. The use of diffusion-weighted MR imaging in the immediate postoperative MRI may help with the identification of ischemic areas around the surgical cavity that may show enhancement with further follow-up.

Follow up assessments will be done using RANO criteria (while considering T2/FLAIR).

Baseline evaluations:

- Group A and B: baseline MRI is defined as MRI done within 14 days of first dose of TG02. If a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.
- Group C: baseline MRI is defined as MRI done within 14 days of first dose of TG02. For patients with surgery for recurrence, if a 72-hour post-surgery MRI was done and falls within this time window, baseline MRI does not need to be repeated.

MRI Response criteria:

The sites should base their estimate of response on the RANO criteria (Ref. 36) (also considering T2 weighted and FLAIR images), which would also be state of the art outside a clinical trial. In brief, the following definitions apply:

Complete response (CR):

Requires all of the following:

1. complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions;

2. stable or improved non-enhancing (T2/FLAIR) lesions;

3. patients must be off corticosteroids (or on physiologic replacement doses only);

4. and stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.

Partial response (PR):

Requires all of the following:

1. 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks;

2. no progression of non-measurable disease;

3. no new lesions;

4. stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan;

5. the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease.

Progressive disease (PD):

Progression is defined by any of the following:

1. 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids;

2. significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects);

3. any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose;

4. failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non-measurable disease.

Based on the RANO criteria, for the determination of first progression in Group A, after initial radiotherapy plus TG02, the following criteria should be used in addition to those above:

Progressive disease less than 12 weeks after completion of radiotherapy

Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas i.e., 70% tumor cell nuclei in areas, high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.

Progressive disease 12 weeks or more after radiotherapy completion

1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.

2. Increase by 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.

3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.

4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

If the evidence of PD is equivocal (target or non-target lesions), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression.

In case non-measurable tumor is left after surgery i.e. tumor less than 10x10 mm, unequivocal progression of non-target lesion may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increase in the size of a non-target lesion is NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used as the date of progression. This implies that in case of gross total resection of the

enhancing lesion, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor progression.

Stable Disease (SD):

This occurs if the patients did not qualify for complete response, partial response, or progression (see above) and requires: 1) No meaningful change in the appearance of the FLAIR/T2 images compared to baseline or to the nadir (point with the smallest FLAIR/T2 abnormalities) if a decrease occurred.

Evaluation of response, treatment decision and central review:

- For this trial, the primary measure of response and progression will be determined by the locally assessed response according to the RANO criteria. The time point of progression will be determined at the sites, although the centers in Zurich and Vienna (Reference Neuroradiology) will be happy to provide support.
- Study treatment is completed at the time of first progression. Follow-up until death or the end of data acquisition is required within this trial.
- To ensure a homogeneous radiological evaluation, all MRI images will be retrospectively centrally reviewed by Vienna [redacted] study coordinator, study co-coordinator and Tragara pharmaceuticals representative as a secondary analysis and specific study MRI protocol will be used.

7.3 Evaluation of safety

7.3.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug-related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events. A change in grading will be collected by giving an outcome date to the initial AE. A new adverse event needs to be reported to reflect the change in severity.

The collection period will start from patient enrollment.

All adverse events will be followed until resolution while the patient remains on study treatment. When the patient discontinues study treatment, suspected adverse reactions (AEs for which there is a reasonable possibility that the drug caused the AE) that started while on study treatment should be followed for 30 days from the date of the last dose of study drug or until considered chronic/ stable (as judged by the Investigator), whichever comes first.

New SAEs and serious suspected adverse reactions that occur during the 30-day period should be reported and followed until resolved or considered stable / chronic (as judged by the Investigator).

7.3.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/.

Hematological and biochemistry adverse events will be assessed on the basis of at least monthly blood counts, except weekly for the first cycle.

The highest CTCAE grading per cycle and per patient will be computed at the EORTC HQ for analysis.

Planned safety analysis and tabulations are described in the statistics section.

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this Protocol (see chapter 15 on Reporting Serious Adverse Events).

7.3.3 Toxic deaths

Toxic death is defined as death due to toxicity (defined as death from an AE for which there is a reasonable possibility that the study treatment caused the AE). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.3.4 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the sponsor's medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

7.4 Evaluation of frailty using the G8 geriatric screening tool

7.4.1 Background

Older cancer patients have a much more heterogeneous general health status compared to young cancer patients. Some older patients are in perfect general health, while others are vulnerable or frail. Frailty is a well-known concept in geriatric medicine (Ref. 45). It is defined as a multi-factorial syndrome, resulting in a reduction of the physiological reserve and of the capability to resist stressful events (homeostatic capacity). Frailty is associated with an increased risk of unfavorable clinical events: disability, hospitalization, institutionalization, death. In oncology, the construct of frailty is also used to describe patients with increased risk of treatment-associated morbidity and mortality. Presence of frailty can be detected by the (Comprehensive) Geriatric Assessment (GA). Performance of GA is advised in older cancer patients by the International Society of Geriatric Oncology, SIOG (Ref. 46). GA is time consuming (takes about 30 minutes). Therefore, short geriatric screening tools such as the G8 have been developed as a short and easy to use measurement of general health status. The G8 score has been specifically developed in oncology, includes 8 items, takes a few minutes to complete, and can be completed by any health care worker (Ref. 47). The score ranges from 1 to 17. A score greater than 14 indicates that there is little risk that further GA reveals significant problems in the further assessed GA domains. The G8 was shown to strongly predict functional decline and overall survival (Ref. 48). G8 is by far the best studied geriatric screening tool in oncological patients, and also has better performance for detection of geriatric problems than other geriatric screening tools such as VES-13 (Ref. 49).

7.4.2 Assessments

G8 will be measured in all patients in groups A and B. G8 has to be completed by the clinician, the nurse or the trained coder. This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient. The English version of G8 is included in Appendix G.

7.4.3 Objective

The inclusion of the G8 screening tool in EORTC trials will allow a uniform, easy and established approach of frailty at baseline. The G8 tool itself has been developed as a screening tool, and not a tool for follow-up.

The treating physician may decide which actions are needed based on the G8 result (e.g. further geriatric assessment in case of a G8 score of less or equal to 14; geriatric interventions if specific problems are detected within specific geriatric domains).

The assessment of frailty as defined by G8 entered in EORTC trials will allow interpretation of whether new treatment strategies have been tested in both fit and less fit patients which has importance for the generalizability of the study results.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

Groups A and B

This is an open label, non-randomized, multi-center trial using the classical 3+3 design.

In both groups A and B, a minimum of 3 patients will be included at each dose level. There is no intention to increase the dose of TG02 above 150 mg in Groups A and B. Within one dose level, patients may be entered simultaneously. The second dose level may be started when all patients of dose level 1 have completed cycle 1 (28 days).

In case of occurrence of 1 DLT, an additional 3 patients will be added in order to ensure the safety profile of this dose level unless a DLT is documented immediately in any additional patient entered at this dose level. If 2 DLT are observed in the first 3 patients dose escalation will stop without need to extend the dose level to 6 patients.

The replacement of patients will be performed in case of patients that progress, die due to disease progression, or leave study for any reason other than DLT prior to completion of the first cycle of therapy.

After determination of the MTD, additional patients will be treated at the highest dose level for additional safety information in the absence of safety issues up to a total of 24 evaluable patients in Group A and up to a total of 12 evaluable patients in Group B (up to 36 evaluable patients for Groups A and B). We consider groups A and B exploratory and independent from each other, with the prime goal of assessing feasibility (tolerability, safety). The difference in size in these two groups reflects the natural distribution of patients into those with tumors without (2/3, group A) and with (1/3, group B) MGMT promoter methylation. The elderly patient population is ideally suited to explore safety, tolerability and efficacy of TG02 with the two backbones of glioblastoma treatment, radiotherapy (group A) and temozolomide (group B), in isolation. Finally, there is a feasibility consideration: we anticipate that doctors and patients are more willing to omit temozolomide in group A than to omit radiotherapy in arm B although such a strategy is consistent with the EANO guideline updated in 2017 (Ref. 35).

Number of Patients with DLT at a Dose Level	Dose Escalation Decision Rule in Groups A and B
0 out of 3	Enroll 3 patients at the next dose level up to a maximum TG02 dose of 150 mg.
≥2 out of 3 or 6	Dose escalation is stopped. If it occurs at 100 mg then trial is stopped without MTD. If it occurs at 150 mg then 100 mg is considered the MTD and as the recommended dose for phase II. The safety at the MTD will also be assessed in additional patients up to a maximum of 24 patients in group A and 12 patients in group B. These totals include all patients recruited in the 3+3 escalation phase.
1 out of 3	Enroll at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level up to a maximum TG02 dose of 150 mg. If it occurs at 150 mg then 150 mg is considered the MTD and as the recommended dose for phase II. If 1 or more of this Group experience DLT, then dose escalation is stopped. If it occurs at 100 mg then trial is stopped without MTD. If it occurs at 150 mg then 100 mg is considered the MTD and as the recommended dose for phase II. The safety at the MTD will also be assessed in additional patients up to a maximum of 24 patients in group A and 12 patients in group B. These totals include all patients recruited in the 3+3 escalation phase.

DLT = dose limiting toxicity

MTD = maximum tolerated dose

The MTD corresponds to the highest dose at which not more than 1 patient out of a maximum of 6 experiences a DLT. A compliance of 75% for TG02 and either RT (Group A) or TMZ (Group B) is required to assess the toxicity.

Group C

Further to the IDMC recommendations, the initial dose of TG02 was reduced from 200 to 150 mg with potential to escalate to 200 mg in case the first full cycle was well tolerated. During the follow-up IDMC meeting, the IDMC recommended to stop escalation to 200 mg. The initial statistical design remains applicable to eligible patients treated at initial dose of 150 mg.

Data collected at initial dose 200 mg (n=18) and 250 mg (n=6) will be analyzed for descriptive purpose only i.e., will not be included in the analysis below (primary analysis.)

Based on an A'Hern one-stage design, 45 eligible patients who started treatment will be evaluated for PFS at 6 months. It is estimated that the total sample size should not be larger than 50 assuming a dropout of 10%.

The following hypotheses apply:

- P0 is the largest PFS rate at 6 months which, if true, implies that the therapeutic activity of TG02 is too low. In the present trial, P0 has been taken as 20%.
- P1 is the lowest PFS rate at 6 months which, if true, implies that the therapeutic activity of TG02 is adequate. In the present trial, P1 has been taken as 40%.

- α is the probability of accepting adequate activity of TG02 with a true PFS rate at 6 months equal to or lower than P0. In the present trial, α has been taken as 0.10.
- β is the probability of rejecting adequate activity of a drug with a true PFS rate at 6 months at least equal to P1. In the present trial, β has been taken as 0.05.

A decision rule for efficacy will be performed amongst the 45 patients:

- If < 13 patients are free of progression and alive at 6 months, the conclusion will be that TG02 should not be further investigated.
- If ≥ 13 patients free of progression and alive at 6 months are observed, we will conclude that TG02 should be further investigated. In this case, the one-sided 90% confidence interval excludes P0.

8.1.2 Randomization and stratifications

No randomization or stratification will be used in this study.

8.2 Statistical analysis plan

Each of the three groups will have a separate final analysis report. These reports and related publications can be released at different time points.

8.2.1 Analysis populations

- Intention-to-treat population: All enrolled patients will be analyzed in the arm they were allocated by.
- Efficacy population: All patients who are eligible and have started their allocated treatment (at least one dose of TG02).
- Safety population: All patients who have started their allocated treatment (at least one dose of TG02 and were not replaced in phase Ib).

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician of the EORTC Brain Tumor Group at time of medical review.

8.2.2 Statistical methods

Group A and B

Primary endpoints are the determination of the Maximum Tolerated Dose (MTD) and the recommended phase II combination dose. All analyses will be performed in the safety population. Analyses will be descriptive only presented with tables and listings (i.e. no formal inference). Objective response rate will be reported with exact (binomial) 95% two-sided confidence interval. The PFS-6 and OS-9 and the medians will be extracted from their Kaplan-Meyer curves. The 95% two-sided confidence intervals will be computed based on the Greenwood's formula and based on the Reflected Method for the median. The best overall response will be presented in contingency table with numbers and percentages. The objective response (CR+PR) and complete response (CR) rates will be reported with exact (binomial) 95% two-sided confidence interval. Duration of objective response and complete response will be estimated using Kaplan-Meier methodology. Median duration of objective and complete response with corresponding 95% two-sided confidence interval provided by the Reflected Method will be displayed. Hematological and biochemistry parameters will be presented with clinical significance (CS vs NCS).

Safety and efficacy data in patients excluded from the safety population will be reported separately.

Group C

- Number of patients free of progression at 6 months (primary analysis)

In the efficacy population:

All patients will be observed during a minimum follow-up of 6 months. The number of patients free of progression and alive at 6 months will be computed and the above-mentioned decision rule applied. Patients lost to follow-up or who died before 6 months are considered as failures at the time of analysis. In case more than 45 eligible patients are recruited, the decision rule will be applied as such on the first 45 eligible patients. The proportion of patients free of progression at 6 months will be presented with 80% two-sided confidence intervals computed based on the Exact Binomial distribution.

- Progression free survival

In the efficacy population:

The primary endpoint, PFS rate at 6 months (PFS6) and the median PFS will be extracted from the Kaplan-Meyer PFS curve. For PFS6, 80% two-sided confidence intervals and 95% two-sided confidence intervals will be computed based on the Greenwood's formula. For the median the Reflected Method will provide 95% two-sided confidence intervals.

These estimates will be presented both based on investigator and centrally reviewed progression data.

- Overall survival

In the efficacy population:

The OS rate at 9 months (OS-9), 1 year (OS-12) and the median will be extracted from the Kaplan-Meyer OS curve. For OS-9 and OS-12 95% two-sided confidence intervals will be computed based on Greenwood's formula. For the median the Reflected Method will provide 95% two-sided confidence intervals.

- Response and duration of response

In the efficacy population:

The best overall response will be presented in contingency table with numbers and percentages. The objective response (CR+PR) and complete response (CR) rates will be reported with exact (binomial) 95% two-sided confidence interval.

Duration of objective response and complete response will be estimated using Kaplan-Meier methodology. Median duration of objective and complete response with corresponding 95% two-sided confidence interval provided by the Reflected Method will be displayed.

These estimates will be presented both based on investigator and centrally reviewed response data.

- Success rate

In the efficacy population:

The success rate will be reported with exact (binomial) 95% two-sided confidence interval.

Success rate will be presented both based on investigator and centrally reviewed response data.

- Neurologic progression free survival

In the efficacy population:

The NPFS rate at 6 months (NPFS6) and the median NPFS will be extracted from the Kaplan-Meyer PFS curve. For NPFS6, 95% two-sided confidence intervals will be computed based on the Greenwood's formula. For the median the Reflected Method will provide 95% two-sided confidence intervals.

- Comparison of PFS by local investigator and by central review and comparison of NPFS and CDFS.

In the efficacy population:

The differences of times to event between these estimates will be tabulated.

- Safety and tolerability

In the safety population:

The safety and tolerability analyses will be presented at baseline and up to 30 days after the last administration of study drug. Baseline will include all information recorded up to the nearest date prior to or at randomization. Exceptionally in absence of this assessment, the first assessment performed after randomization but before start of protocol treatment can be considered as baseline.

Baseline laboratory and AE grades will not be accounted for in whole treatment safety analyses.

Laboratory events of clinical significance (CS) will be reported on the adverse events CRFs and will be reported separately.

- Hematological parameters

The worst value of each hematological category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated. A table with grade 3/4 frequencies and percentages will also be displayed. The frequencies and percentages of patients with at least one grade 1 or one grade 3 or 4 hematological toxicity will be presented.

- Biochemistry parameters

The worst value of each biochemical category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated. A table with grade 3/4 frequencies and percentages will be displayed. The frequencies and percentages of patients with at least one grade 1 or one grade 3 or 4 biochemistry toxicity will be presented.

- All adverse events

The worst grade of each AE item will be identified for each patient. Frequencies and percentages of each category will be tabulated. Tables with all grades, grades 3 or 4 and grades 5 frequencies and percentages will be displayed. The frequencies and percentages of patients with at least one grade 1 or one grade 3 or 4 or one grade 5 AE will be presented.

- Related AEs

The worst grade of each likely related AE item will be identified for each patient. Frequencies and percentages of each related AE category will be tabulated. Tables with related grades, grades 3 or 4 and grade 5 frequencies and percentages will be displayed. The frequencies and percentages of patients with at least one related grade 1 or one related grade 3 or 4 or one related grade 5 AE will be presented.

- SAEs and Related SAEs

After reconciliation with the SAEs listing extracted from the EORTC pharmacovigilance database, the worst grade of each (related) serious AE category will be identified for each patient. Frequencies and percentages of each category will be tabulated. Tables with all (related) grades, (related) grades 3 or 4 and (related) grades 5 frequencies and percentages will be displayed. The frequencies and percentages of patients with at least one (related) grade 1 or one (related) grade 3 or 4 or one (related) grade 5 SAE will be presented.

8.2.3 Pre-planned sensitivity or exploratory analyses

As sensitivity analysis in group C, PFS and OS analyses will also be presented in the intent to treat population.

As exploratory analysis, in group A and B, baseline frailty scores will be correlated with safety, tolerability and efficacy.

In all groups, correlation of molecular markers including MYC, MCL-1, CDK9 and CDK5 proteins level (but not exhaustively) with response, success, PFS and OS will be explored.

8.2.4 Prognostic factor analyses

Data of this trial will be added to the EORTC GBM data warehouse for further research projects (e.g. pooled analyses of prognostic factors).

8.2.5 Data recording and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of enrollment – date of past event + 1) and presented using the median and range. For example, on the enrollment checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of enrollment – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, laboratory data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

No interim analysis will be done.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Trial Governance and Data Monitoring

9.1 Study committees

9.1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, clinical operations manager and data managers) and the principal study coordinator.

The EORTC Headquarter team is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study management Group also performs the medical review as indicated below.

9.1.2 Study Steering Committee (SSC)

The Study Steering Committee for this study is composed of the study coordinators, the representatives of Academic Groups collaborating to the study, at least one representative of the EORTC Headquarters (Study Clinical Research Physician or Clinical Scientist) and one representative of the Sponsor, if the sponsor is not the EORTC.

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

9.1.3 Independent data monitoring committee (IDMC)

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study. The composition of the IDMC is described in EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (ref. EORTC POL004) and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the clinical operations manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups…).

9.2 Data Monitoring

9.2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the clinical research physician assisted as needed by the study management group. The main study coordinator will, in particular, support the Study Clinical Research Physician during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The main study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

For blinded trials, the medical review is conducted blinded to treatment allocation.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC).

9.2.2 Monitoring by the IDMC

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up.

The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants.

The IDMC will also review the intermediate reports of accumulating data according to the study interim monitoring plan described in the statistical section of this protocol. If a decision is made to continue without change, the IDMC may advise on the frequency of future reviews of the data on the basis of accrual and event rates.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

10 Quality of life assessment (Groups A and B only)

10.1 Rationale

Health-related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general well-being reflecting physical, psychological, and social well-being and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient's subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.

Reducing mortality and morbidity is still the most important goal in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish a patient's HRQoL even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

Due to the poor overall prognosis of the study population in this study (i.e. frail, elderly high-grade glioma patients) improvement of the well-being during the remaining survival is an important factor for the patient.

10.2 Objective

Since elderly patients are more prone to side-effects from novel treatments and since maintaining HRQoL is a major consideration in de-escalating treatments that provide little benefit, e.g., TMZ in patients with tumors without MGMT promoter methylation, this phase Ib trial will also capture data on HRQoL in Group A (addition of TG02 to postoperative RT in MGMT-unmethylated, IDH1^{R132H}-non-mutant WHO grade III and IV glioma) and B (addition of TG02 to postoperative TMZ chemotherapy in MGMT-methylated IDH1^{R132H}-non-mutant WHO grade III and IV glioma). Therefore, in the present study, HRQoL is an exploratory endpoint.

The main objective of this study is to explore the impact of combined treatment on overall global health and HRQoL in this fragile, elderly (> 65 years) high-grade glioma patient population. A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side-effects may have a (temporary) negative influence on the health related domains of HRQoL of these patients with a particular emphasis on fatigue, nausea/vomiting and diarrhea in the light of the expected side effects of TG02.

10.3 HRQoL instrument

Quality of life will be assessed using an ad-hoc questionnaire based on the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 50). The average time to complete the questionnaire is approximately 10 minutes. The EORTC QLQ-C30 version 3 has been translated in over 50 languages according to a standardized translation procedure. While this questionnaire is the most used instrument in cancer clinical trials (Ref. 51), it contains some superfluous dimensions while lacking some particular to the QL issues in certain brain cancer. Therefore, the instrument was modified by removing unneeded questions and shortening certain scales by using the equivalent from the PAL15 instrument (Ref. 52). Relevant items were added, mainly from the EORTC Brain Cancer module (QLQ-BN20) (Ref. 53), designed for use in patients undergoing protocol treatment or radiotherapy and from the QLQ-STO22 (Ref. 54).

The final modified questionnaire consists of the EORTC QLQ-C30 version 3 with the following changes:

- Financial difficulties scale removed (-1 question).
- Physical functioning replaced by PAL15 version (-2 questions)
- Emotional functioning replaced by PAL15 version (-2 questions)
- Motor Dysfunction added from BN20 (+3 questions)
- Cognitive Deficit added from BN20 (+3 questions)
- Drowsiness added from BN20 (+1 question)
- Headaches added from BN20 (+1 question)
- Seizures added from BN20 (+1 question)
- Abdominal Pain added from STO22 (+1 question)

All modifications were done using the EORTC Item Library to ensure content validity and adequate translations of the added questions.

10.4 Study design

Patients in Group A and Group B who are eligible for the HRQoL assessment in this study if they fulfill the eligibility criteria (see chapter 3). Should the HRQoL forms not be available in the required language or should the patient refuse to fill out the form, then this should exclude the patient from further participation in the study. Patients will be informed in the patient informed consent form that they will have their quality of life assessed regularly while involved in this trial. In this phase Ib part of study 1608, HRQoL will be an exploratory outcome and evaluated in a longitudinal design in all patients entered in arms A and B of the study.

HRQoL questionnaires must be filled out at the hospital according to the EORTC "Guidelines for administration of questionnaires" (see Appendix F) when patients come for a scheduled visit for a complete neurological examination (NANO). The pre-treatment questionnaires must be filled out within 14 days before enrollment. Subsequent questionnaires are administered at the end of every second cycle (± 8 days) until cycle 6, then at the end of every third cycle (± 8 days), at the end of study visit, and every 3 months (± 14 days) afterwards until death or patient refusal.

The time windows for eligible HRQoL assessments will be as follows:

Assessment	**Time window**
Baseline	Can be completed before or on the day of randomization itself but no earlier than 2 weeks before.
End of cycle 2	Can be 8 days before or after D1 of cycle 3
End of cycle 4	Can be 8 days before or after D1 of cycle 5
End of cycle 6	Can be 8 days before or after D1 of cycle 7
End of cycle 9 + q3W	Can be 8 days before or after D1 of every 3rd cycle after cycle 7 (i.e. cycle 10, 13, 16, …).
End of study visit	End of study visit should take place within 30 days after the last dose of TG02.
Follow-up after end of study treatment	Every 3 months (± 14 days)

Master copies of the HRQoL questionnaires will be sent to the institutions. Additional copies or translations can be provided upon request via the EORTC contact person. The clinical report forms will include a question whether the HRQoL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

10.5 Statistical considerations

The primary HRQoL endpoint that is considered relevant for this study is the Global health/QoL status (GHQs) scale of the QLQ-C30 instrument. Other scales will be analyzed on an exploratory basis as secondary HRQoL endpoints, with a particular emphasis on fatigue and nausea/vomiting and diarrhea in the light of the expected side effects of TG02. The standard deviation of this scale is approximately 20

points. As this is an exploratory analysis in the framework of a phase 1b study with a sample size dependent on toxicity, using a classical phase I dose-escalation design (3+3), we do not provide a sample size calculation.

Data will be scored according to the algorithm described in the EORTC scoring manual (Ref. 55). All scales and single items are scored on categorical scales and linearly converted to 0-100 scales. Reporting of data will be mainly descriptive, as this is an exploratory analysis.

Changes in HRQoL scores over time will be evaluated with a repeated measurement modeling using a mixed effect procedure. A linear mixed model with treatment, a time effect, a time-treatment interaction and possibly other baseline covariates as fixed effects and a patient specific random effect will be fitted. Prior to reducing the model, the most suitable covariance structure should be determined on the basis of Akaike's Information Criterion (AIC). Covariates other than the treatment and the time indicator may be dropped from the model based on a 5% significance level for the Type III fixed effect test. The main test will be obtained by contrasting the scores in the two treatment arms over all post-baseline time-points (F-test). The repeated measures analysis will be supplemented by a cross-sectional analysis. Graphs will display the mean score by treatment group with their 99% confidence intervals.

10.5.1 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

11 Translational research

Translational research in this trial is optional.

11.1 Objective

MYC and Mcl-1 over-expression have been reported in more than 80% and 46% of glioblastomas, respectively (Ref. 5, Ref. 8, Ref. 30). MYC inhibition resulted in reduced proliferation, increased apoptosis and ineffective mitosis in vitro and in experimental glioma models in vivo and has been validated as a therapeutic approach for treatment of gliomas (Ref. 1).

TG02 is a potent inhibitor of cyclin-dependent kinase 9 (CDK9). The primary mechanism of action is blockade of survival signaling. CDK9 is a key regulator of transcription via its substrate, RNA polymerase 2. When transcription of RNA polymerase 2 is blocked through CDK9 inhibition, short-lived cellular proteins (including MYC and Mcl-1) rapidly become depleted (Ref. 23). Depletion of MYC and Mcl-1 undermines survival signaling in tumor cells, resulting in caspase activation, and committing cells to apoptosis.

TG02 is also a potent inhibitor of CDK5. CDK5 is overexpressed in a large number of glioblastomas (Ref. 4, Ref. 42). CDK5 is an atypical CDK, which suppresses the cell cycle without the use of its kinase activity (Ref. 43). CDK5 also regulates the phosphatidylinositol 3 (PI3)-kinase enhancer (PIKE)-A-AKT pathway and promotes glioblastoma cell migration and invasion by PIKE-A GTPase (Ref. 15).

We will determine the CDK9, MYC, Mcl-1 and CDK5 protein levels using immunohistochemistry to assess the potential correlation of CDK9, MYC, Mcl-1 and CDK5 levels prior to treatment with TG02 with efficacy endpoints.

11.2 Samples Collection

For group C patients, tissue from the initial diagnostic operation is required for inclusion. For translational research, for patients undergoing second surgery at progression before enrolment, submission of tissue from the second operation is also encouraged.

Centers are furthermore encouraged to submit tissue from any surgery at progression on TG02 to enable determination of expression of the above-mentioned targets of TG02. Additionally, we will determine the residual TG02 concentration in the tumor tissue to confirm that TG02 reaches the tumor.

Additionally, we will collect blood samples for the following:

- As part of future research for the potential determination of emerging peripheral biomarkers of TG02 sensitivity and correlate these with outcome. Plasma (10 mL) and cell pellet will be collected for collection of ctDNA and gDNA, respectively; serum (10 mL) will be collected for the determination of soluble biomarkers, e.g., cytokines or chemokines.
- As part of a pharmacokinetic study, plasma (10 mL) will be collected for the determination of TG02 blood concentration.

For more details in collection and shipment of samples, refer to the HBM guidelines, provided as a separate document.

11.2.1 Tumor samples: initial surgery and recurrence

The following material is requested:

- A paraffin embedded tumor sample (preferably a tumor block; otherwise 25 unstained slides) from the initial diagnosis of glioblastoma or anaplastic astrocytoma.
- A paraffin embedded tumor sample (preferably a tumor block; otherwise 25 unstained slides) from patients with a surgery planned after recurrence/progression while on TG02. For these patients, TG02 should be continued, if possible, until surgery, and a 10 mL plasma sample should be obtained close to the time of surgery for comparison of TG02 levels in tumor and peripheral blood.

<u>Group A and B</u>

At the end of accrual, tumor samples from patients in groups A and B will be sent by [redacted] to Department of Neurology, University Hospital Zurich to perform the optional translational research program.

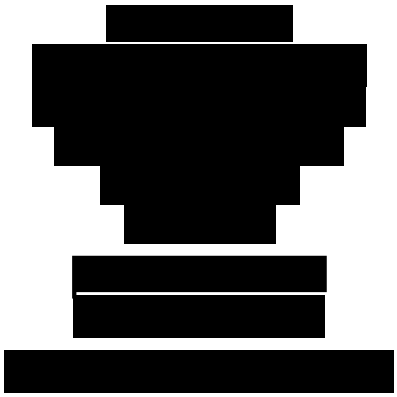
Tissues available from second surgery in groups A and B at progression on TG02 will be sent by the sites after last patient in and upon green light of EORTC HQ to Department of Neurology, University Hospital Zurich for the optional translational research program.

Group C

Tissues available from second (before TG02) and third (after TG02) surgery from group C patients will be sent by the sites after last patient in and upon green light of EORTC HQ to Department of Neurology, University Hospital Zurich for the optional translational research program.

11.2.2 Blood samples: peripheral biomarkers.

Twenty mL blood samples (10 ml plasma, 10 ml serum) will be collected at baseline, C3D1 and at progression/end of study. At the end of accrual upon receiving confirmation by EORTC HQ, all blood samples should be sent by sites to Zurich:



11.2.3 Blood samples: pharmacokinetics.

For patients consented to the PK study in group C, a total of eight (8) blood samples of 6 mL blood each will be collected at C1D1 predose and C1D15 pre-dose and 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours post-dose. When all 8 blood samples for a patient have been collected, the blood samples for that patient should be sent to:

	Timepoints for all groups	Destination	When
FFPE **(tissue sample or 25 unstained slides)**	At diagnosis (*MANDATORY*)	[redacted] (groups A & B) University Hospital Zurich (All groups)	For Groups A & B as soon as consent form is signed For Group C, at end of accrual upon EORTC HQ instructions

	Timepoints for all groups	Destination	When
FFPE **(tissue sample or 25 unstained slides)**	At recurrence (if applicable)	University Hospital Zurich	At end of accrual upon EORTC HQ instructions
10 mL Plasma and cell pellet: **3 blood samples per patient**	At baseline C3D1 At progression or end of study	University Hospital Zurich	At end of accrual upon EORTC HQ instructions
10 mL Serum: **3 blood samples per patient**	At baseline C3D1 At progression or end of study	University Hospital Zurich	At end of accrual upon EORTC HQ instructions
10 mL Plasma: **1 blood sample**	If surgery planned for progression	University Hospital Zurich	At end of accrual upon EORTC HQ instructions
GROUP C ONLY **6 ml blood each sample:** **8 blood samples per patient who consented to the PK study**	C1D1: pre-dose C1 D15: pre-dose; 30 min, 1 hr, 2hrs, 4 hrs, 8 hrs and 24 hrs post-dose	[redacted]	When all samples for a patient have been collected.

11.3 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Bioinformatics and statistical analysis plan will be jointly developed for each project. These documents will be developed and approved before starting any analysis. They will specify the analytical and methodological details. Clinical and patient reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be performed according to applicable policies in each organization (e.g. EORTC POL008) or according to jointly approved data transfer charters.

11.4 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be first sent to [redacted] for MGMT testing then to EORTC Academic Institutions (tumor samples and blood samples to University Hospital Zurich). Thereafter, any leftover material will be either destroyed or returned to the local site.

The following principles apply to storage of HBM:

- The collected HBM should be documented, i.e. the amount remaining and its location.
- The Study Coordinators and the EORTC Brain Tumor Group Steering Committee will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol.
- Final decisions on the use of HBM will be determined by a majority vote of the Brain Tumor Group Steering Committee. Additional expertise may be sought through advisory non-Group Steering Committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate Group's Steering Committee.
- The Group's Steering Committee will prioritize the TR projects. Access procedures defined by the Group's Steering Committee will build on the following key points:
    - Project prioritization
        - should be strongly based on scientific merit,
        - should consider the contribution of the different investigators to the trial and TR project,
        - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
    - Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once the Group's Steering Committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place

and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the Group's Steering Committee and the TR project leader(s), as needed.

12 Investigator authorization procedure (EORTC)

Investigators will be authorized to enroll patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of normal ranges for the investigator’s institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator’s institution.
- The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the CIF.

- The Study Agreement between EORTC and investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the “authorization list”, and will be allowed to enroll patients in the trial as soon as

- All the above-mentioned documents are available at the EORTC Headquarters.
- All applicable national legal and regulatory requirements are fulfilled.

Patient enroll from centers not (yet) included on the authorization list will not be accepted.

13 Patient registration procedure

13.1 Groups A and B

13.1.1 Registration (step 1)

Patient registration will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

Patients should be registered directly on the **EORTC online system**

(ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive enroll program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to enroll patients via the EORTC call center. Enrollment via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems by phone:	+32 2 774 16 00

A patient can only be registered after verification of eligibility. Both the eligibility check and registration must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within your institution*)
- patient's birth date (*01/01/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- date of written informed consent (*day/month/year*)

A **sequential patient identification number (“SeqID”)** will be allocated to the patient. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms, and the online registration of HBM samples via https://samples.eortc.be/ (see section 14.3 and HBM guidelines provided as a separate document).

13.1.2 Central lab review procedure (step 2)

After registration has been completed and shipment of sample has been done, the central laboratory, [redacted] will assess the MGMT promoter methylation status. Patients in Group A and B not registered before the assessment of the MGMT promotor methylation status will not be accepted in the study.

EORTC will receive the MGMT promotor methylation status outcome, results can be expected within 14 days from tissue arrival at [redacted].

Results from the central lab will be entered in the ORTA system (step 2) by EORTC HQ.

When step 2 is completed, the site will be informed by a notification email, following the assessment of the MGMT promotor methylation status, which will indicate in which Group the patient has been assigned to.

During the "Dose Limited Toxicity phase" this e-mail will also indicate whether the patient can proceed to enrollment (step 3) or whether the patient needs to wait (up to 4 weeks). This decision will be based on the number of currently enrolled subjects in the allocated treatment arm.

13.1.3 Enrollment (step 3)

Once all previous steps have been successfully completed, the patient can be enrolled. The enrollment procedure will consist of an exhaustive list of questions to check patient's eligibility.

STANDARD INFORMATION REQUESTED:

- Institution number
- Protocol number (1608)
- Step number: (3 - Existing patient)
- Name of the responsible investigator

Only patients that were already registered in the first step can be selected to enroll. Once identified, select the corresponding patient code. Patient code and date of birth will automatically be inserted in the identification screen.

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values of the eligibility parameters will be requested when applicable

Once eligibility factors have been checked, the site will be informed by an automatic notification email if the patient is eligible.

13.2 Group C

13.2.1 Registration/Enrollment (step 1)

Patient enrollment will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

Patients should be registered directly on the **EORTC online system**

(ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive enroll program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to enroll patients via the EORTC call center. Enrollment via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems by phone:	+32 2 774 16 00

A patient can only be registered after verification of eligibility. Both the eligibility check and enrollment must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within your institution*)
- patient's birth date (*01/01/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- date of written informed consent (*day/month/year*)

Once eligibility has been verified, a **sequential patient identification number ("SeqID")** will be allocated to the patient. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms, and the online registration of HBM samples via https://samples.eortc.be/ (see section 14.3 and HBM guidelines provided as a separate document).

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, *with the exception of the Quality of Life form, the SAE form and the Pregnancy notification form which are paper CRFs.*

Copies of the Quality of Life forms should be sent directly to the EORTC Headquarters by one of the following means:

- By fax, to the attention of [redacted]: [redacted]
- By scanning and e-mailing the forms (see CRF completion guidelines)
- By post to the EORTC Headquarters:

[redacted] EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

14.1.1 Before the treatment starts

The patient must be enrolled in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one hour after the enrollment on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

14.1.2 During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members *with the exception of the paper quality of life form (no signature needed).*

14.2 Data flow

The forms must be completed electronically, *with the exception of the paper forms (the Quality of Life form, SAE form),* according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive enrollment program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data. Corrections of obvious data errors will be done by the EORTC Data Manager, as outlined on the convention list, which can be downloaded from the EORTC trial specific webpage: http://www.eortc.be/protoc/. Queries will be issued in order to resolve other inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

For trials with paper quality of life forms: a copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. If there are queries on the quality of life form, they will be raised electronically on a patient level in the VISTA/RDC system and they must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

For trials with paper quality of life forms: If an investigator (or an authorized staff member) needs to modify the paper quality of life form after the copy has been sent to the EORTC Headquarters, he/she should create a request for data correction on a patient level in the VISTA/RDC system.

14.3 HBM sample registration and tracking

Once the patient is registered, this procedure might take up to one hour, the investigator or his/her authorized staff must log on "Samples" website at https://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be.

"Samples" is a web-based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM management.

15 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

15.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the timeframes defined by national authorities.

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

15.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

15.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v5.0 https://www.eortc.be/services/doc/ctc/.

15.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

15.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following RSI (reference safety information):

- For TG02: IB. The RSI is the IB section entitled “Reference Safety Information”.
- For Temozolomide: SmPC. The RSI is the SmPC section entitled “Reference Safety Information” is section 4.8 in the SmPC

15.6 Reporting procedure for investigators

From the time period when the consent form is signed until randomization/treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to EORTC if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All Serious Adverse Events (SAEs) occurring from the time the subject is enrolled until 30 days after last protocol treatment administration must be reported within 24 hours.

Any SAE that occurs outside of the SAE detection period (after the 30-days period), and considered to have a reasonable possibility to be related to the protocol treatment or study participation also needs to be reported to the EORTC.

Signed Patient Informed Consent 'till enrollment (groups A and B) and first dose of TG02 (group c)	All SAEs only if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention
Enrollment till 30 days after last protocol treatment administration:	All SAEs
From day 31 after last protocol treatment administration:	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed / e-mailed to:

EORTC Pharmacovigilance Unit:

pharmacovigilance@eortc.org

Fax No. +32 2 772 8027

To enable the Sponsor (EORTC) to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product/study treatment if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

15.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs/unexpected events to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM), Tragara and all participating investigators whenever applicable.

15.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 6 months after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit

- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

16.2 On-site monitoring

The EORTC Headquarters will perform on-site monitoring visits according to the approved study-monitoring plan.

The first monitoring visit in a participating site will be performed within 3 to 6 months after the first patient's registration at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

16.3 Audits

The EORTC is responsible for the performance of the EORTC investigators.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters Compliance and Audits immediately (contact at: Complianceandaudits@eortc.org).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

16.4 External review of histology

There is generally high interobserver agreement in the histological diagnosis of glioblastoma and anaplastic astrocytoma. Moreover, immunohistochemistry for $IDH1^{R132H}$ has to be provided at study registration. However, the histological diagnoses will be reconfirmed at the institute of Pathology in Lille. This review will be done post-hoc. If the diagnosis is not confirmed, the patient will not be excluded and will not be replaced.

16.5 Other central review procedures

16.5.1 Imaging

16.5.1.1 Scan submission

All imaging data for this trial will be centrally collected and stored, using the EORTC Imaging Platform. Sites are requested to submit the scans in a timely fashion manner to allow prospective QA/QC to be performed.

In case sites are not able to transfer the imaging data electronically, the data will be sent to EORTC HQ on a CD/DVD via courier and the EORTC imaging team will be in charge of uploading the data on the EORTC imaging platform. Further details about the imaging data transfer can be found in the study specific imaging guidelines.

The EORTC HQ will track all scans of all patients received from the sites and will request/query missing and /incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format (other than DICOM), the site will be informed to provide substitute scans.

16.5.1.2 Imaging guidelines “read and understood” acknowledgment signature page

Every site participating in an EORTC study with imaging, must comply with the minimum requirements established as specified in the imaging guidelines. The first page of the imaging guidelines must be signed and returned to the EORTC HQ for every new version of the imaging guidelines. The page must be signed by the department lead radiologist. This is mandatory from all institutions in this study before activation to participate in the trial.

16.5.1.3 Prospective scan quality control

QC will be performed prospectively, on an on-going basis for all imaging data collected for the trial.

The EORTC Imaging Officer or his back-up will be reviewing all scans for all patients to check for artifacts and to ensure compliance with the imaging guidelines and study protocol requirements.

Every subsequent scan on the same patient must be done with the same scanner across all visits. In case of scanner breakdown or change of scanners in the department, you need to notify the EORTC HQ.

More information about scan settings and acceptable / non-acceptable deviations can be found in the study specific imaging guidelines.

16.5.1.4 Central review

A Blinded Independent Central Review (BICR) will be organized retrospectively to review all collected scans in this study.

The BICR will remain blinded regarding the treatment group of the patients. Furthermore, the reviewers will be blinded regarding the site's assessment which will only be unblinded to the study coordinator.

BICR ensures an independent evaluation of patient scans in a specific study by experts in the specific imaging modality. For further details about the Independent Central Review, please refer to the Central Review Charter, that will be provided as a separate guidelines document.

16.5.2 Quality assurance in radiotherapy

Radiotherapy Quality Assurance will be conducted through the EORTC RTQA platform.

Radiotherapy dosimetry and treatment data will be collected on all patients in Group A of the study.

The RTQA procedure consists of completing the following prior to institution authorization:

- Level I: Facility Questionnaire (FQ) and Beam Output Audit (BOA)
- Level II: Dummy Run
- Level V: Credentialing for the use of IMRT
- During the trial, the following RTQA patient-specific procedure must be performed:
- Level IV: Extensive Individual Case Review (E-ICR)

16.5.2.1 Prior to authorization

16.5.2.1.1 Facility questionnaire (FQ) and Beam Output Audit (BOA)

All EORTC centers at authorization must have a valid EORTC FQ and a valid BOA performed by an external auditor. Both must be not older than 2 years. The questionnaire must be filled in electronically and submitted on line. Additional information can be found at the EORTC website under the Study Tools section.

To determine if a previously submitted FQ and or BOA is valid please contact rtqa1608@eortc.org and along with EORTC institution number.

16.5.2.1.2 Dummy Run

All EORTC centers prior to authorization should perform a Dummy Run. The procedure consists of uploading the anonymized plan of a patient -treated at the institution for Anaplastic Astrocytoma or Glioblastoma- through the EORTC platform, to test the connection between institution and EORTC. Previous completion of a Dummy Run for another study might be considered sufficient if recent.

16.5.2.1.3 Complex Dosimetry check

All EORTC centers prior to authorization must be credentialed for the use of their IMRT technique via a recent complex dosimetry check, provided by an EORTC recognized external institution, or via the Virtual Phantom Procedure (VPP). The VPP consists of irradiating the site's in-house phantom based on the RT plan created for the Benchmark Case. Further details can be found in the "RTQA Guidelines".

16.5.2.2 Patient-specific RTQA program

For all patients in group A, all patient digital treatment data and completed Radiotherapy planning eCRF must be submitted as soon as possible. Patients will be reviewed retrospectively.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

17.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth or year of birth (as allowed per applicable legislation) will also be reported on the case report forms.

17.3 Informed consent

All patients will be informed about:

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters.

The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

18 Administrative responsibilities

18.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team.

The study coordinator should convene a teleconference with PI, co-PI, TRAGARA and EORTC HQ at the end of each dosing cohort during dose escalation in Groups A and B. The study team should review the cohort and make a determination for dose escalation.

The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

18.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
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18.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.org.

Brain Tumor Group EORTC group

Chairman:

19 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
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e-mail: eortc@eortc.org

20 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

21 Results Dissemination policy

21.1 Study disclosure

21.1.1 Trial Registration

This trial will be registered in a public database (https://www.clinicaltrialsregister.eu). As the clinical trial (CT) regulation 536/2014 of the European Union (EU) becomes applicable, more information about this trial will be uploaded in this public database in compliance with European requirements on transparency. Information posted, among others, will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

In accordance with applicable EU regulations, a summary of the trial results will be made publically available within one year of the end of study declaration.

EORTC as Sponsor of this trial will submit the summary of the results based on the final analysis report in compliance with the regulations.

21.1.2 Final Analysis Report

A Final Analysis Report that reports summary statistics of all the data collected for the study and presents an interpretation of the study results will be issued by the EORTC Headquarters. It will form the basis for the manuscript intended for publication. The Final Analysis Report or a summary thereof will be distributed to all participating groups, the supporting companies and ethics committees and the results will be posted in relevant public databases.

21.2 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Publication Policy” version 5.0 dated 23 November 2020 or later.

In accordance with the Policy 009, results of the present study will be made public once the study data are mature for the final analysis of the primary study endpoint (as described in the section “statistics” of the present protocol), irrespective of the findings (positive or negative). Deviations from the results disclosure rules specified in the Policy require authorization by the Independent Data Monitoring Committee (IDMC).

The primary trial publication will be written on the basis of the final analysis report and shall be published in a peer-reviewed scientific journal within 1 year of the date of the database lock. The principal study coordinator is responsible for drafting the manuscript.

All publications ((papers, abstracts, presentations…) must be reviewed and approved by at least one EORTC Headquarters staff prior to submission to journal or congress or presentation. Approval and review by third parties involved in the study comply with all contractual agreement in place.

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors (http://icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and will be attributed for each publication in line with EORTC Policy referred above. All contributors who do not meet sufficient criteria for authorship will be acknowledged in the publication.

Investigators will not independently publish site-specific results about the study endpoints until results of the whole study are published (or after one year following database lock if there is no publication). Deviations from this rule are authorized by the study IDMC.

Sources of funding or support to the study will be disclosed and acknowledged in the publication.

The name “EORTC” and of any collaborative Group must be visible in the publication's header of all publications.

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Appendix B: Abbreviations

2D	Two-dimensional
3D	Three-dimensional
5-HT3	5-hydroxytryptamine
AA	Anaplastic astrocytoma
ADC maps	Apparent diffusion coefficient
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AIC	Akaike's Information Criterion
AIDS	Acquired immune deficiency syndrome
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AR	Adverse reaction
ASCO	American Society of Clinical Oncology
ASSET	Array Spatial Sensitivity Encoding Technique
ATRX	Alpha-thalassemia/mental retardation syndrome X-linked
BCL	B cell lymphoma
BICR	Blinded Independent Central Review
BIW	Bi-weekly
BOA	Beam Output Audit
BOR	Best overall response
BTG	Brain Tumor Group
BUN	Blood Urea Nitrogen (Urea)
BW	Body weight
C1D1	Cycle 1 day 1
CCI	Charlson Comorbidity Index
CCNU	Lomustine
CDFS	Clinical Deterioration Free Survival
CDK	Cyclin-dependent kinase
CGA	Comprehensive Geriatric Assessment
CHF	Congestive heart failure
CHRU	Centre hospitalier régional universitaire

CIF	Confirmation of interest by Principal Investigator Form
CLL	Chronis lymphoid leukemia
Cmax	Maximum serum concentration
CML	Chronic myeloid leukemia
CR	Complete Response
CRO	Contract research organization
CT	Computer Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Connective tissue disease
CTV	Clinical Target Volume
CV	Curriculum Vitae
CVA	Cerebro-vascular accident
D50%	Half maximal inhibitory dose
DICOM	Digital Imaging and Communications in Medicine
dl	Deciliter
DLT	Dose-Limiting Toxicity
DOR	Duration of objective response
DOR	Duration of response
DVD	Digital Video Disc
DVH	Dose volume histogram
DWI	Diffusion Weighted Imaging
DWI	Diffusion-Weighted Imaging
ECG	Electro Cardiograph
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EI-AED	Enzyme-inducing anti-epileptic drugs
EORTC HQ	European Organisation for Research and Treatment of Cancer headquarter
EPI	Echo Planar Imaging
ESMO	European Society for Medical Oncology
etc.	Et cetera
EU	European Union
EVCTM	EudraVigilance Clinical Trial Module

FFPE	Formalin Fixed Paraffin Embedded
FLAIR	Fluid-attenuated inversion recovery
FOV	Field Of View
FQ	Facility questionnaire
FSE	Fast Spin Echo
Fup	Follow-up
GA	Geriatric Assessment
GBM	Glioblastoma
Gd	Brain gadolinium
Gd-DTPA	Gadolinium diethylene triamine pentaacetic acid
GHQs	Global health/QoL status
GRAPPA	Generalized Autocalibrating Partially Parallel Acquisition
GTV	Gross Target Volume
Gy	Gray
h	Hour
H3-K27m	Immunostaining for histone 3 K27M
HBM	Human biological material
HDPE	High-density polyethylene
hERG	Human Ether-a-go-go-Related Gene
HRQoL	Health-related quality of life
i.e.	Id est
IADL	Instrumental Activities of Daily Living
IBBL	Integrated Biobank of Luxembourg
ICH/GCP	International Conference on Harmonisation /Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
IDH	Isocitrate dehydrogenase
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IMRT	Intensity-Modulated Radiotherapy
INR	International Normalized Ratio
IR FSPGR T1w	Inversion Recovery Fast Spoiled Grass Sequence Time 1-weighted
K+	Potassium ion
KPS	Karnofsky Performance Score

L,R	Left, Right
LDH	Lactate dehydrogenase
LMWH	Low-molecular weight heparin
MCL	Mantle Cell Lymphoma
mg	Milligram
Mg++	Magnesium ion
MGMT	O6-methylguanine DNA methyltransferase
mL	Milliliter
mm	Millimeter
mmol	Millimol
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
N/A	Not applicable
NANO	Neurologic Assessment in Neuro-Oncology
NB	Nota bene
NCI	National Cancer Institute
NF	National Formulary
NHL	Non-Hodgkin's lymphoma
NPFS	Neurologic progression free survival
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OAR	Organs at risk
ORR	Overall response rate
ORTA	Online randomized trials access
OS	Overall survival
PCR	Polymerase Chain Reaction
PD	Progression
PFS	Progression-free survival
PHT	Portal hypertension
PI	Principal investigator
PI3	Phosphatidylinositol 3
PIKE	Phosphatidylinositol 3-kinase enhancer

PISIC	Patient Information / Informed Consent sheet
PK	Pharmacokinetics
POL008	Policy 008
PR	Partial Response
PT	Prothrombin time
PTT	Partial thromboplastin time
PTV	Planning Target Volume
PUD	Peptic ulcer disease
PV	Polycythemia vera
q	Cycle
QA&C	Quality Assurance and Control Unit
QA/QC	Quality Assurance/Quality Control
QOL	Quality of life
QT interval	Interval between Q and T wave
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RANO	Response Assessment in Neuro-Oncology
RDC	Remote Data Capture system
RP	Responsible person
RT	Radiation therapy
RTQA	Radiotherapy Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable disease
SENSE	Sensitivity Encoding
seqID	Sequential patient identification number
SIOG	International Society of Geriatric Oncology
SLE	Systemic lupus erythematosus
SMASH	Simultaneous Acquisition of Spatial Harmonics
SMG	Study Management Group
SmPC	Summary of product characteristics
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction

TE	Echo Time
TI	Inversion Time
TIA	Transient ischemic attack
TIW	Tri-weekly
TMZ	Temozolomide
TR	Translational Research
TRAC	Translational Research Advisory Committee
TSE	Turbo Spin Echo
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
VES-13	Vulnerable Elders Survey
VISTA	Visual Information System for Trial Analysis
W1	Week 1
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women Of Childbearing Potential

Appendix C: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The EORTC Headquarters web site https://www.eortc.be/services/doc/ctc/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix E: Karnofsky scale for performance status

Index	Performance scale
100	Normal; no complaints.
90	Able to carry on normal activities; minor signs or symptoms of disease.
80	Normal activity with effort.
70	Cares for one self. Unable to carry on normal activity or to do active work.
60	Ambulatory. Requires some assistance in activities of daily living and self-care.
50	Requires considerable assistance of frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization indicated though death not imminent.
20	Very sick; hospitalization and active supportive treatment.
10	Moribund.
0	Dead.

Appendix F: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. Who is the responsible person (RP) for QOL data collection?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the questionnaire?

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the questionnaires.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self-administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the questionnaire?

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

5. When should they complete the questionnaire?

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed questionnaire

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation.

ENGLISH

EORTC QLQ-C30 modified

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year): 36 

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
4. Were you limited in doing either your work or other daily activities?	1	2	3	4
5. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
6. Were you short of breath?	1	2	3	4
7. Have you had pain?	1	2	3	4
8. Did you need to rest?	1	2	3	4
9. Have you had trouble sleeping?	1	2	3	4
10. Have you felt weak?	1	2	3	4
11. Have you lacked appetite?	1	2	3	4
12. Have you felt nauseated?	1	2	3	4
13. Have you vomited?	1	2	3	4
14. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
15. Have you had diarrhea?	1	2	3	4
16. Were you tired?	1	2	3	4
17. Did pain interfere with your daily activities?	1	2	3	4
18. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
19. Did you feel tense?	1	2	3	4
20. Did you feel depressed?	1	2	3	4
21. Have you had difficulty remembering things?	1	2	3	4
22. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
23. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you:

24. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

25. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Please go on to the next page

ENGLISH

EORTC QLQ - BN20 modified

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
26.	Did you have headaches?	1	2	3	4
27.	Did you have seizures?	1	2	3	4
28.	Did you have weakness on one side of your body?	1	2	3	4
29.	Did you have trouble finding the right words to express yourself?	1	2	3	4
30.	Did you have difficulty speaking?	1	2	3	4
31.	Did you have trouble communicating your thoughts?	1	2	3	4
32.	Did you feel drowsy during the daytime?	1	2	3	4
33.	Did you have trouble with your coordination?	1	2	3	4
34.	Did you feel unsteady on your feet?	1	2	3	4
35.	Have you had pain in your stomach area?	1	2	3	4

Appendix G: G8 geriatric screening tool (Version 1.0 - December 2010)

To be completed by: Clinician, nurse or trained coder.

Notes: This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient.

Score: Total score by adding up coded answers.

G8 Screening tool			
	Items	**Possible answers**	**Score**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	**0:** severe reduction in food intake **1:** moderate reduction in food intake **2:** normal food intake	……..
B	Weight loss during the last 3 months?	**0:** weight loss >3kg **1:** does not know **2:** weight loss between 1 and 3 kg **3:** no weight loss	……..
C	Mobility	**0:** bed or chair bound **1:** able to get out of bed/chair but does not go out **2:** goes out	……..
E	Neuropsychological problems	**0:** severe dementia or depression **1:** mild dementia or depression **2:** no psychological problems	……..
F	Body Mass Index (weight in kg/height in m^2)	**0:** BMI less than 19 **1:** BMI 19 to less than 21 **2:** BMI 21 to less than 23 **3:** BMI 23 or greater	……..
H	Takes more than 3 medications per day	**0:** yes **1:** no	……..
P	In comparison with other people of the same age, how does the patient consider his/her health status?	**0:** not as good **0,5:** does not know **1:** as good **2:** better	……..
	Age	**0:** >85 **1:** 80-85 **2:** <80	……..
	Total score (0-17)		……..

Appendix H: Dosing Calendars

Group A: Dosing Schedule

			D1	D2	D3	D4	D5	D6	D7
Cycle 1	**W1**	TG02	X			X			
		RT	*X*	*X*	*X*	*X*	*X*		
	W2	TG02	X			X			
		RT	*X*	*X*	*X*	*X*	*X*		
	W3	TG02	X			X			
		RT	*X*	*X*	*X*	*X*	*X*		
1 week break	**W4**	*No treatment*							
Cycle 2+	**W1**	TG02	X			X			
	W2	TG02	X			X			
	W3	TG02	X			X			
	W4	TG02	X			X			

Group B: Dosing Schedule (28-day cycle)

			D1	D2	D3	D4	D5	D6	D7
CYCLE 1	**W-1**	TG02	X			X			
	W1	TG02	X			X			
		TMZ	*X*	*X*	*X*	*X*	*X*		
	W2	TG02							
	W3	TG02							
	W4	TG02	X			X			
Cycle 2+	**W1**	TG02	X			X			
		TMZ	*X*	*X*	*X*	*X*	*X*		
	W2	TG02							
	W3	TG02							
	W4	TG02	X			X			

Group C: Dosing Schedule (28-day cycle)

			D1	D2	D3	D4	D5	D6	D7
CYCLE 1	**W1**	TG02	X			X			
	W2	TG02	X			X			
	W3	TG02	X			X			
	W4	TG02	X			X			
Cycle 2+	**W1**	TG02	X			X			
	W2	TG02	X			X			
	W3	TG02	X			X			
	W4	TG02	X			X			

Appendix I: Neurologic Assessment in Neuro-Oncology (NANO) scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Patient Identifier: _____

Date Assessment Performed (day/month/year): _____

Study time point (i.e. baseline, cycle 1, day 1, etc):_____

Assessment performed by (please print name): _____

Domains	Key Considerations
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3 attempts
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

Appendix J: MR-Sequences

Localizer / Scout

2D FLAIR

Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence

TE: 90-140ms

TR: 6000-10000 ms

TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)

SENSE / SMASH / GRAPPA / ASSET allowed

Slice orientation: transverse

Slice thickness: 5 mm

Slice gap: 0

Number of slices: same **as sequence 2 (DWI)**

Slice positioning as in **sequence 2 (DWI)**

FOV: 240 mm x 240 mm

Matrix: 256 x 256 or higher

DWI

Single shot EPI sequence

Minimum TE

TR > 3000 ms

Spectral fat suppression

b: 0 and 1000 s/mm^2 (3 directions)

SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.

Slice orientation: transverse

Slice thickness: 5 mm

Slice gap: 0

Number of slices: Full brain coverage

FOV: 240 mm x 240 mm

Matrix: 128 x 128 or higher

Post-processing: Calculation of ADC maps (diffusion trace maps)

3D T1w pre-contrast (MPRAGE, 3D IR FSPGR T1w)

minimum TE

TI, TR and flip angle according to manufacturer recommendations for optimum image quality

SENSE / SMASH / GRAPPA / ASSET allowed

Slice/3D slab orientation: sagittal or transverse

FOV: 256 mm x 256 mm

Matrix: 256x256

Slice thickness: ≤ 1.5 mm

Full brain coverage

Contrast agent injection

0.1 mmol/kg BW of a Gd-based contrast agent

T2w-TSE

Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence

TE: 80-120ms

TR: $^{14}_{12}$2500 ms

SENSE / SMASH / GRAPPA / ASSET allowed

Slice orientation: transverse

Slice thickness: 5mm

Slice gap: 0

Number of slices: same as sequence 2 (DWI)

Slice positioning as in sequence 2 (DWI)

FOV: 240 mm x 240 mm

Matrix: 256 x 256 or higher

3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)

Sequence parameters and slice positioning as **in sequence 1 (3D T1w pre-contrast)**

Appendix K: Highly effective birth control methods

Women of childbearing potential (WOCBP) are defined as premenopausal females capable of becoming pregnant (i.e. females who have had evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy).

A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)

Appendix L: Specific protocol instructions during COVID-19 pandemic

Note: All instructions listed in this Appendix will be solely applicable during the COVID-19 crisis. Furthermore, please ensure that any protocol deviations resulting from COVID-19 are:

Adequately documented in the eCRF's as well as the patient's medical records or in a NTF to be stored in your Study binder (ISF).

Always begin deviation text with "COVID-19"

Introduction

Current information suggests that cancer patients have a higher risk of infection and serious complications from infections including COVID-19, than other patients.

It is strongly recommended that investigators exercise medical/clinical judgement, and decisions regarding each patient should be individualized after considering the overall goals of treatment, the patient's current oncologic status and treatment tolerance as well as their general medical condition.

In addition, investigators should adhere to local and institutional guidelines for SARS-CoV-2 infection and suspected COVID-19 infection

Risk-benefit assessment:

Introduction to trial

The 1608 trial will evaluate a new drug TG02 combined with either radiotherapy or temozolomide, based on the MGMT status in frail, elderly patients (> 65 years old) with newly diagnosed glioblastoma WHO grade 4 and anaplastic astocytoma. The drugs will also be evaluated as treatment for glioblastoma and anaplastic astrocytoma after first relapse. Assessment of safety and efficacy are objectives of the trial.

Benefits

Benefits from the new approach in frail, elderly patients are to provide a safe and efficient treatment in a patient group that is considered not fit enough to undergo the standard treatment. Through a 3+3 model, the Maximum Tolerated Dose (MTD) will be assessed to be used in the following Phase II trials. The use of TG02 in patients after first relapse can be a new efficient treatment in a disease setting where a standard of care has not yet been established.

Risks

On the other hand, there are risks about these treatments, and especially during the COVID-19 crisis, that are increased:

The fact that included patients need to come for regular visits to the hospital increases their exposure risk to persons who are contagious for COVID-19. General rules like social

distancing and avoidance of persons with possible signs or confirmed diagnosis can be applied. But COVID-19 may also be contagious in persons who do not have symptoms. And age alone might be a very important risk factor for dying from COVID-19 infection.

The treatment regimens in all 3 arms of 1608 (Radiotherapy or chemotherapy with TG02 (arms A and B) and as a single agent (arm C)) decrease the patients' immune function temporarily via bone marrow suppression. This may lead to an increased risk of acquiring COVID-19 infection.

Deviations from the protocol treatment regimen, e.g. delays or interruptions that are COVID-19 related, can negatively influence the efficacy of the drugs and thus the benefits of the treatment for the patients.

Proposed measures for patients already enrolled during the COVID-19 crisis and recruitment

The study coordinators in collaboration with EORTC, propose the following guidelines as long as the current COVID-19 crisis is ongoing.

Please ensure that any protocol deviations resulting from COVID-19 crisis are reported to the EORTC study team (1608@eortc.org) without delay, so can be adequately reported to regulatory bodies if needed.

Please ensure that each deviation to the protocol instructions are adequately documented in the eCRFs as well as in the patient's medical records or in a Note to File (NTF) to be stored in your Study binder (ISF).

N.B. Always specify the reason of the deviations: "COVID-19".

1. Specific Guidelines during COVID-19 PandemicCOVID-19 vaccination:

As per the European Medicines Agency (EMA):

If physicians decide to administer SARS-CoV-2 vaccines in patients enrolled in the study, decisions should be individualized based on the risk of SARS-CoV-2 complications and potential benefit from the vaccine, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore, the country guidelines and/or institutional guidelines, must be followed.

The available SARS-CoV-2 vaccines, that are not live attenuated vaccines, are not contra-indicated in patients on immunotherapy.

Treatment schedule should not be altered because of the COVID-19 vaccination.

The administration of a SARS-CoV-2 vaccine including the name of the vaccine (e.g. Moderna, Pfizer BioNTech, AstraZeneca Oxford, …) shall be added in the concomitant medication form in the eCRF and noted in the patient's Medical file. Any possible vaccine related AE should be captured in the AE forms in the eCRFs, specifying the potential relationship to the vaccine.

2. Guidelines for study assessments

2.1 With respect to study imaging procedures:

For the baseline study imaging procedures, the protocol requirements have to be fully met.

For on-study imaging procedures, it is preferred that the patient have imaging performed at the investigative site as directed in the protocol.

If difficulties are encountered to perform the imaging as directed in the protocol, there are several possibilities, in order of preference:

Have the imaging performed offsite/locally according to the protocol-specified timing. Guidance should be given by the site to the local imaging facility about conducting scans according to all applicable requirements (modality etc. as per 1608 Imaging Guidelines).

Have the imaging performed at the site but delayed to a significant extend (a window of 2 weeks instead of 1 week will be allowed) due to travel restriction/safety of the participant.

Have the imaging performed offsite but delayed (a window of 2 weeks instead of 1 week will be allowed) due to travel restriction/safety of the participant.

Skip the imaging only if impossible to perform due to travel restriction/safety.

Note: If a patient cannot go to site to receive the imaging results because of safety or isolation or travel risks, the results can be communicated by telephone, video visit.

2.2 With respect to study treatments:

In general, patients with a deadly cancer such as anaplastic astrocytoma or glioblastoma should receive the best possible treatment, also during the ongoing pandemic. Withholding or interrupting tumor-specific treatment should therefore be avoided whenever possible. For the ongoing EORTC-1608-BTG (STEAM) trial, the goal is therefore – taking in account guidance of local and national authorities - to treat patients as closely to the protocol guidelines as possible, without endangering their safety and keeping the risk / benefit ratio for the patient acceptable.

Patients on treatment will be treated as per protocol, in all arms. Protocol assessments should be performed as per protocol as much as possible, taking in account local and/or national guidance.

Assessments should be done at the investigative site if possible.

In the event it is not possible or not in the best interest of a patient to travel to the treating site because of COVID-19, the following options are proposed:

- If assessments are required prior to study treatment (TG 02/ TMZ) administration, as stated in the protocol and administration of study treatment cannot be postponed the following should be considered:

Arrange the exact date of the visit (and time) in the center and perform the assessments in advance

Provide standard laboratory assessments of the subject either by qualified staff of contracted laboratories or contractually secured healthcare providers whom employ appropriate safety measures and excludes patients whom are quarantined or living with or have been quarantined with a confirmed COVID-19 case

- Treatment related laboratory exams can be done in certified off-site facilities.

Visits that do not involve administration of study treatment, and that cannot be met because of the COVID-19 crisis can be replaced by a telephone consultation.

These deviations will not to be considered as protocol violations and must be documented clearly both in the eCRFs as well as in the patients' medical file on site as a COVID-19-related deviation (please specify every deviation in the eCRF with “COVID-19”). All other COVID-19-related deviations to the protocol will be documented equally. In case of doubt, the 1608 medical monitor can always be contacted to discuss (1608medmon@eortc.org / 1608@eortc.org). COVID-19-related deviations will not be considered protocol violations as long as they do not endanger the safety of the patient.

- With respect to **TG02 (in Arms A, B and C)**

Patients should be seen at the participating site at every planned visit if possible. If hospital visits are not possible because of travel restrictions or safety issues, the per protocol assessments may be performed offsite, see above, and patients may receive TG02 supply through courier from site to their home address under responsibility of the PI and the pharmacist. In this case, please always contact the EORTC study team. The process for shipping directly to subjects from sites must be fully documented and traceable.

Important note: Patient should be reminded to complete patient diaries.

Before the continuation of TG02, the investigator must provide his/her approval to the patient or the qualified person in charge of patient care, based on the assessments performed as per protocol.

- With respect to **Temozolomide (TMZ)**

TMZ will continue to be provided to the patient as per the sites local practice.

2.3 With respect to shipment of investigational medicinal products to subjects:

In case of home delivery, please inform patients about the following:

To insure the continuity of your treatment and therefore your vital interests, your name and address will be communicated by your investigator or the staff of your hospital to the organization responsible for the drug supply.

EORTC and/or your hospital will ensure that your name and address are processed in the secure way and are not used for any other purpose than for delivering your drugs to you

EORTC and/or your hospital will ensure that this additional information is not anymore stored by the drug suppliers once these exceptional measures are over and your treatment and/or follow-up are back to the normal

Important note: Investigators should be informing their patients about the fact that drug suppliers will be receiving their name and address for delivery and that they will not store this information beyond the crisis should be reminded to complete patient diaries.

2.4 With respect to patient physical visits:

Patient physical visits which are not crucial for the safety of the patient and that cannot be met because of the COVID-19 crisis can be replaced by a telephone consultation.

- With respect to patient reported data

Quality of Life (QoL) and G8 questionnaires can be collected through phone or a video conference. Voice scripts are available on the study web documentation for the QoL questionnaires.

If phone assessment cannot be arranged, the QoL and G8 questionnaires can be collected by providing the questionnaires to the patients. Patients should be instructed to complete the questionnaires within the intended timepoint (according to protocol). Patients should also complete the date on the form with the date they completed the questionnaire. Sites are requested to make their own guidelines to patients in their own language.

2.5 With respect to collection of biomaterial:

If the collection of a sample is part of the inclusion criteria (only arm A & B - FFPE tumor tissue block or 24 tumor tissue slides 5µm) and if impossible to collect the sample(s) due to travel restriction and/or safety concerns, the patient cannot be enrolled in the trial.

The collection of sample(s) can be skipped only if all following (2) criteria are met

- The HBM samples are not part of the inclusion criteria and
- The collection of the HBM samples is impossible to perform due to travel restrictions and/or safety concerns

If these 2 criteria are fulfilled, the sample collection can be skipped and a deviation must be entered, as this was not according to the protocol.

Please begin deviation text with “COVID-19” followed by the reason of the non-collection

2.6 With respect to on-site monitoring visits

All on-site monitoring visits are currently suspended. EORTC CRAs will contact your staff to schedule the next monitoring visit, when the situation will evolve positively and in compliance with the Governments and sites recommendations. In the meantime, CRAs will keep in touch with your staff to provide any support deemed necessary by the study team.

3. Serious adverse event reporting:

Sites should follow the SAE reporting as described in the protocol i.e. sites should continue to report SAEs immediately and no later than 24 hours from the time the investigator or site staff became aware of the event. There are no specific adaptations to the protocol defined SAE reporting procedure due to COVID-19.

Should sites have any SAE reporting related questions, please contact us at pharmacovigilance@eortc.org

Should there be a suspected or confirmed serious case of COVID-19 infection, report it as SAE:

Please remember to provide the mandatory SAE information as per protocol and as per the CRF completion guidelines.

Please indicate if the COVID-19 infection was confirmed by a test.

Please provide as much information as available.

4. Informed consent

If an amendment is initiated during the COVID-19 pandemic period, requiring re-consent of already enrolled patients, alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.

The previous also applies to consent of patients for the implementation of changes to the trial conduct during the COVID-19 pandemic, if required.