Phase 2 Study of Sym004 for Adult Patients with Recurrent Glioblastoma

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

	Sponsor:	PI – Duke Cancer Institute
	Funding Source:	Symphogen A/S
	Protocol Source:	PI - Duke Cancer Institute
	Duke IRB#:	Pro00063483
	IND#	127275

Principal Investigator
Annick Desjardins, MD, FRCPC
The Preston Robert Tisch Brain Tumor Center at Duke
Room 047 Baker House
DUMC 3624
(919) 681-4047
(919) 684-6674
Annick.desjardins@duke.edu

Sub-Investigator(s)
Henry Friedman, MD
Henry.friedman@duke.edu

Roger McLendon, MD
Roger.mclendon@duke.edu

Katherine Peters, MD, PhD
Katherine.peters@duke.edu

Dina Randazzo, DO
Dina.randazzo@duke.edu

Gordana Vlahovic, MD, MHS
Gordana.vlahovic@duke.edu

Statistician
James E. Herndon, II, PhD
James.herndon@duke.edu

Lead Study Coordinator
Woody Massey
Woody.massey@duke.edu

Lead Regulatory Coordinator
Elizabeth S. Miller
Elizabeth.s.miller@duke.edu

Lead Data Manager
Eric Lipp
Eric.lipp@duke.edu

Original version: 7/9/2015
Amended version: 03/15/2016
05/13/2016
07/5/2017

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BDI-II	Beck depression inventory II
Beta-HCG	Beta Human Chorionic Gonadotropin
BEV	Bevacizumab
CAP	College of American Pathologists
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CPC	Cancer Protocol Committee
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCI	Duke Cancer Institute
dL	Deciliter
DLP	Data Lock Point
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DSUR	Development Safety Update Report
DUHS	Duke University Health System
EGFRwt	Epidermal Growth Factor wild type
EGFRvIII	Epidermal Growth Factor variant type III
ESCC	Esophageal Squamous Cell Carcinoma
FACIT-Fatigue	Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale
FACT-BR	Functional Assessment of Cancer Therapy-Brain
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GBM	Glioblastoma
Gd-DTPA	Gadolinium-diethylene Triamine Pentaacetic Acid
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HRQoL	Health Related Quality of Life
ICS	Investigational Chemotherapy Service
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Research Board
IV (or iv)	Intravenously
KPS	Karnofsky Performance Status
MAb	Monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MG	Malignant Glioma

Mg	Magnesium
mg	Milligram
mL	Milliliter
mM	Millimolar
MRI	Magnetic Resonance Imaging
NSCLC	Non-small Cell Lung Cancer
OARC	Office of Audit, Risk, and Compliance
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PFS6	Progression Free Survival at 6 months
p.o.	per os/by mouth/orally
PR	Partial Response
PRO	Patient-Reported Outcome
PRTBTC	Preston Robert Tisch Brain Tumor Center
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RDSPs	Research Data Security Plans
RR	Response Rate
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOC	Safety Oversight Committee
ULN	Upper Limit of Normal
WHO	World Health Organization
XRT	Radiation Therapy

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

The purpose of this study is to assess the activity of Sym004, a recombinant antibody mixture that specifically binds to EGFR, in patients diagnosed with recurrent glioblastoma whose tumor is EGFR amplified.

Primary Objective:
Assess the activity of Sym004 in patients with recurrent glioblastoma that are either non-bevacizumab failures (Cohort 1) or who have previously failed bevacizumab (Cohort 2), in terms of 6-month progression-free survival (PFS6).

Secondary Objectives:

1. Determine the safety of Sym004 in recurrent GBM patients.
2. Estimate response rate (RR) within the two cohorts of recurrent GBM patients.
3. Describe overall survival (OS) within the two cohorts of recurrent GBM patients.

Exploratory Objectives:

1. Assess the impact of EGFRvIII expression on efficacy (OS and PFS) of Sym004.
2. Describe patient-reported quality of life outcomes.

Hypothesis
This study hypothesizes that Sym004 will have greater activity in terms of PFS6 than standard treatment for patients with recurrent GBM.

3.2 Design and Procedure

This is a phase 2 study that will accrue patients with WHO grade IV recurrent malignant glioma (glioblastoma or gliosarcoma) in two cohorts to assess the efficacy of Sym004. Cohort 1 will include patients who are non-bevacizumab failures; whereas, Cohort 2 will include patients who have progressed after prior treatment with bevacizumab (bevacizumab-failure). Both cohorts will accrue simultaneously, with 36 subjects in Cohort 1 and 25 subjects in Cohort 2 (see Section 13.8 for justification of sample size). All patients will be treated with Sym004, a recombinant antibody mixture that specifically binds to EGFR. For that reason, only patients whose tumor is determined to be EGFR-amplified (i.e. greater than 15% of cells exhibiting > 5 copies of EGFR loci) will be accrued on this study.

Prior to Amendment 31, approximately 25 subjects received Sym004 at 18 mg/kg intravenously every two weeks. After the approval of Amendment 31, subjects who enroll on study will receive Sym004 at 24 mg/kg intravenously every 2 weeks. A total of 65 additional subjects (36 in Cohort 1 and 29 in Cohort 2) will be treated at the 24 mg/kg dose level. In addition, subjects who enrolled at the 18 mg/kg dose and who tolerated this dose of Sym004 well (i.e. no skin toxicities ≥ grade 3) will have the option to increase their dose to 24 mg/kg upon approval of Amendment 31. A treatment cycle will be 4 weeks. The patients will have repeat MRIs of the brain every 8 weeks.

The accrual of the first 3-6 patients at the 24 mg/kg dose level, regardless of cohort assignment, will be at a controlled rate for initial safety monitoring. Details concerning this initial accrual at the 24 mg/kg dose level can be found in Section 13.7.4.

For an exploratory objective, we will determine EGFRvIII status at baseline for all patients using archival tumor tissue. If a subject has more than one source of archival or frozen tissue, each source may be requested to determine if EGFRvIII expression has changed over time.

3.3 Selection of Subjects

Selection of subjects will be completed by meeting the subject eligibility criteria listed in this section.

Inclusion Criteria (answer must be YES to all criteria listed below)

1. Patients must have histologically confirmed diagnosis of WHO grade 4 malignant glioma and radiographic evidence of recurrence or disease progression (as defined by the RANO criteria as a greater than 25% increase in the largest bi-dimensional product of enhancement or a new enhancing lesion, or a significant increase in T2/FLAIR abnormality without another co-morbid cause);
2. Age ≥ 18 years;
3. Karnofsky Performance Status ≥ 70%;
4. No more than 3 prior progressions;
5. Cohort 1 only: Non-bevacizumab failure, i.e. either no prior bevacizumab or bevacizumab stable/responder, which is defined as stable for at least 6 months from prior treatment with bevacizumab without experiencing a bevacizumab adverse event of special interest (AESI) while on a bevacizumab-containing regimen, such as:
    a. ≥ grade 3 hypertension not controlled by medication, hypertensive crisis, or hypertensive encephalopathy
    b. ≥ grade 3 proteinuria that does not resolve or nephrotic syndrome
    c. Any grade GI perforation
    d. ≥ grade 3 infusion-related reaction
    e. ≥ grade 3 wound healing complications
    f. ≥ grade 3 hemorrhage or any grade CNS hemorrhage or ≥ grade 2 hemoptysis
    g. Any grade arterial thromboembolic event (e.g. myocardial infarction or cerebral infarction) or ≥ grade 3 venous thromboembolic event
    h. Any grade posterior reversible encephalopathy syndrome (PRES)
    i. ≥ grade 3 congestive heart failure
    j. ≥ grade 2 non-gastrointestinal (GI) abscesses and fistulae;
6. Cohort 2 only: Prior progression on a bevacizumab-containing regimen (defined as having progressed/grown through bevacizumab by RANO criteria within 2 months of prior bevacizumab treatment);
7. Pathology consistent with EGFR-amplification of tumor (i.e. greater than 15% of cells exhibiting > 5 copies of EGFR loci); archival tissue may be tested for EGFR status in a separate consent;
8. ANC ≥ 1,000 cells/µl, platelets ≥ 100,000 cells/µl, hemoglobin ≥ 9 g/dL;
9. Adequate renal function as indicated by the following:
    a. Serum creatinine ≤ 1.25 times upper limit of normal or calculated creatinine clearance ≥ 50 ml/min;
    b. Urine dipstick for proteinuria < 2+ unless a 24-hour urine protein <1 g of protein is demonstrated;
10. Adequate liver function as indicated by the following:
    a. Total bilirubin ≤ 1.6 mg/dL;
    b. AST/ALT ≤ 2.5 x the ULN;
11. Magnesium ≥ 0.9 mg/dL;
12. For subjects on corticosteroids, they must be on a stable dose for *7 days* prior to anticipated start of study drug;
13. No evidence of > grade 1 active CNS hemorrhage on the baseline MRI or CT scan;
14. Signed informed consent approved by the Institutional Review Board prior to patient entry;
15. If the patient is a sexually active female of child bearing potential whose partner is male, or if the patient is a sexually active male whose partner is a female of child bearing potential, the patient must agree to use appropriate contraceptive measures for the duration of the treatment of the tumor and for 6 months afterwards as stated in the informed consent. Female patients of child bearing potential must have a negative serum pregnancy test within 48 hours of starting study treatment;

16. Fertile male subjects must agree to use a medically acceptable contraceptive method (allowed methods of birth control include vasectomy or condom with spermicide) during the trial and for a period of at least 6 months following the last administration of trial drugs.

Exclusion Criteria (answer must be NO to all criteria listed below):

1. Pregnancy or breastfeeding;
2. Prior treatment with EGFR-targeted therapy, including, but not limited to, the following examples: Gilotrif® (afatinib),Tarceva® (erlotinib), Erbitux® (cetuximab), Iressa™ (gefitinib), Vectibix® (panitumumab), Caprelsa® (vandetanib), Tykerb® (lapatinib), CDX110, D2C7-immunotoxin);
3. Active infection requiring intravenous antibiotics within 7 days before enrollment;
4. Prior, unrelated malignancy requiring curent active treatment with the exception of cervical carcinoma in situ and adequately treated basal cell or squamous cell carcinoma of the skin;
5. Less than 12 weeks from radiation therapy, unless progressive disease outside of the radiation field or 2 progressive scans at least 4 weeks apart or histopathologic confirmation;
6. Treated with immunotherapeutic agents, vaccines, or Mab therapy within 4 weeks before enrollment, unless the patient has recovered from the expected toxic effects of such therapy;
7. Treated with alkylating agents within 4 weeks (6 weeks for nitrosoureas) before enrollment or treated within 1 week before enrollment with daily or metronomic chemotherapy, unless the patient has recovered from the expected toxic effects of such therapy to their baseline or to grade 1;
8. Prior treatment (non-alkylating agents) within 2 weeks before enrollment, unless the patient has recovered from the expected toxic effects of such therapy;
9. Known hypersensitivity reactions to any of the components of Sym004;
10. Known current drug abuse or alcohol abuse;
11. Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection. Testing is not required as part of this study.

3.4 Data Analysis and Statistical Considerations

Kaplan-Meier curves will be generated to describe the PFS and OS experience of patients enrolled on this protocol within each cohort and dose level. Progression-free survival (PFS) is defined as the time interval between initiation of protocol treatment and either disease progression or death. If the patient is alive and progression-free, PFS will be censored at the date last known alive. Overall survival (OS) is defined as the time interval between initiation of protocol treatment and death, or date of last follow-up if alive. Estimates with confidence intervals will be generated for median PFS and OS, as well as 2 month intervals for PFS for the first year (2, 4, 6, etc..) and 6 month intervals for OS for the first 2 years (6, 12, 18, 24) from the time the subject goes on study.

Radiographic response rate will be estimated as the proportion of treated patients with a complete or partial response (see Appendix B). An exact binomial confidence interval will be generated.

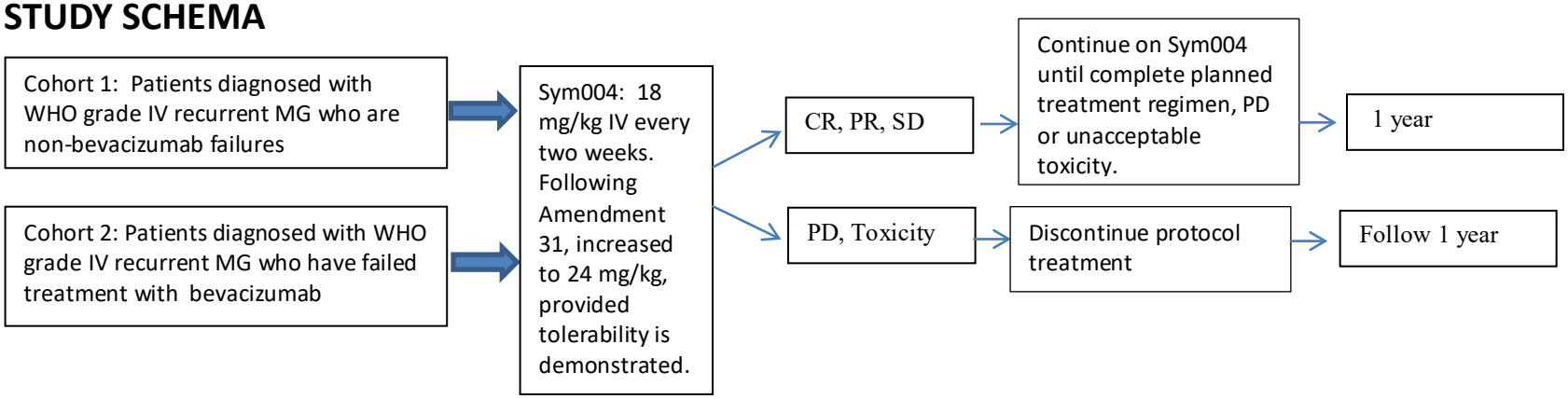
For each type of toxicity, the maximum grade experienced by each patient will be summarized with frequency distributions within each cohort and dose level. Two adverse experience tabulations will be generated, one that includes all toxicities regardless of attribution, and one that includes only toxicities that are possibly, probably, and definitely related to Sym004 treatment.

Cox proportional hazards model will be used to examine the association between EGFRvIII expression and PFS and OS.

At the 18 mg/kg dose level, interim analyses will be conducted after 19 total patients across both cohorts have been treated with Sym004. These interim analyses will focus on the prevalence of skin toxicities.

With each cohort of the study at the 24 mg/kg dose level, the study is designed as a two-stage study to assess 6-month PFS. After the initial stage, interim futility analyses will be conducted.

4 STUDY SCHEMA



5 BACKGROUND AND SIGNIFICANCE

5.1 Study Disease

There is an unmet clinical need for the therapy of malignant gliomas with a median survival of <20 months despite available therapies. The current standard of care is radiation therapy with daily temozolomide followed by 6 cycles of temozolomide.[1]

Glioblastoma (GBM) is a highly angiogenic, aggressive malignant primary brain cancer; it is the most common and aggressive type of primary brain tumor in humans. It accounts for 52% of all primary brain tumor cases and 20% of all intracranial tumors. The median progression-free survival for patients treated with surgery followed by radiation and temozolomide is under 7 months. Median overall survival is under 15 months. No effective therapy exists following recurrence.[2] Few cytotoxic drugs are available for the treatment of GBM because of the difficulty of crossing the blood-brain barrier. Temozolomide, an alkylating agent, is the current standard of care [3,4] in combination with surgical resection and radiation therapy.[5] Recurrent GBM has an initial response to temozolomide therapy. Although different dosing regimens have been tried to reduce the tumor burden, GBM loses sensitivity to temozolomide.[5] Overall survival is not improved and tumor progression results.[4] Effective treatment remains an unmet medical need.

5.2 Study Agent

Sym004 is a recombinant antibody mixture that binds specifically to the epidermal growth factor receptor (EGFR). Sym004 contains two mouse-human chimeric IgG1 monoclonal antibodies, futuximab and modotuximab, in a 1:1 ratio. Per the Investigator's Brochure (v. 2.0, 22-Jan-2015), the antibodies bind to non-overlapping epitopes on the extracellular domain III of EGFR. The binding induces a distinct mechanism of action that is dependent on the presence of both antibodies and translates into a superior anti-cancer activity compared to monoclonal reference antibodies. This was demonstrated both in vitro using human cancer cell lines and in vivo using EGFR-dependent tumor xenografts. Sym004 induces highly efficient internalization of EGFR on cancer cells and degradation, which results in inhibition of cancer cell growth. Sym004 is being investigated for the treatment of subjects with advanced metastatic colorectal cancer (mCRC), for the treatment of recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN), for the treatment of non-small cell lung cancer (NSCLC), and for the treatment of esophageal squamous cell carcinoma (ESCC) in Japanese subjects.

Studies have shown that Sym004 is superior at inhibiting EGFR activity compared to cetuximab and/or panitumumab (used as reference antibodies) *in vitro* through a mechanism of action that is dependent on binding of both antibodies. Furthermore, the activity of Sym004 was investigated in several xenograft tumor models in mice and compared to cetuximab and/or panitumumab. In all models, Sym004 was superior or as efficient as these reference antibodies.

Five clinical trials have been completed with Sym004 and 2 clinical trials are currently ongoing ongoing according to the most resent Symphogen Development Safety Update Report (report dated 13 Mar 2017). Sym004 shows early signs of promising activity in the trials conducted so far. Sym004 was shown to induce tumor shrinkage in subjects resistant to combination treatment with platinum-based chemotherapy and cetuximab in recurrent/metastatic SCCHN. The median OS with Sym004 of around 5 months is in the range of the reported median OS in less heavily pre-treated (cetuximab-naïve), platinum-resistant recurrent/metastatic SCCHN subjects treated with compounds such as methotrexate or cetuximab. In subjects with mCRC and acquired resistance to cetuximab, Sym004 showed promising activity as it was able to induce tumor shrinkage in about 30-48% of subjects including several cases of partial response.

5.3 Study Purpose/Rationale

Glioblastomas (GBMs) are highly aggressive and lethal malignant brain tumors. The human epidermal growth factor receptor (EGFR; HER-1) is a transmembrane receptor tyrosine kinase. It is an attractive therapeutic target

for based on its role as an oncogenic driver. EGFR is amplified in 35-40% of primary GBM tumors.[6,7] Approximately 50% of EGFR-amplified GBMs express EGFRvIII,[8] a constitutively active, ligand-independent mutant receptor with impaired down-regulation. So far, most efforts at targeting EGFR have revolved around the utilization of tyrosine kinase inhibitors, which have almost invariably failed to show efficacy in WHO grade IV malignant glioma patients.

Sym004 is a recombinant antibody mixture which binds specifically to EGFR. Sym004 contains 2 mouse-human chimeric IgG1 monoclonal antibodies (Mabs), futuximab and modotuximab. The antibodies bind to non-overlapping epitopes on the extracellular domain III of EGFR. Sym004 is not only designed to block ligand binding, receptor activation and downstream signaling but also elicits effective removal of the EGFR receptors from the cancer cell surface by inducing EGFR internalization and degradation. In addition, unlike the single monoclonal anti-EGFR antibodies which only mediate antibody-dependent cellular cytotoxicity (ADCC), Sym004 mediates both ADCC and complement-mediated cytotoxicity against EGFR-positive tumor targets. The activity of Sym004 was investigated in several xenograft tumor models in mice and compared to cetuximab and/or panitumumab. In all models, Sym004 was either superior to or as efficient as these reference antibodies. Three clinical trials have been completed with Sym004 as a single agent in subjects with recurrent advanced solid tumors (Sym004-01, Sym004-02, and Sym004-06). Sym004 shows signs of promising activity in both trials conducted so far. Skin toxicities were the most frequently reported AEs, seen in 80-97% of subjects.

Given the dire need for new therapies for recurrent GBM, particularly after bevacizumab-failure, the proposed clinical trial is an important step in the field of neuro-oncology. To assure that the appropriate patient population will be enrolled on study, only recurrent WHO grade IV malignant glioma patients with known EGFR amplification as defined in the eligibility criteria (at diagnosis or at recurrence) will be eligible.

6 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	Assess the activity of Sym004 in patients with recurrent glioblastoma that are either non-bevacizumab failures (Cohort 1) or who have previously failed bevacizumab (Cohort 2)	The percentage of subjects who remain alive and progression free at 6 months (PFS6) at each dose level	See Section 13.4
Key Secondary	Determine the safety of Sym004 in recurrent GBM patients	The proportion of patients with grade 3, 4, or 5 treatment-related adverse events at each dose level	See Section 13.5.1
Other Secondary	Estimate response rate (RR) within two cohorts of recurrent GBM patients	Proportion of treated patients with a complete or partial response at each dose level	See Section 13.5.2
Other Secondary	Describe overall survival (OS) within two cohorts of recurrent GBM patients	Median OS at each dose level	See Section 13.5.2
Exploratory	Assess the impact of EGFRvIII expression on efficacy (OS and PFS) of Sym004	Median OS and PFS within subgroups of patients defined by EGFRvIII expression and dose level	See Section 13.6
Exploratory	Describe patient-reported quality of life outcomes (PROs)	Mean change from baseline in each Patient-Reported Outcome (PRO) subscale within each Cohort and dose level	See Section 13.6

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a phase 2 study that will accrue patients with WHO grade IV recurrent malignant glioma (glioblastoma or gliosarcoma) in two cohorts to assess the efficacy of Sym004. Cohort 1 will include patients who are non-bevacizumab failures; whereas, Cohort 2 will include patients who have progressed after prior treatment with bevacizumab (bevacizumab-failure). Both cohorts will accrue simultaneously, with a goal of 36 subjects in Cohort 1 and 25 subjects in Cohort 2 (see Section 13.8 for justification of sample size). All patients will be treated with Sym004, a recombinant antibody mixture that specifically binds to EGFR. For that reason, only patients whose tumor is determined to be EGFR-amplified will be accrued on this study.

Prior to Amendment 31, approximately 25 subjects received Sym004 at 18 mg/kg intravenously every 2 weeks. After the approval of Amendment 31, subjects who enroll on study will receive 24 mg/kg intravenously every 2 weeks. A maximum of 65 additional subjects (36 in Cohort 1 and 29 in Cohort 2) will be treated at the 24 mg/kg dose level. In addition, subjects who enrolled at the 18 mg/kg dose and who tolerated this dose of Sym004 well (i.e. no skin toxicities ≥ grade 3) will have the option to increase their dose to 24 mg/kg upon approval of Amendment 31. A treatment cycle will be 4 weeks. The patients will have repeat MRIs of the brain every 8 weeks. Subjects with CR, PR, or stable disease may continue on study as long there is no evidence of disease progression or toxicities as described in Section 10.8.1.

The accrual of the first 3-6 patients at the 24 mg/kg dose level, regardless of cohort assignment, will be at a controlled rate for initial safety monitoring. Details concerning this initial accrual at the 24 mg/kg dose level can be found in Section 13.7.4.

For an exploratory objective, we will determine EGFRvIII status at baseline for all patients using archival tumor tissue. If a subject has more than one source of archival or frozen tissue, each source may be requested to determine if EGFRvIII expression has changed over time.

7.1.1 Dose Modification

For subjects receiving 18 mg/kg, the dose of Sym004 may be reduced by up to two dose levels, if the subject experiences grade 3-4 non-hematologic toxicities secondary to Sym004, e.g. skin toxicities, electrolyte disturbances, and gastrointestinal symptoms, or grade 4 neutropenia or thrombocytopenia. Following the initial dose of 18 mg/kg every 2 weeks, if the subject needs to have their dose of Sym004 reduced due to an aforementioned toxicity, then their next dose will be 15 mg/kg every 2 weeks. If another reduction in dose is necessary, the subsequent dose will be 12 mg/kg every 2 weeks. If dose reduction is required more than two times, the patient will be removed from the study.

7.1.2 Dose Modification Post-Amendment 31

For subjects receiving 24 mg/kg, the dose of Sym004 may be reduced by up to two dose levels, if the subject experiences grade 3-4 non-hematologic toxicities secondary to Sym004, e.g. skin toxicities, electrolyte disturbances, and gastrointestinal symptoms, infusion-related reactions, or grade 4 neutropenia or thrombocytopenia. Exceptions to this dose reduction include grade 3 nausea, vomiting, diarrhea or fatigue lasting ≤ 5 days with supportive care or grade 3 asymptomatic electrolyte abnormalities. Following the initial dose of 24 mg/kg every 2 weeks, if the subject needs to have their dose of Sym004 reduced due to an aforementioned toxicity, then their next dose will be 18 mg/kg every 2 weeks. If another reduction in dose is necessary, the subsequent dose will be 15 mg/kg every 2 weeks. If dose reduction is required more than two times, the patient will be removed from the study.

7.1.3 Safety Considerations

According to the Sym004 Investigator's Brochure (v. 8.0, 13-Mar-2017), skin toxicities have been the most frequently reported AEs. To date (20 Jan 2017), approximately 380 subjects with solid tumors, including

subjects with recurrent/metastatic SCCHN, mCRC, ESCC and NSCLC, have been treated with Sym004 in weekly doses of up to 12 mg/kg and in doses every other week of up to 18 mg/kg in ongoing Symphogen-sponsored studies. Anti-EGFR related skin toxicities (including rash, pruritus, skin fissures, dry skin, erythema, and paronychia) have been observed in more than 90% of subjects in the completed and ongoing clinical trials. In subjects who had previously received anti-EGFR mAb therapy, Grade 3 skin toxicities were frequently reported; 50-69% of subjects at a dose of 9 or 12 mg/kg weekly (Sym004-01 Parts B and C and Sym004-02) and 33.3% and 41.2% of subjects at dose levels of 12 mg/kg and 18 mg/kg, respectively, every other week (Sym004-01 Parts D and E).

Other adverse events (AEs) associated with anti-EGFR mAbs, such as electrolyte disturbances (in particular hypomagnesemia), mucositis, and diarrhea were also frequently observed in the completed and ongoing trials. In clinical trials for which AE data are available (Sym004-01-Parts A, B, C, D, E, Sym004-02, and EMR 200637-001-Part A) hypomagnesemia was reported in 54-77% of subjects, and 0-38% of subjects experienced Grade 3 or 4 hypomagnesemia. In the Sym004-01 and Sym004-02 clinical trials, events of hypomagnesemia also represented the majority of serious adverse events (SAEs) that were considered to be related to Sym004 therapy. Serious clinical complications of hypomagnesemia have not been observed. Mucositis was observed in up to 40% of subjects, but the number of subjects experiencing Grade 3 mucositis was low (1 subject). Diarrhea has been reported in up to 59% of subjects; and ≤ 10% of subjects experienced Grade 3 diarrhea. Infusion related reactions have also been observed.

Therefore, subjects will be assessed at each clinic visit, beginning with Cycle 1:Day 15, for skin toxicities according to Duke Medicine's "Guidelines for Management of Cutaneous Toxicity for Patients Receiving Epidermal Growth Factor Receptors" (see Appendix A). Patients will be instructed to call if the rash is painful or interfering with daily functioning. In all ongoing clinical trials, premedication with glucocorticosteroids and antihistamines prior to Sym004 infusion is required. Pre-medications in the current study are described in Section 7.1.5 below. Supplemental guidelines on grading and management of skin toxicities due to Sym004 have been provided by Symphogen in their "Skin Management Booklet." This booklet has been used on other Sym 004trials and has been provided as a helpful tool for providers.

7.1.4 Delayed Infusions for Scheduling Issues

A delayed infusion of Sym004, due to scheduling issues, may be re-scheduled within the following 4 days.

7.1.5 Concomitant Medications

Skin toxicities will be treated according to Duke Medicine's "Guidelines for Management of Cutaneous Toxicity for Patients Receiving Epidermal Growth Factor Receptors" (see Appendix A), in conjunction with Symphogen's "Skin Management Booklet" for Sym004. In the current study, subjects should receive the following premedications, according to institutional guidelines and the judgement of the treating physician: diphenhydramine 50 mg IV and a glucocorticoid steroid, such as hydrocortisone 100 mg IV, 30-60 minutes prior to the first dose. Premedication should be administered for subsequent doses based upon clinical judgment and presence/severity of prior need.

Hypomagnesaemia, mucosal inflammation, and diarrhea will be treated according to institutional guidelines and the treating physician's discretion.

7.1.6 Study Drug Blinding

Not applicable.

7.1.7 Randomization

Not applicable.

7.1.8 Quality of Life Assessments

Quality of Life will be assessed using standardized and validated questionnaires. These questionnaires include Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale,[9] Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale, version 4,[10] and Beck depression inventory II (BDI-II).[11]

All quality of life assessments will be completed at baseline, prior to the start of every other cycle beginning with Cycle 3, and at the end of the study. These assessments should be completed prior to other study-related evaluations at study visits, if at all possible. If the subject is found to have progressive disease prior to beginning an even-numbered cycle, when HRQoL assessments are not conducted, they may complete these assessments at any time during the clinic visit.

7.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

Per the Sym004 Investigator's Brochure (v. 7.0, 10-Mar-2017), seven clinical trials have been conducted with Sym004, 3 clinical trials have been completed, and 4 clinical trials are ongoing. More than 365 patients with solid tumors have been exposed to Sym004 thus far in weekly doses of up to 12 mg/kg and in doses every other week of up to 18 mg/kg. Results thus far indicate that the 18 mg/kg every other week dosing results in substantially less issues with skin toxicity than other dosing/scheduling regimens (see Section 7.1.3 for details regarding the frequency of skin toxicities experienced with the Sym004 dosing regimens in ongoing clinical trials). A total of 17 patients have received 18 mg/kg every other week in Part E of the Sym004-01 trial.

In the current trial, interim analysis occurred after 19 patients were treated. After those 19 patients were treated at 18 mg/kg, it was observed that only two patients experienced grade 3 skin toxicity. Of those 19 patients, 16 patients came off study due to disease progression before reaching 6 months and only one patient completed six months of therapy before experiencing disease progression. Multiple EGFR-directed therapy trials have previously reported that patients who experience EGFR-directed therapy side effects (e.g. skin toxicity) are those who receive the greatest therapeutic benefit from this type of therapy. Hence, it is hypothesized that increasing the dose of Sym004 to 24 mg/kg in the current study might increase the frequency of skin toxicity, but also improve the overall tumor response to the therapy. Skin toxicities will continue to be managed according to Duke Medicine's "Guidelines for Management of Cutaneous Toxicity for Patients Receiving Epidermal Growth Factor Receptors" (see Appendix A), along with pre-medications described in Section 7.1.3.

7.3 Definition of Evaluable Subjects, On Study, and End of Study

Safety and efficacy analyses will include all patients who received any Sym004 treatment.

Patients will be considered "on study" once they have signed the informed consent form, and will continue to be considered "on study" as long as they are receiving study-related treatment or are undergoing study-related follow-up tests and procedures. If a patient who signs the informed consent form does not meet the eligibility criteria of the study, he or she will come off study as a "screen failure." Patients who sign informed consent, are eligible to participate, and receive study-related treatment are considered enrolled in the study. Subjects will be considered "off study" when they are no longer receiving study-related treatment and are no longer having study-related follow-up tests and procedures. Once "off study," subjects who are not screen failures will be followed for progression (for patients who came off study prior to disease progression) and survival status (all patients) for at least 1 year, if possible.

7.4 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study will be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.8, which describes procedures and process for prematurely withdrawn patients.

8 STUDY DRUG

8.1 Names, Classification, and Mechanism of Action

Sym004 is a 1:1 mixture of the 2 mouse-human chimeric immunoglobulin (Ig) G1 monoclonal antibodies (mAbs), futuximab and modotuximab. The antibodies bind to non-overlapping epitopes on the extracellular domain III of EGFR. Each antibody is manufactured separately as an individual drug substance. The 2 drug substances are the same with respect to formulation and protein concentration. Sym004 is prepared and released as a mixture of the antibodies.

8.2 Packaging and Labeling

The Sym004 drug product is a sterile liquid product containing 5.0 mg/mL Sym004 active ingredient, filled in 30 mL USP Type 1 glass vials with a FluroTec®-coated halobutyl/butyl rubber stoppers and secured with caps with flip-off seals . For clinical trial administration, each vial of Sym004 drug product has an extractable volume of 30 mL.

The composition, as described in the Investigator's Brochure (v. 7.0, 10-Mar-2016), is presented below:

Name of ingredient	Quantity (per mL)	Function	Grade
Futuximab	2.5 mg	Active pharmaceutical ingredient	In-house
Modotuximab	2.5 mg	Active pharmaceutical ingredient	In-house
Inactive ingredients			
Tri-sodium citrate dehydrate	2.38 mg	Buffer component	Ph.Eur., USP
Citric acid monohydrate	0.37 mg	Buffer component	Ph.Eur., USP
Sodium chloride	8.77 mg	Tonicity adjustment	Ph.Eur., USP
Sodium hydroxide	~ 0.12 mg[a]	pH adjustment	Ph.Eur., USP
Polysorbate 20	0.5 mg	Stabilizer	Ph.Eur., USP
Water for injection	q.s. 1.0 mL	Solvent	Ph.Eur., USP

Ph. Eur=European Pharmacopoeia; USP=United States Pharmacopoeia.

[a] Typical amount required for pH adjustment.

Packaging, labeling, and distribution to site of the Sym004 in 30 mL vials is performed at Catalent Pharma Solutions, United Kingdom. Packaging and labeling will be in accordance with applicable local requirement and applicable GMP guidelines.

8.3 Supply, Receipt, and Storage

Sym004 will be packaged, labeled and supplied for clinical use by Catalent Pharma Solutions, UK. Sym004 is intended for single use and should be stored between 2°C and 8°C (36°-46°F) and must not be frozen. The vial should be kept in the outer carton. Sym004 will be supplied in cartons containing 10 vials.

Sym004 will be filtered using an inline filter (0.2µm) during infusion. The product must be protected from direct sunlight and must not be frozen. The diluted infusion solution of Sym004 does not contain preservatives and must be used within 8 hours of preparation. Preparation of the infusion bag must be done immediately before the infusion is initiated, under aseptic conditions.

8.4 Dispensing and Preparation

Sym004 will be prepared and dispensed by the Duke Investigational Chemotherapy Service (ICS). The dose of Sym004 is determined by the subject's body weight **prior to each infusion**.

Materials needed for preparation of Sym004 infusion bags:

- 1000ml, 0.9% NaCl non–PVC infusion bags (see Table below for selection of infusion bag at different doses)
- Sym004 vials
- Needles
- Syringes
- Pre-printed drug bag labels (provided by Duke ICS)
- Polyethylene lined tubing having the 0.2 or 0.22 µm filter as part of the path or as an extension

Infusion bag containing 0.9% NaCl used for the different dose levels

Dose Level (mg/kg)	Infusion Bag
12	1000 mL
15	1000 mL
18	1000 mL
24	1000 mL

Preparation of Sym004 infusion bags:

- Sym004 is diluted into infusion bags containing 1000 mL 0.9 % NaCl.
- Remove the calculated volume of 0.9% NaCl from the infusion bag.
- Gently mix the vials by swirling clockwise – anticlockwise – clockwise for 10-15 seconds.
- Draw the calculated amount of Sym004 from an appropriate number of the Sym004 vials and inject it into the bag.
- Invert the bag slowly 3 times.
- Label the bag with the completed preprinted label, including the exact time of preparation.
- After Sym004 has been diluted in 0.9% NaCl, it can be kept at room temperature for up to 8 hours.
- Connect the tubing having the 0.2 or 0.22 µm filter as part of the path to the bag. Filtration only occurs at this step of the Sym004 administration.
- Start the infusion at 75 mL/hour. The infusion rate may be doubled every 30 minutes as tolerated, at the investigator's discretion. **The maximum infusion rate is not to exceed 10 mg/min (600 mg/hr)**.

8.5 Compliance and Accountability

Drug accountability records will be maintained for all clinical trial supplies. All empty and partially used clinical trial supplies will be destroyed in accordance with the institution's requirements for a cytotoxic agent. ICS will maintain detailed documentation of the number and identification of vials which are destroyed, and copies of these documents will be provided to Symphogen.

8.6 Disposal and Destruction

Disposition of all unused drug product will be carried out according to instructions provided by Symphogen at the end of the study after drug accountability is performed.

9 SUBJECT ELIGIBILITY

Please see Section 3.3 for a complete list of inclusion and exclusion criteria.

10 SCREENING AND ON-STUDY TESTS AND PROCEDURES

	Time Points									
		Cycle 1		Cycle 2		Cycle 3		Cycle 4…		
Evaluation	Screening [a]	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	End of Treatment
Informed consent	X									
Determination of EGFR amplification [b]	X									
History and complete physical exam, including full neurologic exam & KPS	X					X				X
Interval history and brief physical exam		X [c]	X	X	X		X	X	X	
Vital signs, including blood pressure and weight; calculate BMI [d]	X	X [c]	X	X	X	X	X	X	X	X
CBC with differential [e]	X		X	X	X	X	X	X	X	X
CMP + Mg [e]	X		X	X	X	X	X	X	X	X
Urinalysis	X									
Beta-HCG, if applicable, within 48 hours prior to start of study treatment, if contraception not initiated at time of negative test result prior to that time	X									
MRI of the brain [f]	X					X				X
Determination of EGFRvIII from archival tumor tissue [g]	X									
Quality of life measurements [h]	X					X				X
Skin toxicity assessment [i]	X		X	X	X	X	X	X	X	X
Toxicity assessment		Ongoing								
Pre-medication [j]		X								
Sym004 infusion		X	X	X	X	X	X	X	X	

[a] Within 2 weeks prior to first dose of Sym004. Some tests and procedures (as noted) are for a baseline only, not for eligibility.
[b] Determination of EGFR amplification may be taken from the original pathology diagnosis or maybe be tested from archival tissue as a part of screening by FISH (separate consent).
[c] Interval history with brief physical exam, vital signs, blood pressure, and weight do not need to be repeated if the screening exam and vitals occurred within 3 days of Day 1.
[d] BMI must be calculated before every infusion.
[e] Every 2 weeks, beginning with Cycle 1:Day 15.
[f] MRIs will be obtained every 8 weeks (i.e. every other cycle), prior to the start of the next cycle.
[g] EGFRvIII expression will be determined at baseline using archival tumor tissue; however, if a subject has more than one source of archival or frozen tissue, each source may be requested to determine if EGFRvIII expression has changed over time. EGFRvIII expression will be determined using IHC by the Duke Department of Pathology if not previously obtained.
[h] All quality of life assessments will be completed at baseline, prior to the start of every other cycle beginning with Cycle 3, and at the end of the study. These assessments should be completed prior to other study-related evaluations at study visits, if at all possible. If the subject is found to have progressive disease prior to beginning an even-numbered cycle, when HRQoL assessments are not conducted, they may complete these assessments at any time during the clinic visit.
[i] Skin toxicity will be evaluated at baseline and at each clinic visit, beginning with Cycle 1 Day 15, and patients will be instructed to call if the rash is painful or interfering with daily functioning. If a rash is identified, it should be treated according to Duke Medicine's "Guidelines for Management of Cutaneous Toxicity for Patients Receiving Epidermal Growth Factor Receptors" (see Appendix A).
[j] Pre-medication should include diphenhydramine 50 mg IV and a glucocorticoid steroid, such as hydrocortisone 100 mg IV, 30-60 minutes prior to the first dose. Premedication should be administered for subsequent doses based upon clinical judgment and presence/severity of prior need.

10.1 Screening Examination

If a candidate subject does not have EGFR status in his or her medical records, EGFR and EGFRvIII status may be tested from that patient's archival biopsy. The subject must sign a tissue screening consent before this can take place.

The screening examinations and procedures will take place within 2 weeks of starting study drug treatment. An informed consent must be signed by the patient before any research-related screening procedure takes place.

If screening occurs within 3 days of first study drug infusion, the screening tests can be used as Cycle 1 Day 1 examinations. Pre-treatment evaluations to determine eligibility are listed in the schema above and include the following:

- History and full physical exam, including a full neurologic assessment and KPS, two weeks prior to starting treatment
- Vital signs, including blood pressure and weight
- CBC with differential, CMP+Mg, Beta-HCG if appropriate (within 48 hours of beginning study drug if contraception not initiated at time of negative test result prior to that time)
- Urinalysis
- Baseline MRI of the brain 2 weeks prior to starting treatment
- Determination of EGFRvIII from archival tumor tissue
- Skin assessment, as a baseline measurement
- Quality of life measurements, as a baseline measurement
- Determination of EGFRvIII amplification

If a subject is found to be ineligible to participate in the study, minimal records regarding the subject and the reason for screen failure will be retained in the study database.

10.2 Run-In Period

Not applicable.

10.3 Treatment Period

Please also see the schema above for an itemized list of evaluations in this study and their corresponding time points.

<u>Cycle 1, Day 1</u>

- Interval history and brief physical exam
- Vital signs, including blood pressure and weight (Calculate BMI)
- Toxicity assessment (continuous throughout the study)
- Pre-medication
- Sym004 iv infusion

<u>Cycle 1, Day 15</u>

- Interval history and brief physical exam
- Vital signs, including blood pressure and weight (Calculate BMI)
- Skin toxicity assessment
- Toxicity assessment (continuous throughout the study)
- Hematology including CBC/differential
- CMP + Mg
- Sym004 iv infusion

Cycle 2, Day 1 +/- 4 days (and for even numbered cycles, Day 1) (Tests or procedures should be performed prior to beginning the cycle.)

- Interval history and brief physical exam
- Vital signs, including blood pressure and weight (Calculate BMI)
- Hematology including CBC/differential
- CMP + Mg
- Skin toxicity assessment
- Toxicity assessment (continuous throughout the study)
- Sym004 iv infusion

Cycle 2, Day 15 +/- 4 days (and for even numbered cycles, Day 15)

- Interval history and brief physical exam
- Vital signs, including blood pressure and weight (Calculate BMI)
- Skin toxicity assessment
- Toxicity assessment (continuous throughout the study)
- Hematology including CBC/differential
- CMP + Mg
- Sym004 iv infusion

Cycle 3, Day 1 +/- 4 days (and for odd numbered cycles, Day 1) (Tests or procedures should be performed prior to beginning the cycle.)

- Interval history and full physical exam, including a full neurologic assessment and KPS
- Vital signs, including blood pressure and weight (Calculate BMI)
- Hematology including CBC/differential
- CMP + Mg
- MRI of the brain (MRIs should be obtained every 8 weeks (i.e. every other cycle), prior to the start of the next cycle.)
- Quality of life measurements (should be performed prior to other study-related evaluations at study visits, if at all possible)
- Skin toxicity assessment
- Toxicity assessment (continuous throughout the study)
- Sym004 iv infusion

Cycle 3, Day 15 +/- 4 days (and for odd numbered cycles, Day 15)

- Interval history and brief physical exam
- Vital signs, including blood pressure and weight (Calculate BMI)
- Toxicity assessment (continuous throughout the study)
- Hematology including CBC/differential
- CMP + Mg
- Skin toxicity assessment
- Sym004 iv infusion

10.4 Re-treatment Criteria (day 1 and day 15)

Subjects must meet the following re-treatment criteria prior to infusion with Sym004, in order to receive the next scheduled infusion. Dose modifications are allowed as described in Section 7.1.1.

- ANC ≥ 1,000 cells/µl
- Platelets ≥ 50,000 cells/µl
- AST, bilirubin, creatinine ≤ 2.0 x upper limit of normal
- Resolution of any grade 3 or greater toxicity felt to be possibly, probably or definitely attributable to the study regimen to grade 2 or lower based on the investigator's decision.

If treatment with Sym004 is delayed for longer than 2 weeks due to toxicities (i.e. grade 3-4 non-hematologic toxicities secondary to Sym004, such as skin toxicities, electrolyte disturbances, and gastrointestinal symptoms, or grade 4 neutropenia or thrombocytopenia), the MRI assessment that would normally occur prior to beginning a new cycle or at the end of treatment will still be obtained no later than 8 ± 2 weeks after the previous MRI assessment. Once the toxicities have resolved to meet re-treatment criteria, the subject will resume Sym004. The day Sym004 is resumed will be considered Day 1 of the next cycle expected for the subject, which means that we will omit day 15 infusion for the previous cycle.

10.5 End of Treatment

The End of Treatment visit, i.e. the date of a subject's last treatment visit, should include:

- Interval history and full physical exam, including a full neurologic assessment and KPS
- Vital signs, including blood pressure and weight
- Hematology including CBC/differential
- CMP + Mg
- MRI of the brain
- Quality of life measurements (should be performed prior to other study-related evaluations at study visits, if at all possible)
- Skin toxicity assessment
- Toxicity assessment

If a subject goes off study and does not return to clinic as part of a regular study visit, not all tests listed above may be obtained as part of end of treatment, e.g. magnesium. If this occurs, only the assessments that are reasonably obtainable will be collected as part of end of treatment.

10.6 Follow-up Period

Patients will be followed for safety a minimum of 30 days after last dose of study drug, and also followed for any new and/or unresolved serious adverse events considered related to study therapy. Once "off study," subjects will be followed for progression (for patients who came off study prior to disease progression) and survival status (all patients)at least 1 year, if possible. Subjects not returning to Duke will be contacted via phone or information will be obtained through their local physician every 3 months to determine time of progression or survival.

10.7 End of Study

The study will be considered complete once enrollment has been met, follow-up procedures on all subjects have been conducted, and data analysis is concluded. The study may also be terminated early for any reason by the PI-sponsor. In order to close the study with the Duke IRB, all desired data extraction and analysis must be complete. Therefore, if any articles for publication are derived from the current study, they must be submitted and accepted with no further need for additional data extraction or analysis prior to termination with the IRB.

Subjects that are lost to follow-up will be documented in the patient record and in the 21 CFR Part 11 compliant database. In the eCRF , the subject will be marked as "Patient Status Unknown," along with a corresponding explanation, if any. This status may also be documented on an "Off Study Form" in the eCRF.

10.8 Early Withdrawal of Subject(s)

10.8.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but are not limited to, the following:

- Progressive disease as documented by MRI or physical examination at any time after the completion of therapy
- Pregnancy

- Upon request of the subject
- If, in the investigator's medical judgment, further participation would be injurious to the subject's health or well-being
- Development of intolerable symptoms
- Protocol deviation
- Administrative reasons, such as a major violation of the clinical trial protocol
- Non-compliance of the subject

10.8.2 Follow-up Requirements for Early Withdrawal

If an enrolled subject withdraws from the study prematurely, they will be asked to complete the tests/procedures that would have been conducted at their next scheduled visit, if physically possible. Patients will be followed for a minimum of 30 days after last dose of study drug, and also followed for any new and/or unresolved serious adverse events considered related to study therapy.

10.8.3 Replacement of Early Withdrawal(s)

Subjects that withdraw early from the study will only be replaced if they did not begin study-related treatment with Sym004.

10.9 Study Assessments

10.9.1 Medical History

Standard initial and interval medical histories will be obtained and documented per institutional guidelines, and should include an assessment of toxicities/side effects experienced by the subject.

10.9.2 Physical Exam and Neurological Assessment

Standard full physical exam and neurological assessment will be conducted and documented per institutional and PRTBTC guidelines. Per institutional guidelines, full exams must take place at MRI visits (e.g. Cycle 3, Day 1). Visits where an infusion is received and no is MRI scheduled only include a brief physical, as well as vital signs and weight.

10.9.3 Radiographic Review

The RANO criteria will be used to determine progression and pseudo-progression, as defined by Wen et al., 2010 (see Appendix B).[12]

10.9.4 Skin Toxicity Assessments

Skin toxicity will be evaluated at each clinic visit, beginning with Cycle 1 Day 15, and patients will be instructed to call if the rash is painful or interfering with daily functioning. If a rash is identified, it should be treated according to Duke Medicine's "Guidelines for Management of Cutaneous Toxicity for Patients Receiving Epidermal Growth Factor Receptors" (see Appendix A), in conjunction with Symphogen's "Skin Management Booklet" for Sym004.

10.9.5 Correlative Assessments

We will determine EGFRvIII status as part of an exploratory objective looking at the efficacy of Sym004 in EGFRvIII positive patients. Archival tissue will be used for this purpose; however, if a subject has more than one source of archival tissue, each source may be requested to determine if EGFRvIII status has changed over time. EGFR expression will be determined by FISH and and EGFRvIII expression will be determined using IHC by the Duke Department of Pathology if not previously obtained.

10.9.6 Laboratory Evaluations

The timing of laboratory assessments that will be obtained during the course of the study is given in Section 10. A list of each evaluation and what they include, when done at a Duke facility, is below.

- CBC with differential (hematocrit, hemoglobin, platelet count, white blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, NRBC %, NRBC CT, RDW-CV, absolute lymphocyte count, percent lymphocytes, percent monocytes, percent neutrophils, percent eosinophils, percent basophils, absolute monocyte count, absolute neutrophil count, absolute eosinophil count, absolute basophil count, red blood cell count)
- CMP + Mg (albumin, alanine aminotransferase, alkaline phosphatase , aspartate aminotransferase, total bilirubin , total protein, calcium, potassium, sodium, carbon dioxide creatinine, urea nitrogen, glucose, chloride + magnesium)
- Beta-HCG, if applicable, within 48 hours prior to start of study treatment

10.9.7 Quality of Life Assessments

Quality of Life will be assessed using standardized and validated questionnaires as described in Section 7.1.8. References for these standardized tests are provided in Section 15.

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred. This study will utilize the DCI Safety Desk for all SAE reporting to the Duke IRB and to the study supporter, Symphogen. The study team will follow DCI Safety Desk Standard Operation Procedures (SOPs).

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Sym004, whether or not related to use of the Sym004. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 10.5), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

11.1.1 Overview of Clinical Findings and side effects

According to the Investigator's Brochure (v. 8.0, 13-Mar-2017), skin toxicities were the most frequently reported AEs. To date (20 Jan 2017), approximately 380 subjects with solid tumors, including subjects with recurrent/metastatic SCCHN, mCRC, ESCC and NSCLC, have been treated with Sym004 in weekly

doses of up to 12 mg/kg and in doses every other week of up to 18 mg/kg in ongoing Symphogen-sponsored studies. Anti-EGFR related skin toxicities (including rash, pruritus, skin fissures, dry skin, erythema, and paronychia) have been observed in more than 90% of subjects in the completed and ongoing clinical trials. In subjects who had previously received anti-EGFR mAb therapy, Grade 3 skin toxicities were frequently reported; 50-69% of subjects at a dose of 9 or 12 mg/kg weekly (Sym004-01 Parts B and C and Sym004-02) and 33.3% and 41.2% of subjects at dose levels of 12 mg/kg and 18 mg/kg, respectively, every other week (Sym004-01 Parts D and E).

Other adverse events (AEs) associated with anti-EGFR mAbs, such as electrolyte disturbances (in particular hypomagnesemia), mucositis, and diarrhea were also frequently observed in the completed and ongoing trials. In clinical trials for which AE data are available (Sym004-01-Parts A, B, C, D, E, Sym004-02, and EMR 200637-001-Part A), hypomagnesemia was reported in 54-77% of subjects, and 0-38% of subjects experienced Grade 3 or 4 hypomagnesemia. In the Sym004-01 and Sym004-02 clinical trials, events of hypomagnesemia also represented the majority of serious adverse events (SAEs) that were considered to be related to Sym004 therapy. Serious clinical complications of hypomagnesemia have not been observed. Mucositis was observed in up to 40% of subjects, but the number of subjects experiencing Grade 3 mucositis was low (1 subject). Diarrhea has been reported in up to 59% of subjects; and ≤ 10% of subjects experienced Grade 3 diarrhea. Infusion related reactions have also been observed.

The expected adverse drug reactions are related to the biological mode of action of Sym004 through internalization and degradation of the EGFR receptor and to infusion of a foreign protein agent (infusion-related reactions).

At a minimum, the following relevant categories of adverse drug reactions are expected to occur in relation to administration of Sym004:

- Electrolyte imbalances, including hypomagnesaemia, hypocalcemia and hypokalemia (early and aggressive replacement therapy of magnesium is emphasized)
- Dermatological toxicities, acneiform rash, skin drying and fissuring, and secondary infections. Prophylactic treatment is allowed.
- Infusion reactions of variable severity, requiring medical intervention and potential discontinuation
- Other adverse drug reactions cannot be excluded. Therefore, the patients must be closely monitored and Sym004 should be administered in an environment where full resuscitation facilities are available.

11.1.2 **Reporting of AEs**

Symphogen Global Pharmacovigilance will be provided via secure email with AE listings as appropriate, in order for analysis to be performed for the Symphogen Development Safety Update Report (DSUR) (after Data Lock Point [DLP] for the report on January 20th).

11.2 Serious Adverse Events

An AE is considered "serious," if in the opinion of the investigator, it results in one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

11.2.1 **Reporting of SAEs to Duke Cancer Institute Safety Desk**

Adverse events that are serious and unexpected are considered reportable. Reportable events that occur during the study, beginning at the time of first study drug treatment infusion) to within 30 days following cessation of study drug treatment are reportable.

The study team will complete the DCI SAE Report Form and the DCI Safety Review Form, which will both be submitted to the DCI Safety Desk (Fax #: 919-681-9357 or secure email to dcccsafe@dm.duke.edu) and to the PI, Dr. Annick Desjardins, MD, FRCPC (email: annick.desjardins@duke.edu) or her designee within 24 hours of knowledge of the event.

The initial report for each SAE should include at minimum the following information:

- protocol # and title
- patient initials, study identification number, sex, age or date of birth
- date the event occurred
- description of the SAE
- dose level and cycle number at the time the SAE occurred
- description of the patient's condition
- indication whether the patient remains on study
- causality or causal relationship

The DCI Safety Desk will track individual SAE reports into their internal tracking database and complete the initial processing within 2 business days of receipt. For unanticipated study-related event(s), these will be processed within 1 business day of receipt.

De-identified source documentation (i.e. admission notes, discharge notes, applicable laboratory results, radiology/diagnostic testing results, etc.) should be sent with the SAE Report Form, if available at the time of the report. Any follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to the DCI Safety Desk, as soon as possible using the same forms mentioned above. The study team should keep a copy of the initial SAE forms submitted to the DCI safety desk and any SAE follow up forms for reference.

The DCI Safety Desk will use the information provided in the DCI SAE Report Form and the DCI Safety Review Form to complete a FDA Form 3500A, and will submit it to the Duke University IRB, if it meets Duke IRB reporting requirements (see below).

Only adverse events that the Duke Sponsor-Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e. more likely than not) related to the research must be reported to the Duke IRB. Those adverse events will be submitted in the electronic IRB (eIRB) system, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related adverse event;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.
- The Sponsor-Investigator must report to the FDA, in an IND safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:
    - Suspected adverse reaction (i.e. there is a reasonable possibility that the drug caused the adverse event)
    - Serious
    - Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

11.2.2 Reporting to the FDA

All SAE's that are possibly/probably related (i.e. there is evidence to suggest a causal relationship) and unexpected must be reported to the FDA as IND Safety Reports. The Sponsor-Investigator is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected (possibly/probably related) adverse reactions) per 21CFR312.32.

The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other adverse events will be reported to the FDA in the Annual Report.

This will be done by the study team in cooperation with the DCI Safety Desk.

11.2.3 Safety Reporting to Symphogen Global Pharmacovigilance

The Investigator shall have full responsibility for the scientific, medical and legal/regulatory conduct of the trial, as well as for study documentation and safety reporting responsibilities. The Investigator shall promptly report to Symphogen all safety-related information obtained from the study as follows:

For all expedited SAE reports (Initial or Follow-up) and any death (regardless of causality) that occurs while a subject is on study, i.e. within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug, Symphogen Global Pharmacovigilance must be notified by telephone, fax, or secure email within 2 business days of the PI or designee first becoming aware of the event and the study team notifying the DCI safety desk of the event. Any urgent safety issue or communication with FDA concerning such issue should be made known to Symphogen within 24 hours of the PI or designee first becoming aware of the event and the study team notifying the DCI safety desk of the event.

All SAEs require that a Serious Adverse Event Report Form (either DCI Safety Desk SAE Report and Safety Review Forms or a MedWatch Form 3500A) be completed and forwarded to Symphogen either via fax transmission or secure email. The SAE Form must include a description narrative, inclusive of the investigator's causality assessment.

All non-expedited serious adverse events (SAEs) will be forwarded to Symphogen Pharmacovigilance within 7 calendar days of first knowledge of the event by secure email or fax transmission.

Any request by Symphogen for safety data that would need to be incorporated into the DSUR generated by Symphogen for its reporting purposes will be provided in a timely fashion, in order for Symphogen to meet its reporting timelines.

Contact Information for Symphogen Global Pharmacovigilance

Email Forms: GlobalPV@symphogen.com

Drug Safety Telephone line: 908-378-9630

Safety Fax line: 908-378-9654

11.2.4 Exposure in Utero

While reports of pregnancy are not considered SAEs, these events will be tracked for follow-up purposes and assessing outcome in the infant. If any trial subject or the female partner of a male trial subject becomes pregnant during the time of receiving study drug, or is found to be pregnant within 90 days of

the last dose of study drug, Symphogen will be notified by the DCI Safety Desk within 1 business day of the DCI Safety Desk learning of the event via fax or email and a Pregnancy Reporting Form will need to be completed. The pregnancy will be followed to term and all pregnancy information will be tracked within the Symphogen safety database.

11.3 Emergency Unblinding of Investigational Treatment
Not applicable.

11.4 Other Reportable Information
Not applicable.

11.5 Special Warnings and Precautions
Not applicable.

11.6 Safety Oversight Committee (SOC)
The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase 1 and 2, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews include but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

11.7 External Data and Safety Monitoring Board (DSMB)
Not applicable.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring
The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. Monitoring additional to the standard practice of the DCI may occur as per contractual agreement with Symphogen.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

12.2 Audits
The Duke School of Medicine Office of Audit, Risk, and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC and

auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. Audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize "best practices" in the research/clinical trials environment.

12.3 Data Management and Processing

12.3.1 Case Report Forms (CRFs)

The electronic CRF (eCRF) will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff (the PI, the research coordinators, the research nurses, the data management team, and the clinical trials manager) are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system, which will be a 21 CFR Part 11 compliant database. All users of this system will complete user training, as required or appropriate per DCI requirements and other regulations.

12.3.2 Data Management Procedures and Data Verification

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data management team and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.3 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the PI must be approved by the statistician before publication or presentation.

With Amendment 31, the study has been modified to allow the assessment of activity of two different doses of Sym004: 18 mg/kg and 24 mg/kg. With the increase to 24 mg/kg dose, we intend to treat 65 additional subjects at that dose level (36 in Cohort 1, and 29 in Cohort 2). The maximum accrual goal for this study is the number of subjects accrued before Amendment 31 plus 65 more.

13.1 Analysis Sets

Safety and efficacy analyses will include all patients who received any Sym004 treatment.

13.2 Patient Demographics and Other Baseline Characteristics

Socio-demographic and clinical characteristics of patients enrolled onto this study will be summarized by study cohort and dose level. For categorical variables, frequencies and percentages will be provided. Means with standard deviations or medians/percentiles will summarize non-categorical variables.

13.3 Treatments

Within each cohort and dose level, a frequency distribution will be generated for the number of doses of Sym004 administered. In addition, the frequency of dose reduction will also be tabulated.

13.4 Primary Objective

The primary objective of the study is to assess the activity of Sym004 within two cohorts of patients with recurrent glioblastoma based upon PFS6: patients who are non-bevacizumab failures (Cohort 1) and patients who have previously failed bevacizumab (Cohort 2). This assessment will be done at both dose levels.

13.4.1 Variable

The primary endpoint is PFS6, which is defined as the proportion of patients who remain alive and progression-free 6 months after initiation of Sym004 treatment. The use of PFS6 as an endpoint in phase II clinical trials is recommended by Ballman (2007) and Lamborn (2008) given the strong association between progression-free survival status and overall.[13,14]

13.4.2 Statistical Hypothesis, Model, and Method of Analysis

Based upon the Kaplan-Meier estimator, the proportion of patients who are alive and progression-free 6 months after initiation of Sym004 treatment will be estimated. Details about the hypothesis test that will be conducted is provided in Section 13.8.

The primary analyses will focus on the dose group to which the patient was originally assigned. No more than 2 of the patients treated initially at the 18 mg/kg dose will have their dose escalated to 24 mg/kg. Efficacy analyses will be generated with and without these patients to assess the impact of these patients with dose escalation on inferences.

13.4.3 Handling of missing values, censoring, and discontinuations

The sample size justification provided in Section 13.8 assumes that all patients will be followed for their clinical status for at least 6 months or until death. Historical data within the Preston Robert Tisch Brain Tumor Center suggests that such an assumption is fully achievable. If patients are lost to follow-up prior to their 6-month outcome, estimates of PFS6 will be appropriately adjusted for such censoring in the estimation of the outcome from the Kaplan-Meier estimator.

13.5 Secondary Objectives

Secondary objectives are to determine the safety of Sym004 in recurrent GBM patients and to determine response rate (RR) and overall survival (OS) in recurrent GBM patients. These analyses will be generated for both dose levels.

13.5.1 Key Secondary Objective: Safety

Within each cohort and dose level, the proportion of patients who experience grade 3, 4, or 5 adverse events that are possibly, probably, and definitely related to protocol treatment will be estimated.

In addition, for each type of toxicity, the maximum grade experienced by each patient will be summarized with frequency distributions. Two adverse experience tabulations will be generated, one that includes all toxicities regardless of attribution, and one that includes only toxicities that are possible, probably, and definitely related to Sym004 treatment.

Patients who have their dose escalated from 18 mg/kg to 24 mg/kg will be included in toxicity summaries for 18 mg/kg and 24 mg/kg. The toxicity experienced prior to dose escalation will be summarized with the other patients treated at the 18 mg/kg dose level; whereas, the toxicity experienced after dose escalation will be included in the summary of adverse events associated with 24 mg/kg.

13.5.2 Other Secondary Objectives: Response Rate and Survival

Within each cohort and dose level, radiographic response rate will be estimated as the proportion of treated patients with a complete or partial response. An exact binomial confidence interval will be generated.

Kaplan-Meier curves will be generated to describe the PFS and OS experience of patients treated with Sym004 within each cohort and dose level. Progression-free survival (PFS) is defined as the time interval between initiation of protocol treatment and either disease progression or death. If the patient is alive and progression-free, PFS will be censored at the date last known alive. Overall survival (OS) is defined as the time interval between initiation of protocol treatment and death, or date of last follow-up if alive. Estimates with confidence intervals will be generated for median PFS/OS, as well as 2 month intervals for PFS for the first year (2, 4, 6, etc..) and 6 month intervals for OS for the first 2 years (6,12, 18, 24) from the time the subject goes on study.

The analyses of response rate, OS, and PFS will focus on the dose group to which the patient was originally assigned. The impact that the few patients treated initially at the 18 mg/kg dose and subsequently with 24 mg/kg will be assessed by generating analyses with and without these patients.

13.6 Exploratory Objectives

There are two exploratory objectives for this study: (1) Assess the impact of EGFRvIII expression on OS and PFS, and (2) Describe patient-reported quality of life outcomes (PROs).

Within each cohort, dose level, and EGFRvIII expression group, Kaplan-Meier curves will be used to describe OS/PFS and to estimate median OS/PFS. For each cohort, Cox proportional hazards model will be used to examine the joint effect of dose and EGFRvIII expression on PFS/OS.

Descriptive statistics (e.g. means and standard deviations) will be used to summarize each quality of life subscale at each follow-up assessment. These statistics will be generated for each cohort and dose level.

13.7 Interim Analysis

13.7.1 Interim Efficacy Analysis for 18 mg/kg Sym004

Interim analyses for efficacy will not be conducted given the expected rapidity of patient accrual relative to the length of time required to observe the study's primary outcome. If a two-stage design were conducted with PFS6 as an endpoint, accrual would be suspended for up to 6 months to observe outcome for all patients within the first stage. Depending upon the cohort, accrual to both stages of the study could have been completed during that period of accrual suspension.

13.7.2 Interim Efficacy Analysis for 24 mg/kg Sym004

With Amendment 31, the design of the study will be modified. Within each cohort, a two-stage study design is used to assess outcome. The statistical properties of this design are provided in section 13.8.2. However, the stopping rules for each cohort are summarized below.[15] After stage 1 enrollment is completed, accrual will be temporarily suspended while data from the first stage matures unless at that point 1 or more patients have survived 6-months progression-free.

Patients who have their dose escalated from 18 mg/kg to 24 mg/kg will not be considered in these interim efficacy analyses for 24 mg/kg Sym004.

Monitoring Rules		
	Cohort 1	Cohort 2
Statistical Hypothesis	PFS6 ≤ 20% vs PFS6 ≥ 40%	PFS6 ≤ 3% vs PFS6 ≥ 20%
Stage 1	Accrue 19 patients	Accrue 12 patients
Criteria for Accrual to Stage 2	>3 patients who live 6+ months progression-free	>0 patients who live 6+ months progression-free
Stage 2	Accrue 17 more patients	Accrue 17 more patients

13.7.3 Skin Toxicity Monitoring among Patients Treated with 18 mg/kg Sym004

Interim analyses that focus on the physiologic consequences of Sym004 treatment will be conducted after 19 total patients across both cohorts have been treated with Sym004. The goal of the interim analysis is to determine whether the dose of Sym004 needs to be increased or decreased. The basis of this decision will partly be based upon the prevalence of ≥ Grade 3 skin toxicity after the administration of 2 doses. However, other factors may contribute to this decision-making. Accrual will be not be suspended while this assessment of skin toxicity is occurring. The decision-making could result in 3 outcomes: increase the dose, decrease the dose, or continue accruing at the current dose. If a decision is made to modify the dose, the protocol will be appropriately amended.

If the prevalence of skin toxicity is truly 30% (Symphogen unpublished data), then the dose of Sym004 is considered acceptable. However, if the true prevalence of skin toxicity is much less or much greater than 30%, then the dose of Sym004 may need modification. Observing skin toxicity in 2 or fewer patients or 9 or more patients is an indication that the data concerning dosing needs to be carefully scrutinized along with other available data. The probability of observing this extent of skin toxicity as a function of the true probability of skin toxicity is tabulated below.

True Probability of Skin Toxicity	Probability of observing either 2 or fewer patients with skin toxicity, or observing 9 or more patients with skin toxicity
0.05	0.933
0.1	0.705
0.3	0.130
0.5	0.677
0.55	0.816
0.6	0.912
0.65	0.965

13.7.4 Initial Toxicity Monitoring among Patients Treated with 24 mg/kg Sym004

Given limited experience with 24 mg/kg Sym004, the first 3-6 patients will be slowly accrued and carefully monitored for unacceptable toxicity (see Section 7.1.2).

The first patient, regardless of cohort, will be treated and observed for 1 cycle before the accrual of a second patient. During this period of observation, the patient will receive at minimum 2 full doses of Sym004 and be followed until the end of Cycle 1. If the patient experiences an unacceptable adverse event (refer to Section 7.1.2), the study will be suspended and the patient's experience will be discussed with Symphogen to determine whether patient accrual should continue. Otherwise, 2 additional patients will be treated.

The second and third patient can be accrued at the same time. However, further accrual after the 3rd patient is suspended until completion of 1 cycle of therapy. After the first 3 patients have been observed, the number of patients with unacceptable toxicity will be determined.

- If none of the first 3 patients has an unacceptable toxic event, accrual will continue without further slowed accrual.
- If 2 of the first 3 patients has an unacceptable toxicity, the study will remain suspended. Results will be discussed with Symphogen with the expectation that accrual will be terminated.
- If 1 of the first 3 patients has an unacceptable toxicity, an additional 3 patients can be accrued after which accrual will be suspended until all patients have been observed for at least 1 cycle. If none of the additional 3 patients experiences an unacceptable toxicity, then accrual will resume without the requirement of staggered entry. If 1 of these 3 patients experiences an unacceptable toxicity, the study will remain suspended while a discussion occurs with Symphogen to determine if accrual is terminated.

For initial monitoring of the 24 mg/kg dose of Sym004, an unacceptable adverse event is defined as any grade 3, 4, or 5 adverse event that is definitely, possibly, or potentially related to Sym004 treatment.

Patients who have their dose escalated from 18 mg/kg to 24 mg/kg **will** be considered as part of this interim analyses of toxicity at the 24 mg/kg if they are among the first 3 (or 6) patients who receive Sym004 at the 24 mg/kg dose level.

13.8 Sample Size Calculation

13.8.1 Sample Size Requirements for 18 mg/kg Sym004

The sample size requirements within each cohort of patients will be considered separately.

Non-Bevacizumab Failures (Cohort 1): In a recent phase 3 study among patients with recurrent glioblastoma, a PFS6 rate of 19% (approximate 95% confidence interval: 12% - 30%) was observed for patients treated with lomustine.[16] If the true PFS6 associated with SYM004 is comparable to that seen with lomustine or approximately 20%, there is limited interest in further investigation of SYM004 in this patient population. However, if the true PFS6 is 40% or greater, there is interest in further investigation of the experimental treatment within this patient population. With 36 patients, there is 90% power to differentiate between a PFS6 rate of 20% and 40% assuming a test conducted at the 0.1 level of significance (1-tailed). If 11 or more patients of the 36 patients live more than 6 months without disease progression, the treatment will be considered worthy of further investigation in this patient population.

Bevacizumab Failure (Cohort 2): A recent publication from the Preston Robert Tisch Brain Tumor Center reported a PFS6 rate of 2.3% (95% CI: 0.2, 10.4) among patients who received non-bevacizumab treatment after progression on bevacizumab treatment administered in the recurrent setting.[17] If the true PFS6 associated with SYM004 within this patient population is comparable to that observed in this publication or about 3%, there is limited interest in further investigation of the agent in this setting. However, if the true PFS6 rate is 20% or greater, there is interest in further clinical investigation. With 25 patients, there is 90% power to differentiate between a PFS6 rate of 3% and 20% assuming a test conducted at the 0.1 level of significance. If 3 or more patients of the 25 live more than 6 months without disease progression, the treatment is worthy of further investigation.

13.8.2 Sample Size Requirements for 24 mg/kg Sym004

Prior to Amendment 31, the original goal was to accrue 61 subjects to receive 18 mg/kg Sym004, with 36 patients in Cohort 1 and 25 in Cohort 2. After the approval of Amendment 31, no additional subjects will be enrolled at 18 mg/kg.

After Amendment 31, the effect of 24 mg/kg Sym004 treatment on PFS6 will be assessed in two cohorts with a maximum of 36 patients in Cohort 1 and 29 in Cohort 2. With Amendment 31, the design of the study will be modified. Within each cohort, either a two-stage minimax or two-stage optimal design will be used to assess PFS6.[15] The same benchmarks that were used with 18 mg/kg Sym004 are used here with the same targeted type I and II error rates (i.e. $\alpha = \beta = 0.1$).

Patients originally treated at the 18 mg/kg dose level who have their dose escalated to 24 mg/kg will not be considered in these analyses.

Non-Bevacizumab Failures (Cohort 1): A minimax two-stage design will test the hypothesis that the true PFS is 20% or less versus the alternative that the true PFS is 40% or greater. After testing the treatment on 19 patients in the first stage, the trial will be terminated if 3 or fewer patients live 6 months or more progression-free. Otherwise, additional patients will be accrued so a total of 36 patients will be treated. If the total number of patients living 6 months or more progression-free is less than or equal to 10, then the treatment is rejected as not worthy of further investigation in this patient population. The expected sample size of 28.26 and the probability of early termination is 0.455. The type I and II error rates are 0.086 and 0.098, respectively.[18]

Bevacizumab Failure (Cohort 2): An optimal two-stage design will be used to test the hypothesis that the true PFS is 3% or less versus the alternative that the true PFS is 20% or greater. After testing the treatment on 12 patients in the first stage, the trial will be terminated if 0 patients live 6 months or more progression-free. Otherwise, the trial will continue and a total of 29 patients will be studied. If 2 or more patients live 6 months or more progression-free the treatment will be considered worthy of further investigation. The expected sample size of 21.64 and the probability of early termination is 0.561. The type I error rate if 0.038 and the type II error rate is 0.10.[18]

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4 Study Documentation

Study documentation includes, but is not limited to, source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder," which includes, but is not limited to, approved protocol versions, approved informed consent forms, FDA Form 1572s, and CAP and CLIA laboratory certifications.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. DUHS utilizes Epic Maestro Care as an electronic health record. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

14.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room in Duke Cancer Center Clinic 3-1. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated 21 CFR Part 11compliant database, which is housed in an encrypted and password-protected on a secure network drive. Access to electronic databases (without edit rights) will be limited to the PI, the study coordinator, and the statistical team. The only personnel with both access and edit rights to the electronic databases are the data management team,

including the clinical trials manager. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy, i.e. all files and documents that relate to the protection of human research participants are retained for at least 6 years following study completion (see Section 14.8 below for other study document storage guidelines).

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to the Safety Monitoring and Reporting section and the Quality Control and Quality Assurance section.

14.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

14.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- At least two years after the date on which a New Drug Application is approved by the FDA (if an IND is involved)
- At least two years after formal withdrawal of the Duke IND associated with this protocol (if an IND is involved)
- At least six years after study completion (Duke policy)

15 REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-96, 2005

2. Reardon DA, Wen PY, Desjardins A, et al: Glioblastoma multiforme: an emerging paradigm of anti-VEGF therapy. Expert Opin Biol Ther 8:541-53, 2008

3. Cancer Genome Atlas Research N: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455:1061-8, 2008

4. Jones-Bolin S, Zhao H, Hunter K, et al: The effects of the oral, pan-VEGF-R kinase inhibitor CEP-7055 and chemotherapy in orthotopic models of glioblastoma and colon carcinoma in mice. Mol Cancer Ther 5:1744-53, 2006

5. Dresemann G: Temozolomide in malignant glioma. Onco Targets Ther 3:139-46, 2010

6. Ohgaki H, Kleihues P: The definition of primary and secondary glioblastoma. Clin Cancer Res 19:764-72, 2013

7. Wong AJ, Bigner SH, Bigner DD, et al: Increased expression of the epidermal growth factor receptor gene in malignant gliomas is invariably associated with gene amplification. Proc Natl Acad Sci U S A 84:6899-903, 1987

8. Sugawa N, Ekstrand AJ, James CD, et al: Identical splicing of aberrant epidermal growth factor receptor transcripts from amplified rearranged genes in human glioblastomas. Proc Natl Acad Sci U S A 87:8602-6, 1990

9. Weitzner MA, Meyers CA, Gelke CK, et al: The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer 75:1151-61, 1995

10. Van Belle S, Paridaens R, Evers G, et al: Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. Support Care Cancer 13:246-54, 2005

11. Beck AT, Steer RA, Ball R, et al: Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 67:588-97, 1996

12. Wen PY, Macdonald DR, Reardon DA, et al: Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28:1963-72, 2010

13. Ballman KV, Buckner JC, Brown PD, et al: The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol 9:29-38, 2007

14. Lamborn KR, Yung WKA, Chang SM, et al: Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 10:162-170, 2008

15. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989

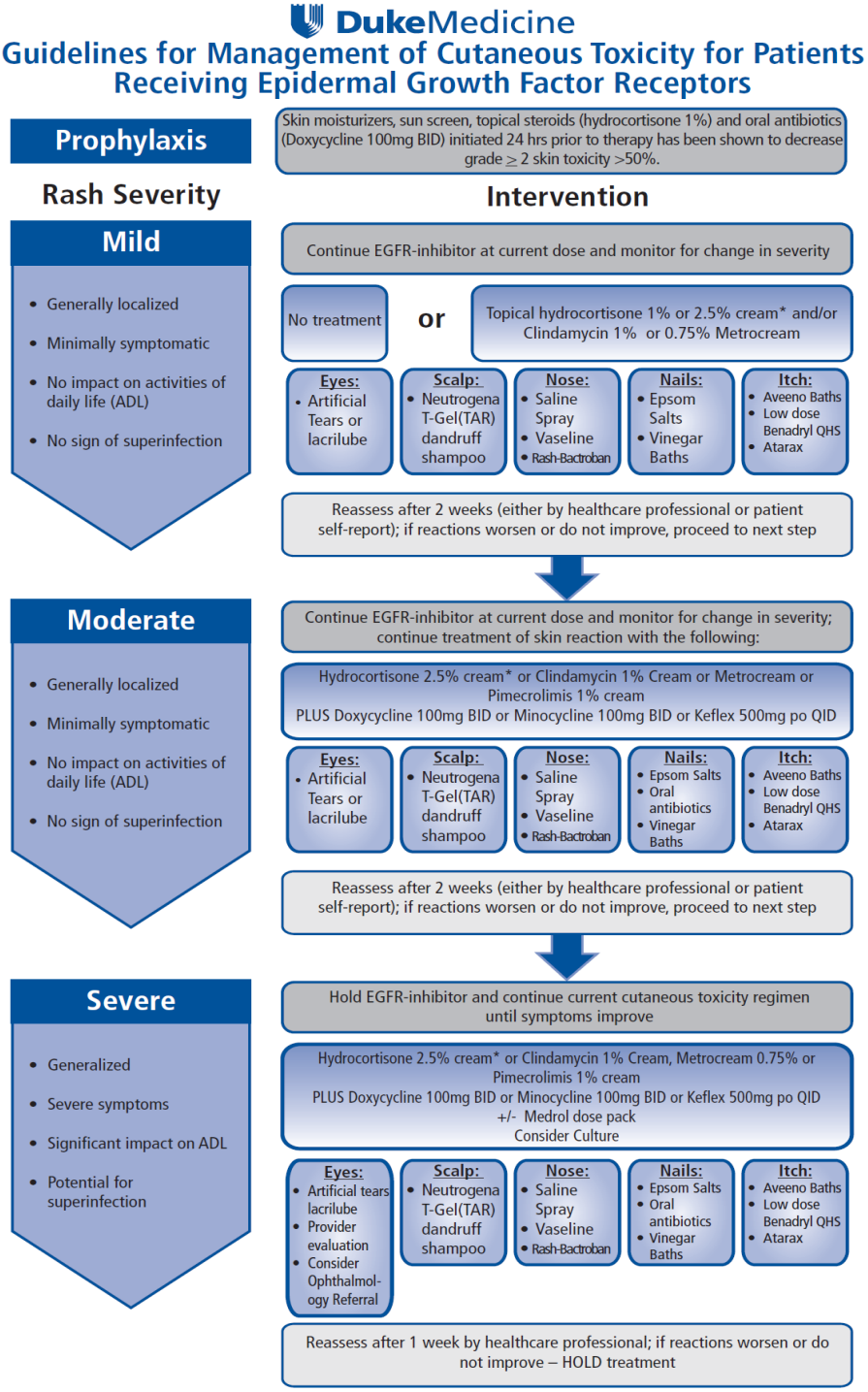
16. Wick W, Puduvalli VK, Chamberlain MC, et al: Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol 28:1168-74, 2010

17. Reardon DA, Herndon JE, Peters KB, et al: Bevacizumab continuation beyond initial bevacizumab progression among recurrent glioblastoma patients. British Journal of Cancer 107:1481-1487, 2012

18. PASS 15 Power Analysis and Sample Size Software. Kaysville, Utah, USA, NCSS, LLC, 2017

16 APPENDICES

16.1 Appendix A



References:
Lynch TJ Jr, Kim ES, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. Oncologist. 2007;12(5):610-621.
Viale PH, Zitella L. Effective Management Strategies for Skin Toxicities Associated With Epidermal Growth Factor Receptor (EGFR)-Inhibitor Therapy. The Oncology Nurse. 2008; 1(3):supplement.
M. E. Lacouture, E. P. Mitchell, H. Shearer, N. Iannotti, B. Piperdi, M. V. Pillai, F. Xu, M. Yassine. Impact of pre-emptive skin toxicity (ST) treatment (tx) on panitumumab (pmab)-related skin toxicities and quality of life (QOL) in patients (pts) with metastatic colorectal cancer (mCRC): Results from STEPP. GI ASCO 2009, Abstract No. 291.

P&T approved 02/2009

16.2 Appendix B

THE
PRESTON ROBERT TISCH
BRAIN TUMOR CENTER
at Duke…there is HOPE

Name: BTC Imaging SOP- Procedures for Provider Reading of MRIs and CTs
Effective Date: 4/2012
Review/Revision History:

Definitions:
MRI stands for magnetic resonance imaging with and/or without contrast
CT stands for computed tomography with and/or without contrast
Radiation therapy (RT) means treatment of the patient's tumor with radiation treatment, typically for about 6 ½ weeks. It may include stereotactic radiosurgery, which is a nonsurgical RT technique that delivers ionizing radiation to the tumor. **Pseudoprogression** means a transient increase in contrast-enhancement on MRI without true tumor progression
Pseudoresponse means marked decrease in contrast enhancement possibly due to anti-angiogenic therapy
Non-enhancing disease progression means progression of the tumor with components that are non-enhancing on MRI
Anti-angiogenic agents means a drug or substance inhibiting the growth of blood vessels
Seizure means any episode, caused by abnormal electrical conduction in the brain, resulting in the abrupt onset of transient neurologic symptoms
Steroids means a group of drugs that includes the corticosteroids, similar to hormones produced by the adrenal glands
Immunotherapy means treatment of disease by inducing, enhancing, or suppressing an immune response
FLAIR stands for fluid-attenuated inversion recovery [image sequences]
RANO stands for the Response Assessment in Neuro-Oncology (RANO) [1]

1. Determine Patient Background Information

A. Determine the patient's medical history.

B. Has the patient had prior surgery?

C. Has the patient had Gliadel (carmustine) wafers placed into the resection cavity? Note: Be careful with therapeutic effect

D. Has the patient undergone radiation therapy or stereotactic radiosurgery?

Note: Be careful with pseudoprogression

E. Has the patient taken any anti-angiogenic agents, such as bevacizumab (Avastin), sunitinib (Sutent), or cediranib (Recentin)? Note: Be careful with pseudoresponse and non-enhancing disease progression

F. Has the patient experienced seizure activity recently?

G. Has the patient tapered up or down in their dose of steroids? H. Has the patient undergone any form of immunotherapy?

2. Pick the right date of previous MRI/CT to which you want to compare the new MRI

A. For high grade patients off therapy, go back to the MRI when they stopped therapy.

B. For low grade patients off therapy, go back to baseline MRI. The best baseline MRI is normally 2-

4 months post-operative (post-operative changes must have resolved and at the nadir of cavity collapse).

C. For patients on treatment, compare to baseline (response) and to nadir (progression).

3. Look at T1 pre-contrast images/non contrasted images

A. Is there new blood?

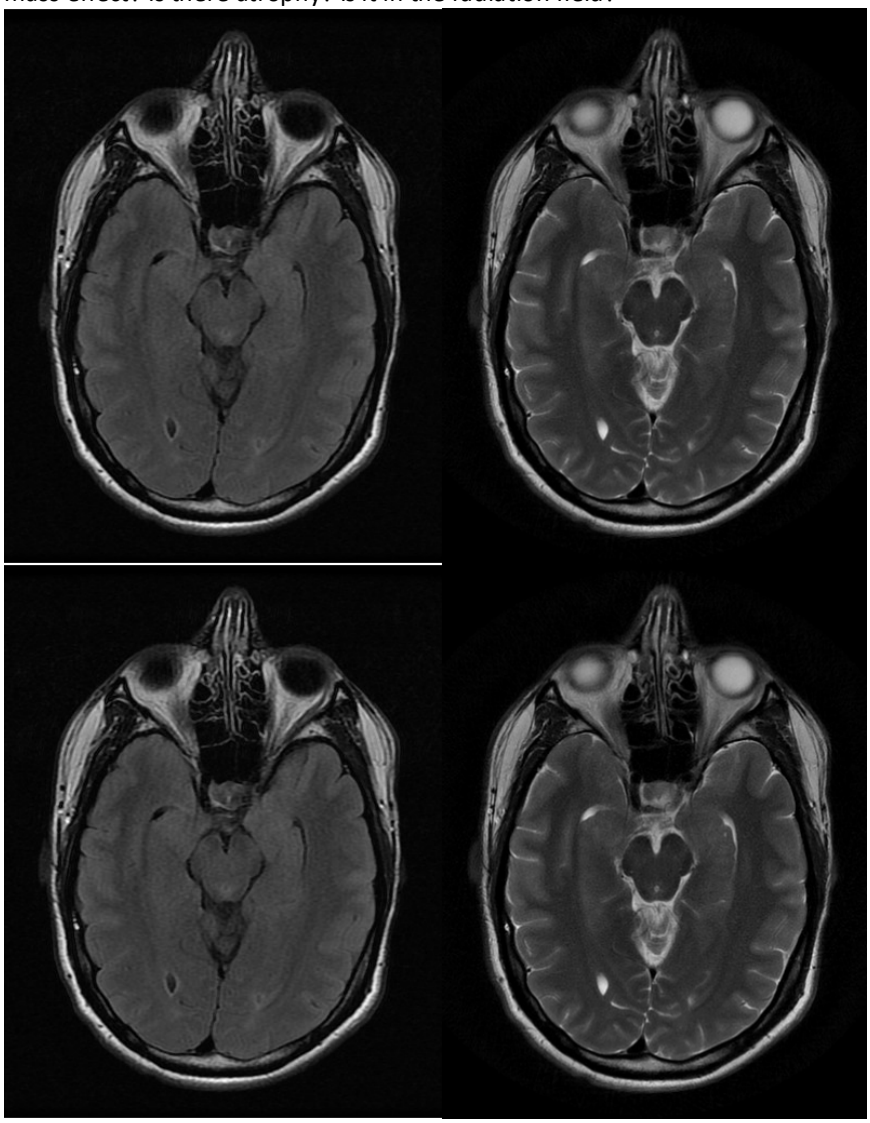
B. Are there calcifications?

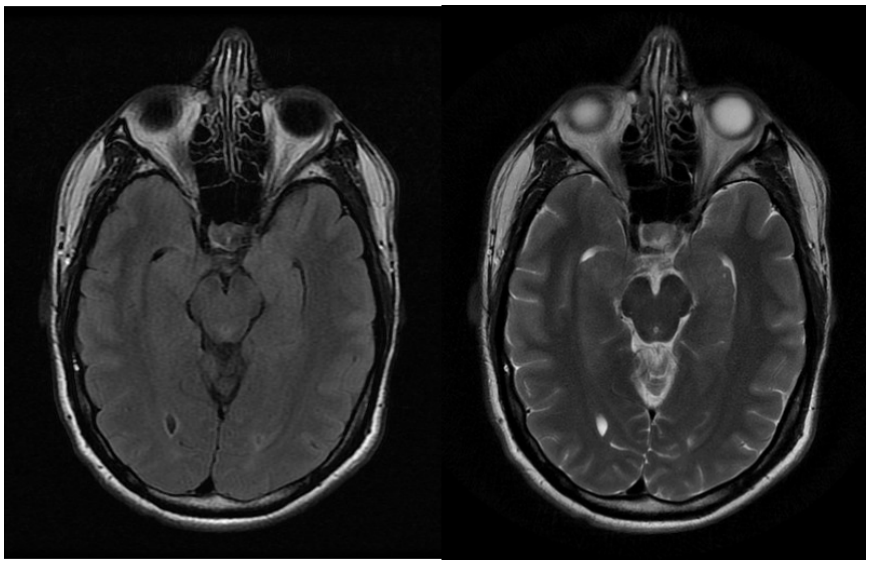
4. Look at T2 and/FLAIR images (Note: my preference is for FLAIR images)/non contrasted images

A. Most frequently, we look at axial FLAIR images.

B. Determine RANO – T2/FLAIR lesion response.

C. Be careful with increase T2/FLAIR from tumor progression vs. treatment effect. Is there increased mass effect? Is there atrophy? Is it in the radiation field?





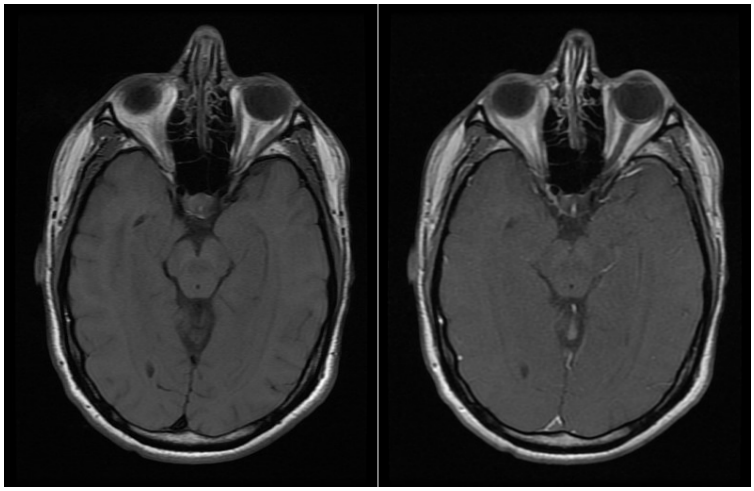
FLAIR **T2**

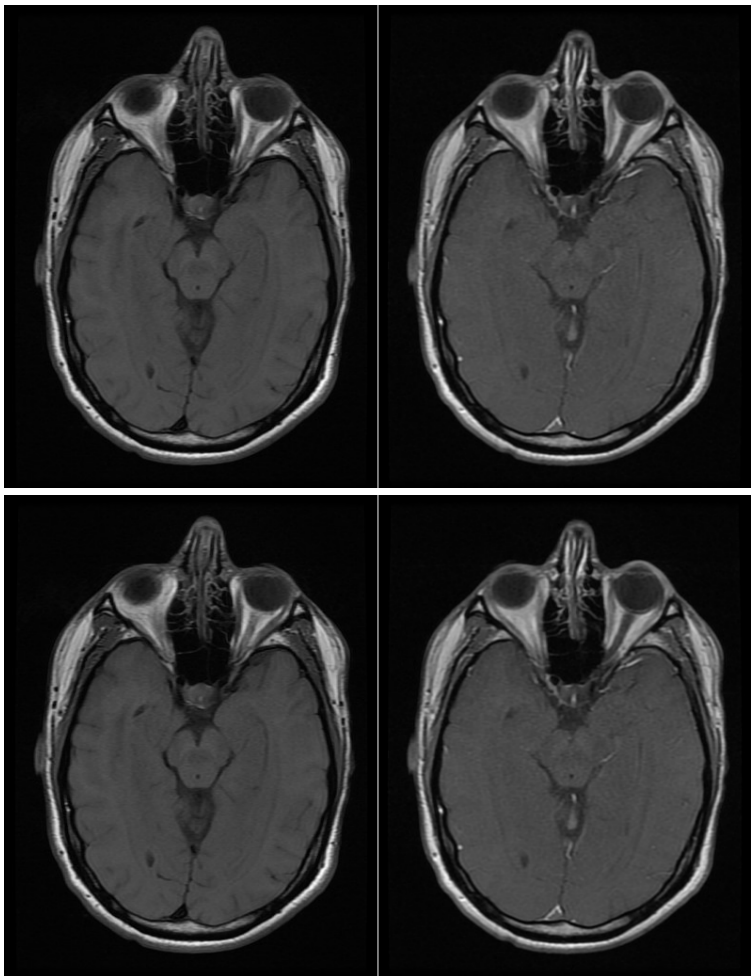
Response	Definition
Improved	Signal abnormality decreased
Unchanged	Unchanged compared to prior imaging
Worse	Unequivocal worsening/progression of signal abnormality (due to tumor - make sure this is not due to infection, infarction, demyelination, radiation)
Unable to Assess (UA)	Unable to evaluate non-enhancing lesions because of technical factors

5. Post contrast T1-weighted images/post contrast images

A. Look at **two planes**: Axial, Coronal, Sagittal.

B. Make sure you are looking at the post contrast scans. Is the nasal mucosa white (post contrast) or the same grey shade as the brain parenchyma (non contrasted)?





T1 pre contrast

T1 post contrast

C. Pick target lesion.

i. Some lesions are followed quantitatively, some qualitatively.

ii. Measurable lesions are those that t you COULD follow quantitatively

iii. Target lesions are those that you WILL follow quantitatively

iv. Only enhancing lesions can be quantitative.

D. Measurable lesions must have the following criteria:

v. Contrast enhancing

vi. Clearly defined, bi-dimensionally measurable margins

vii. Two perpendicular diameters ≥10mm

viii. If slice thickness + gap is >5mm, size threshold is 2 x total

ix. Do not include surgical cavity, cyst, or necrotic area

E. Non-measurable lesions meet the following criteria:

x. Less than 1 cm in any diameter (e.g. 12 x 8 mm)

xi. Poorly defined margin

xii. Hemorrhagic or predominantly necrotic

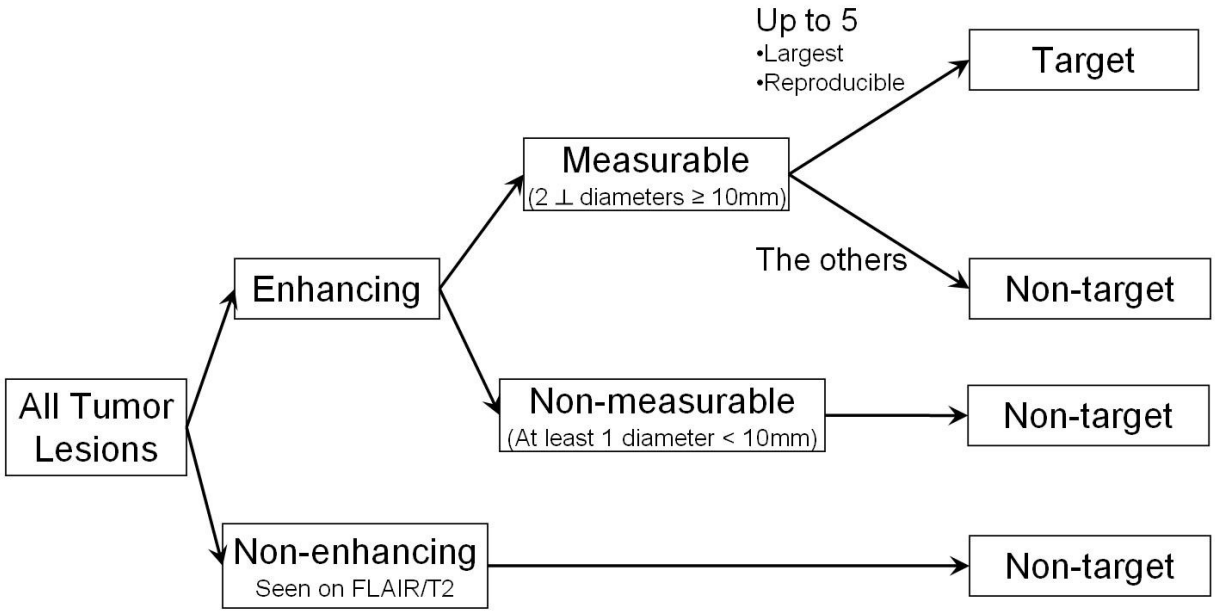
xiii. Tumor around a cyst or surgical cavity, unless nodular component ≥ 10 x 10 mm

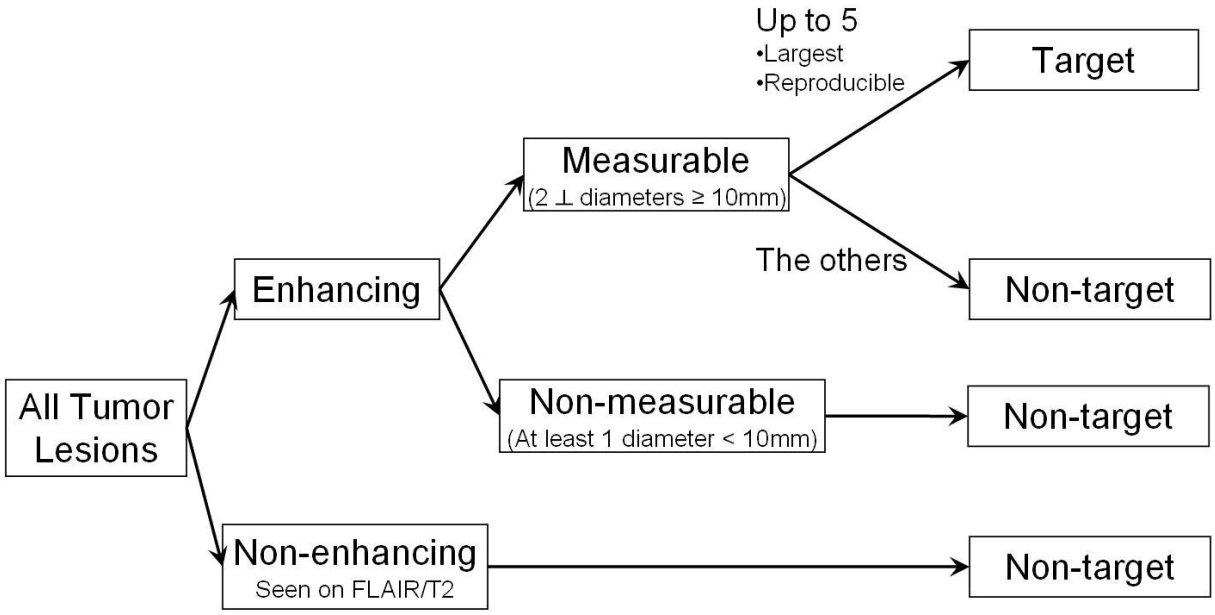
F. Choosing target lesions:

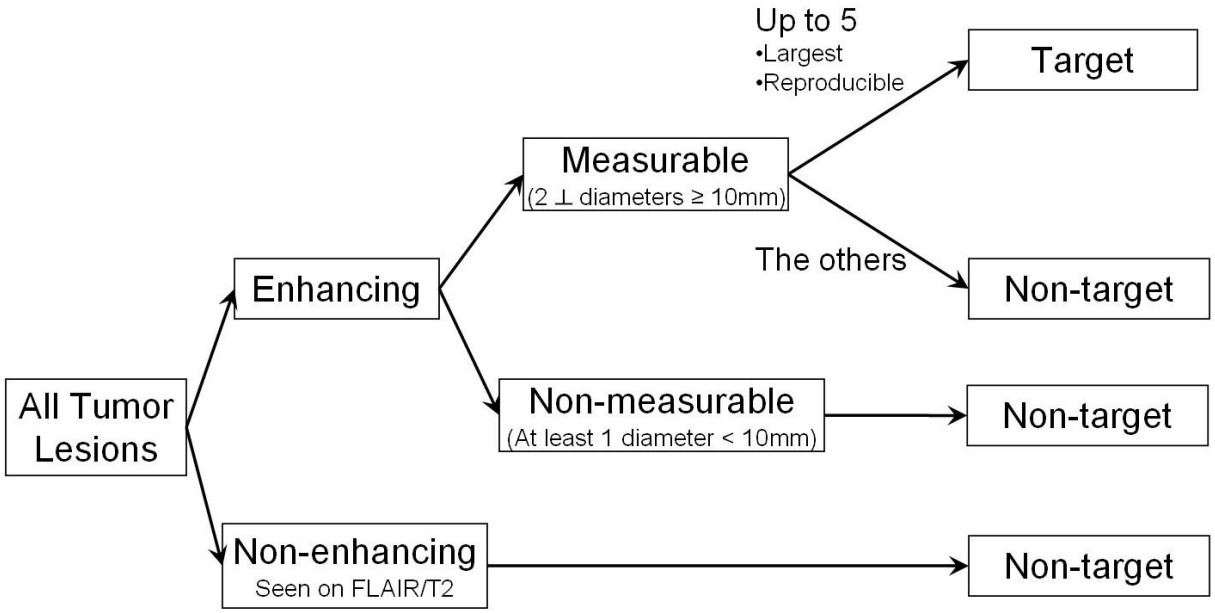
xiv. If there is more than one, pick up to 5.

xv. Choose the largest lesions.

xvi. Should have reproducible measurement.




Up to 5
•Largest
•Reproducible
Target
Measurable
(2 ⊥ diameters ≥ 10mm)
The others
Non-target
Enhancing
All Tumor Lesions
Non-measurable
(At least 1 diameter < 10mm)
Non-target
Non-enhancing
Seen on FLAIR/T2
Non-target


Up to 5
•Largest
•Reproducible
Target
Measurable
(2 ⊥ diameters ≥ 10mm)
The others
Non-target
Enhancing
All Tumor Lesions
Non-measurable
(At least 1 diameter < 10mm)
Non-target
Non-enhancing
Seen on FLAIR/T2
Non-target

G. Determine RANO – Target lesion measurement/response
   i. Axial plan is recommended, unless patient has been followed in coronals
   ii. Pick the slice where the lesion is the largest
   iii. Measure the longest diameter (A)
   iv. Next, measure the greatest perpendicular diameter (B)
   v. Calculate the target lesion size - product of the diameters (AXB)
   vi. With multiple target lesions, calculate the sum of the product of the diameters (SPD) = Area001 + Area002
   vii. Follow-up evaluation:
      a. Measure the previously defined target lesions bi-dimensionally and calculate the SPD (Note: CR and PR have to be confirmed ≥4 weeks later; otherwise, it's just SD)
      b. If apparent PD within 12 weeks of radiation, keep watching. If SPD stable or decreased on next visit, drop baseline value when picking "nadir" to compare against.
      c. Are there new lesions?

H. RANO – Enhancing non-target lesion response
   i. All non-measurable lesions
   ii. All measurable lesions beyond upper limit of 5
   iii. All other measurable lesions not selected as target lesion

Response	Definition
Complete Response (CR)	All target lesions have completely disappeared. (look out for pseudoresponse)
Partial Response (PR)	SPD decreased by ≥ 50% from baseline value (look out for pseudoresponse)
Stable Disease (SD)	SPD < 50% decrease to < 25% increase
Progressive Disease (PD)	SPD increased by ≥ 25% from nadir value (smallest seen during the trial) (look out for pseudoprogression)
Unable to Assess (UA)	One or more of the target lesions cannot be evaluated because of technical factors

   iv. Assessed subjectively

Response	Definition
Complete Response (CR)	All enhancing non-target lesions have disappeared completely
Incomplete Response /Stable Disease (IR/SD)	Enhancing lesions present, and stable or decreased in size compared to prior imaging
Progressive Disease (PD)	Unequivocal progression of enhancing lesions (see below)

Unable to Assess (UA)	Unable to evaluate enhancing lesions because of technical factors

I. Pseudoresponse
   i. Anti-angiogenic drug effects can look like response
   ii. Apparent response may appear within 4 weeks
   iii. This should be confirmed with follow-up imaging 4+ weeks later

J. Pseudoprogression
   i. Enhancement that looks like tumor growth but isn't
   ii. Radiation effect can look like tumor
   iii. Apparent PD within 12 weeks of RT
   iv. Call it pseudoprogression (psPD) initially v. Re-evaluate at next imaging visit
   vi. If further increase, call it PD on the first visit vii. If stable or decreased, psPD is confirmed
   viii. Do not consider baseline for choosing nadir – looking for progression
   ix. Still use baseline when looking for response x. New lesions
   xi. PD within the 12 weeks of completion of chemoradiation can only be assigned if:
      a. Majority of the new enhancement is outside of the radiation field
         OR
      b. Pathologic confirmation of progressive disease (tricky)
      c. Lesion continues to enlarge

Baseline	Visit 1 (8 weeks)	Visit 2 (16 weeks)	Visit 3 (24 weeks)
100	140 psPD	120 SD	150 → PD 130 → SD 65 → SD 45 → PR

K. RANO – From lesion to timepoint (radiological)

Target Lesions	Enhancing Non- Target Lesions	FLAIR/T2 Lesions	New Lesions	Radiological Timepoint Response
CR	**CR**	**Not worse**	**No**	**CR**
CR	**IR/SD or UA**	**Not worse**	**No**	**PR**
PR	**Any non-PD or UA**	**Not worse**	**No**	**PR**

SD	**Any non-PD or UA**	**Not worse**	**No**	**SD**
UA	**Any non-PD**	**Not worse**	**No**	**UA**
PD	**Any**	**Any**	**Yes/No**	**PD**
Any	**PD**	**Any**	**Yes/No**	**PD**
Any	**Any**	**Any**	**Yes**	**PD**
Any	**Any**	**Worse**	**Yes/No**	**PD**
NA*	**CR**	**Not worse**	**No**	**CR**
NA*	**SD**	**Not worse**	**No**	**SD**
NA*	**NA****	**Not worse**	**No**	**No Change**
NA* = No target lesions identified at baseline. NA = No non-target lesions identified at baseline**				

L. RANO – Radiological and clinical factors

Overall Visit Response	Definition
CR	• CR by MRI • No steroids above physiological levels • Clinical status stable or improved compared to baseline
PR	• PR by MRI • Steroid dose not increased compared to baseline • Clinical status stable or improved compared to baseline
SD	• SD by MRI • Steroid dose not increased compared to baseline • Clinical status stable or improved compared to baseline

PD	• PD by MRI • Steroid dose stable or higher compared to visit at which best MRI response was seen • Clinical status worsened compared to either baseline or the visit which showed the best MRI response, and not attributable to a non tumor-related cause
NC	• NC by MRI (possible only if no visible tumor at baseline) • Steroid dose not increased compared to baseline • Clinical status stable or improved compared to baseline
UA	• UA by MRI • Steroid dose not increased compared to baseline • Clinical status stable or improved compared to baseline

M. RANO response criteria

	CR	PR	SD	PD
T1-Gd +	**None**	**≥ 50% ↓**	**< 50% ↓ - < 25% ↑**	**≥ 25% ↑***
T2/FLAIR	**Stable or ↓**	**Stable or ↓**	**Stable or ↓**	**↑***
New Lesion	**None**	**None**	**None**	Present*
Corticosteroids	**None**	**Stable or ↓**	**Stable or ↓**	**NA**
Clinical Status	**Stable or ↑**	**Stable or ↑**	**Stable or ↑**	**↓***
Requirement for response	all	all	all	Any*

	CR	PR	SD	PD
T1-Gd +	**None**	**≥ 50% ↓**	**< 50% ↓ - < 25% ↑**	**≥ 25% ↑***
T2/FLAIR	**Stable or ↓**	**Stable or ↓**	**Stable or ↓**	**↑***
New Lesion	**None**	**None**	**None**	Present*
Corticosteroids	**None**	**Stable or ↓**	**Stable or ↓**	**NA**
Clinical Status	**Stable or ↑**	**Stable or ↑**	**Stable or ↑**	**↓***
Requirement for response	all	all	all	Any*

	CR	PR	SD	PD
T1-Gd +	**None**	**≥ 50% ↓**	**< 50% ↓ - < 25% ↑**	**≥ 25% ↑***
T2/FLAIR	**Stable or ↓**	**Stable or ↓**	**Stable or ↓**	**↑***
New Lesion	**None**	**None**	**None**	Present*
Corticosteroids	**None**	**Stable or ↓**	**Stable or ↓**	**NA**
Clinical Status	**Stable or ↑**	**Stable or ↑**	**Stable or ↑**	**↓***
Requirement for response	all	all	all	Any*

N. Additional info to help

i. Split lesion: measure all and add them together

ii. Merge: measure the big thing

iii. If CR by MRI but still on steroids : PR

iv. If PR by MRI but steroids up : SD

v. SD by MRI with steroids up (but neurological exam OK): SD for now

a. If next visit shows either neurologic or MRI worsening, call PD when the steroids were increased.

vi. For patients with non-measurable disease only at baseline:

a. Cannot have a CR or PR.

b. Best response possible is SD.

Reference

1. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. 28(11):1963-72; 2010.