STUDY NUMBER: **UCCI-BRAIN-16-01**

STUDY TITLE: Feasibility Study of Modified Atkins Ketogenic Diet in the Treatment of Newly Diagnosed Malignant Glioma

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AGENT*:* Temozolomide

SCHEMA:

1. Diagnosis of High Grade Glioma (-28 days)
2. Pretreatment Visit 1: Meet with Physician and/or Nurse Practitioner (NP) for chemotherapy teaching. (day -28 to day -7)
    a. Check lipid profile, complete metabolic panel, complete blood count with differential (CBC with diff), and hemoglobin A1C
    b. Take medical history concerning pancreatitis, recent cholecystectomy or gallbladder dysfunction, diabetes, dairy allergies and/or lactose intolerance, in-born errors of metabolism
    c. Obtain informed consent
    d. Obtain tissue from biopsy or resection

3. Pretreatment Visit 2: Meet with Nurse Practitioner for chemotherapy teaching (day -28 to day -7)
    a. Laboratory Correlatives
        i. Serum beta-hydroxybutyrate (BHB)
        ii. Complete metabolic panel, fasting serum glucose and insulin
        iii. Vital signs, height, body weight, waist circumference
        iv. Platelet mitochondrial labs
        v. Neurocognitive testing (See Appendix VI)
        vi. Quality of Life (FACT-Br) survey (See Appendix I)
        vii. MRI planning scan

4. Pretreatment Visit 3: Meet with registered RD (RD) for nutritional education concerning carbohydrate restricted diet (Modified Atkins Diet (MAD)) (day -28 to day -7)
    a. Diet education consultation with RD – 1.5 hours. Distribute week 1 food diary with education concerning completion (Appendix II)
    b. Confirm above histories and labs
    c. Random assignment to MAD ketogenic diet with radiation therapy day -7

5. Radiation/Chemotherapy commences (Day 0-Day 42)
    a. Collect daily food diaries
    b. Weekly visits with NP/MD
        i. Serum BHB
        ii. Complete metabolic panel, fasting serum glucose and insulin levels
        iii. Vital signs, body weight, waist circumference
        iv. Quality of Life (FACT-Br) survey (See Appendix I)
    c. Weekly telephone contact with RD to address diet related concerns

6. Radiation and temozolomide treatment terminated
    a. Continued MAD until MRI (Day 43-70)

7. MRI and post-treatment visit #1 (approximately Day 70)
    a. Meet with RD

i. If patient wishes to discontinue research diet, RD will instruct patient on 3-day titration back to pre-study carbohydrate intake levels.
ii. If patient wishes to continue longer term discuss supplement use to prevent nutritional deficiencies from long-term diet.

b. Meet with attending physician
   i. Review MRI findings
   ii. Review post-intervention maintenance chemotherapy
   iii. Laboratory Correlatives
      i. Lipid profile, complete metabolic panel, complete blood count with differential (CBC with diff), and hemoglobin A1C
      ii. Serum BHB
      iii. Fasting serum glucose and insulin
      iv. Vital signs, body weight, waist circumference
      v. Platelet mitochondrial Labs
   iv. Adverse Events
   v. Performance Status
   vi. Quality of life (FACT-Br) survey (See Appendix 1)
   vii. Neurocognitive testing (See Appendix VI)

8. MRI and Ppost-treatment visit #2 (approximately day 126-154 after post-treatment MRI)
   a. Meet with attending physician
      i. Review MRI findings
      ii. Review post-intervention maintenance chemotherapy
      iii. Laboratory Correlatives
         i. Lipid profile, complete metabolic panel, complete blood count with differential (CBC with diff) and hemoglobin A1C
         ii. Serum beta-hydroxybutyrate
         iii. Fasting serum glucose and insulin
         iv. Vital signs, body weight, waist circumference
         v. Platelet Mitochondrial Labs
      iv. Performance Status
      v. Quality of life (FACT-Br) survey (See Appendix 1)
      vi. Neurocognitive testing (See Appendix VI)

1. OBJECTIVES

1.1. Hypothesis/Rationale of the Study: Modified Atkins diet (MAD) concurrent with radiation therapy will produce ketosis and improve outcomes in patients with malignant gliomas due to increased sensitivity of the tumors to radiation therapy.

1.2. Primary Objectives

1.2.1. Assessment of feasibility of inducing ketosis with MAD concurrent with radiation therapy by measuring serum beta-hydroxybuterate

1.2.2. Assessment of fasting glucose and insulin levels with MAD concurrent with radiation therapy

1.2.3. Assessment of compliance with MAD concurrent with radiation therapy

1.3. Secondary Objectives

1.3.1. Assessment of 6-month progression-free survival in patients with high-grade gliomas with MAD concurrent with radiation therapy as compared to historical controls

1.3.2. Safety of MAD concurrent with radiation and chemotherapy therapy

1.4. Exploratory Objectives

1.4.1. Assessment of QOL changes with MAD concurrent with radiation therapy

1.4.2. Assessment of cognitive function changes with MAD concurrent with radiation therapy

1.4.3. Assessment of 2-year survival of patients with high-grade primary brain neoplasms with MAD concurrent with radiation therapy as compared to historical controls

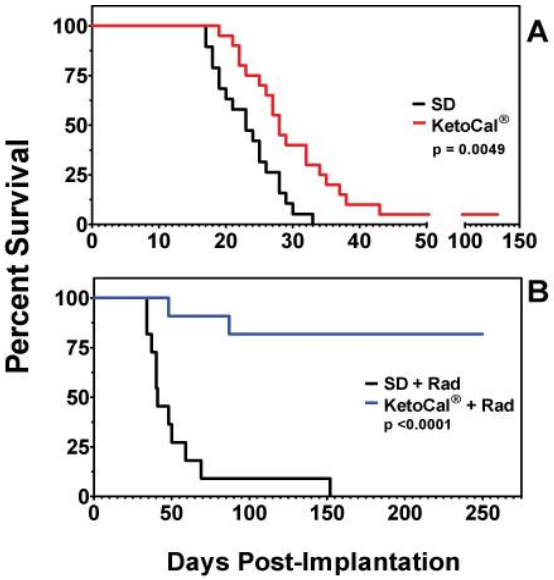
1.4.4. Assessment of mitochondrial respiration in peripheral platelets and correlate with cognitive findings

2. BACKGROUND

2.1. **Malignant Gliomas:** Malignant gliomas are among the most virulent tumors. High-grade gliomas are divided into Grade III gliomas (including anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytomas) and Grade IV which are termed Glioblastoma Multiforme (GBM). GBM is the most common primary brain tumor and the most aggressive. The five-year survival for GBM is dismal and multiple treatment modalities have been unsuccessful. Stupp et al[i] defined the standard of care in 2005 with the combination of temozolomide and radiation therapy increasing the 2-year survival with this regimen from 10.3% in the radiation only arm to 26.5% in the combination arm. This has defined the standard of care but still just 3% of patients are surviving at 5 years.

2.2. **Ketone metabolism:** Gliomas cells in contrast to normal glial cells rely on glucose and glycolysis for division and survival. Normal glial cells can survive on ketones alone but it is hypothesized that glioma cells cannot utilize ketone bodies as energy substrate.[ii] The Akt/phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) (AKT/PIK3/MTOR) pathway has been implicated in the inhibition of cell death and is activated by glucose and glycolysis. This pathway is found in many gliomas.[iii] Ketone metabolism has been used to control childhood epilepsy for many years and this is thought to be through inhibition of the AKT/PIK3/MTOR pathway and other mechanisms.[iv] Abdelwahab implanted mice

with malignant glioma cells to study the effect of ketosis on survival and glioma control. The mice had a modest increase in survival with ketone metabolism as compared to control mice not on the ketogenic diet. However, when radiation was added to the treatment (with or without the ketogenic diet) there was a significant increase in survival so much so that tumor cells could no longer be detected in the ketogenic arm. The mice were switched to a non-ketogenic diet after 101 days and no signs of recurrence were seen for over 200 days in the radiation and ketogenic diet arm.[v]



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Treatment	Cohort Size	Median Survival (Days)
SD	19	23
KetoCal®	19	28
SD + Rad	11	41
KetoCal® + Rad	11	Undefined

Ketone bodies may act as a radiation sensitizing agent and this would explain the significantly increased survival in the mice that received the ketogenic diet with radiation as compared to the mice that received the ketogenic diet alone.

Caloric restriction is also important in glioma control. Seyfried et al. injected mice with CT-2A glioma cells. Mice were placed on a caloric restriction diet or a regular diet with and without ketone body supplementation. The ketone supplemented diet alone did not predict increased overall survival. Caloric restriction was an important contributor to decrease in tumor size and increase in overall survival. Caloric restriction inhibits the insulin growth factor-1 pathway (IGF-1) pathway and therefore inhibits tumor growth. Combined caloric restriction and serum ketosis achieved greater tumor control and mouse survival.[vi] Seyfried, however, conducted this study without radiation. *From this data, our hypothesis is that both decreased glucose and ketosis in conjunction with radiation are necessary to produce tumor reduction in gliomas.*

There is limited data in humans with ketogenic diets and cancer but because of the preliminary data in mice of the effect of ketones and radiation on gliomas and the retrospective data in humans with glioblastoma that hyperglycemia decreases survival, [vii] there are multiple on-going trials. Champ et al. retrospectively studied 6 patients with glioblastoma on the ketogenic diet. The six patients had lower blood glucose and higher ketone levels than their counterparts and tolerated the diet well.[viii] Nebeling et al studied two pediatric patients with anaplastic astrocytoma (high grade gliomas) and found that the diet was tolerated and safe. The two patients had significant decreases in glucose, increases in ketone levels and decreases in glucose

uptake on FDG-PET.[ix] Again given the retrospective nature of these studies, it is difficult to draw any unbiased conclusions from this data.

2.3. **Modified Atkins Diet (MAD):** The form of the KD used in pediatric epilepsy is composed of a 4:1, fat to carbohydrate plus protein ratio. However, the modified Atkins diet (MAD) (<20 grams of carbohydrates per day) produces ketosis and has been used in the treatment of adults with epilepsy with the same efficacy. Notably, there is better compliance with the MAD than with the traditional KD. Many studies have also shown improved tolerability the MAD in the adult population as compared to the traditional ketogenic diet .[x]

2.4**. Cognitive Outcomes:** We have shown in older adults with Mild Cognitive Impairment (MCI), a risk condition for Alzheimer's disease, that dietary ketosis achieved through carbohydrate restriction, improves memory performance (Fig 1).

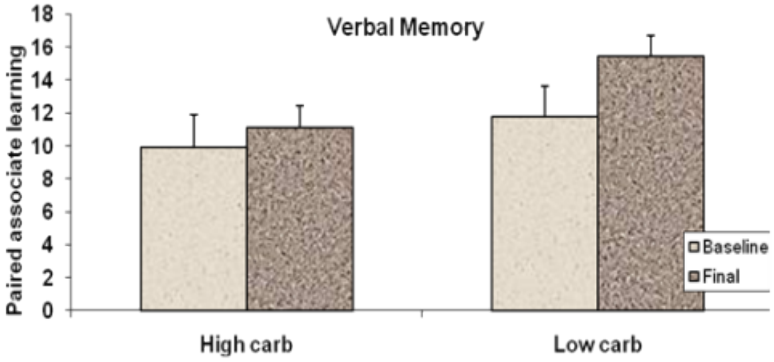


Figure 1. Pre- and post-intervention memory performances for low and high carbohydrate participants with MCI as measured by the Verbal Paired Associate Learning Test, $F(1,20) = 6.45$, $p = 0.01$, Cohen's $f = 0.26$ (Krikorian et al. 2012).

In addition to these improvements in memory performance in older adults, we observed preliminary indications that dietary ketosis is associated with enhanced neuronal integrity and increased bioenergetic function in pre- and post-dietary intervention studies using proton magnetic resonance imaging (^{1}H MRS) in older adults with MCI (Krikorian et al. 2014; Fig 2).

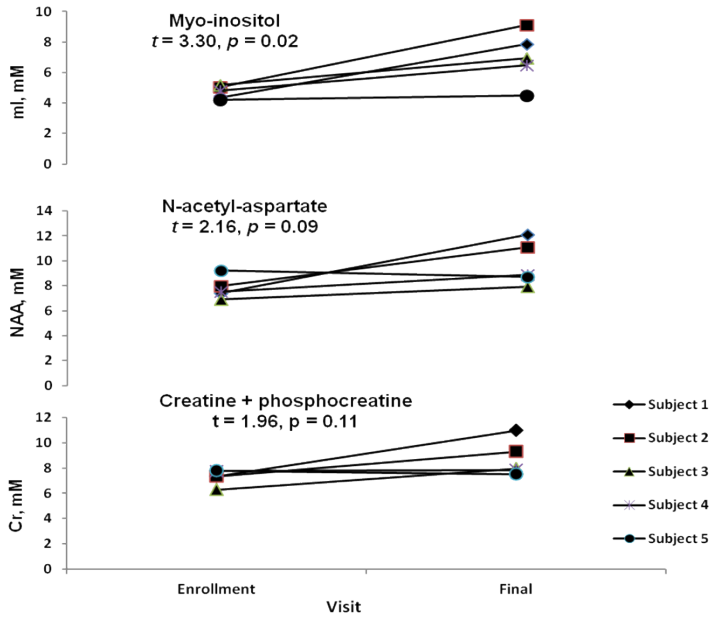


Figure 2. Effect and trends indicating increased myo-inositol, N-acetyl-aspartate, and creatine + phosphocreatine in older adults with MCI following six weeks of nutritional ketosis induced by carbohydrate restriction.

In addition, our colleague, Dr. Patrick Sullivan at the University of Kentucky, has developed a method to assess platelet mitochondrial function and *demonstrated significant changes in mitochondrial function in blood platelets preceding changes in brain mitochondrial function* in a trichloroethylene (TCE) rodent model. Mitochondrial respiratory capacity in platelets isolated from animals (n=3-5/group) that had been exposed to TCE (1000 mg/kg, oral gavage daily) was assessed for different periods (1 hour to 7 days). Chronic TCE exposure induces a Parkinsonian disease state. (Fig 3**)**. In addition, wild type (WT) mice and mice overexpressing human wild type alpha synuclein (aSyn), a pathological factor in Parkinson's disease neuropathology, under the Thy1 promoter (Thy1-aSyn) were placed on a ketogenic or control diet. Mitochondrial respiration was measured in mitochondria isolated from the striatum from mice fed a ketogenic or standard diet for 28 days. Thy1-aSyn mice fed a standard diet displayed significantly diminished mitochondrial efficiency compared to WT mice on the standard diet and Thy1-aSyn mice fed the ketogenic diet displayed mitochondrial efficiency rates similar to WT mice (Fig 4).

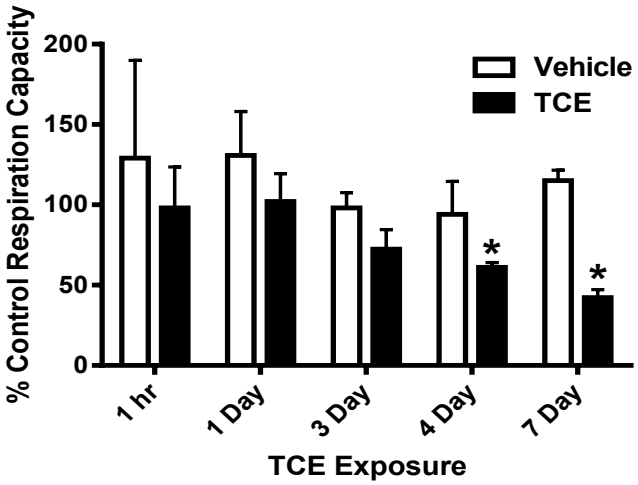


Figure 3. TCE exposure reduces mitochondrial function in a progressive manner. In contrast, measurable change in brain mitochondria requires two weeks of chronic exposure. Thus, the peripheral measure may function as an early marker brain mitochondrial dysfunction in animal and human PD. Bars = means ±SD

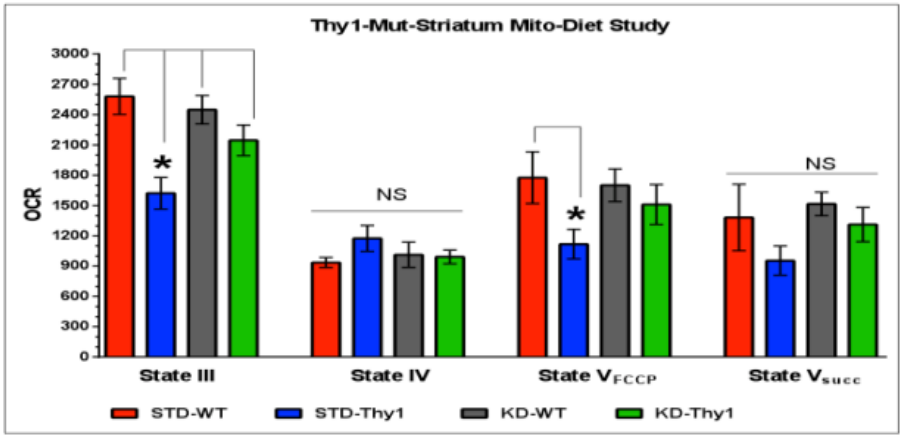
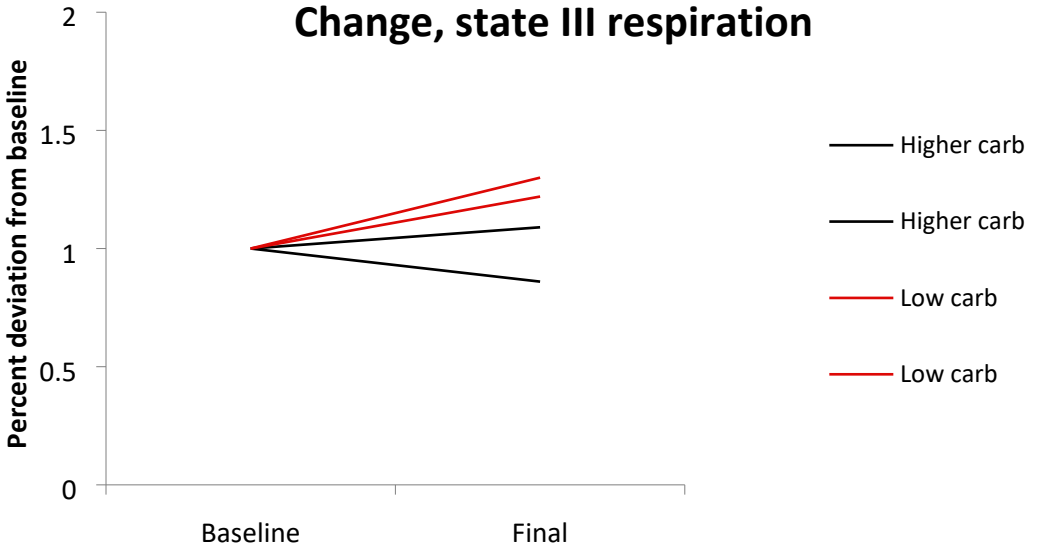
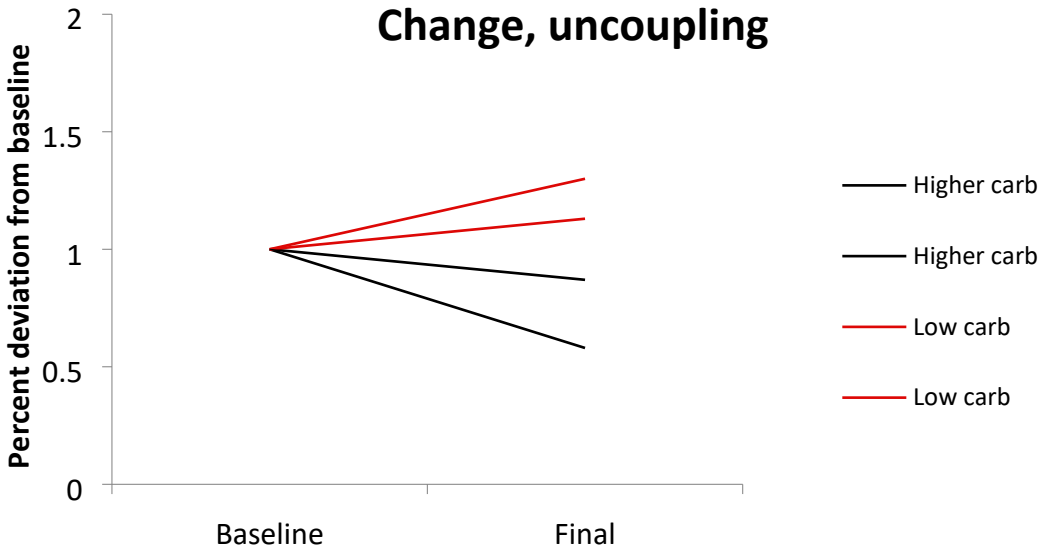


Figure 4: Mitochondria were isolated from striatum and oxygen consumption rate (OCR) was measured in WT and Thy1-aSyn mice at 3m of age and 28 days on a ketogenic or standard diet. Mitochondrial oxygen consumption is significantly reduced in Thy1-aSyn mice fed a standard diet but not in Thy1-aSyn mice fed a ketogenic diet. N=3 in each condition, * Represents $p<0.05$, ANOVA

Very recently, we obtained data demonstrating enhanced peripheral platelet mitochondrial efficiency through nutritional ketosis in overweight, middle-aged individuals with memory complaints, factors that confer greater risk for late-life dementia. Figure 5 shows preliminary data from four participants randomized to either the higher carbohydrate or

lower carbohydrate ketogenic protocols. Platelet assays from participants randomized to the low carbohydrate arm exhibited enhanced state III respiration and uncoupling.





These preliminary studies demonstrate our ability to administer the carbohydrate-restricted, ketogenic diet with research participants and the efficacy of this intervention with respect to neurocognitive function. Further, in collaboration with Dr. Sullivan, we have shown in animal and, more recently in humans, that this intervention influences mitochondrial function favorably.

3. STUDY DESIGN

3.1. This is a single arm feasibility study.

3.2. Study Diet: Patients will be screened for study eligibility and written informed consent will be obtained prior to enrollment. Patients will meet with the registered dietitian (RD) one to four weeks prior to initiation of concurrent radiation and chemotherapy. At that visit, the RD will provide education on all aspects of MAD including meal planning and daily food diary completion (Appendix II). The diet will begin approximately 7 days prior to the initiation of concurrent radiation and chemotherapy and the patient will continue the study diet until the first post-radiation MRI, a time period of approximately 10 weeks. We will obtain blood to assess serum BHB, fasting insulin and glucose, and other chemistries as well as body weight weekly, according to the standard of care, while on chemotherapy and radiation therapy. Participants will receive weekly phone calls from the RD to address any questions or concerns the patient may have regarding the MAD and daily food diary. A food diary (Appendix II) will be used to assess adherence during the 10-week period. All macronutrient intake from food diaries will be entered by study agent into nutrient analysis software. This macronutrient breakdown will be utilized to identify potential problematic macronutrient intake which may be preventing patient from achieving ketosis. This is available online as well.

3.2.1. Temozolomide and radiation will be given according to the standard protocol described by Stupp et al.[i] Patients will receive 75 mg/m^2 of temozolomide concurrent with radiation therapy at standard dose. The dose of radiation and/or chemotherapy and/or steroid may be modified by the attending physician based on clinical indications.

3.2.2. Correlative platelet mitochondrial studies will be drawn on the pre-treatment visit #2, the post-treatment visit #1 and the post-treatment visit #2. Patients are already having blood drawn at these visits as standard of care. This sample will be transported within 6 hours to the laboratory Dr. Matthew Skelton at Cincinnati Children's Hospital Medical Center for assessment of mitochondrial respiration in the platelets.

3.2.3. QOL studies will be done at the pre-treatment visit #2, pre-treatment visit #3, weekly during chemotherapy and radiation, at the post-treatment visit #1 and then at post-treatment visit #2

3.2.4. Neurocognitive testing will be performed at the pre-treatment visit #2, at the post-treatment visit #1 and then at post-treatment visit #2

3.3. **Number of Participants:** Thirty evaluable patients will be enrolled. Because this is a feasibility study, ECOG performance status and MGMT methylation which are both predictors of survival will be recorded but not used for stratification.

4. PATIENT SELECTION

4.1. Inclusion Criteria

4.1.1. Patients must have a histologically confirmed primary malignant glioma (Grade III (1p/19q intact) or Grade IV tumor). Patients can have a radiographically confirmed diagnosis if biopsy is not possible, but this must be approved by the primary investigator.

4.1.2. No uncontrolled infection or other active malignancy or chronic systemic immune therapy.
4.1.3. Age ≥ 18 years.
4.1.4. ECOG performance status ≤ 3 (see Appendix A).
4.1.5. Life expectancy > three months.
4.1.6. Ability to understand and willingness to sign a written informed consent document.
4.1.7. Patients can be on an investigational study but will not be eligible if the investigational drug is given during the intervention
4.1.8. Physician must have the intent to treat with the Stupp Protocol. (http://www.nejm.org/doi/full/10.1056/NEJMoa043330)
4.1.9. Patient must be on steroid dose of dexamethasone ≤ 8 mg at study entry.
4.1.10. Adequate renal function, defined as follows: Serum creatinine ≤ institutional ULN within 14 days prior to registration. Creatinine clearance (CC) ≥ 60 ml/min within 14 days prior to registration determined by 24- hour collection or estimated by Cockcroft-Gault formula: CCr male = [(140 – age) x (wt in kg)] [(Serum Cr mg/dl) x (72)]; CCr female = 0.85 x (CrCl male)
4.1.11. Adequate hepatic function defined as follows: Total bilirubin < 2 x institutional ULN within 14 days prior to registration; AST or ALT < 3 x institutional ULN within 14 days prior to registration.

4.2. Exclusion Criteria: The presence of <u>any</u> of the following will exclude a patient from study enrollment.
4.2.1. Patients who are pregnant
4.2.2. Patients with a genetic disorder of fat metabolism.
4.2.3. Patients with IDDM or Type 2 diabetes diagnosed with a hemoglobin A1C>6.4
4.2.4. Patients who are allergic to dairy or lactose intolerance
4.2.5. Patients with known inborn errors of metabolism of primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, beta-oxidation defects, pyruvate carboxylase deficiency and porphyria.
4.2.6. Patients with pancreatic insufficiency or history of pancreatitis within last 5 years
4.2.7. Patients with gallbladder dysfunction or disease
4.2.8. Decompensated congestive heart failure

4.3. **Inclusion of Women and Minorities:** Men, women and members of all races and ethnic groups are eligible for this trial.

5. <u>REGISTRATION</u>

5.1. To register a patient, the following documents should be completed by the research nurse or data manager and faxed (Fax 513-584-5680) or emailed to the UCCC CTO Study Coordinator:
5.1.1. Signed patient consent form
5.1.2. Eligibility Screening Worksheet and registration form
5.1.3. HIPAA authorization form

6. TREATMENT PLAN

6.1. **Modified Atkins Diet (MAD) education and treatment plan:** The modified Atkins diet (MAD) approximates a diet with a 1:1 ratio of macronutrients: 1 part fat to 1 part protein and carbohydrate combined. It is referred to as "modified" because it is lower in carbohydrate content (< 20 net grams/day) than the original Atkins diet used for weight loss. In the MAD, fat and protein are not limited; however, protein intake may be assessed and limited if a patient is not able to achieve and/or maintain ketosis with < 20gm net carb intake as documented per daily food diary. Intake of protein in excess of that required for normal cell maintenance/repair can enter gluconeogenic pathways resulting in increases in serum glucose. A registered dietitian (RD), specially trained in managing ketogenic diets, will provide diet education and monitoring of diet-related side effects of the patients throughout the study period of 10 weeks, as per the schema. As part of this education, the RD will provide recommendations for meal planning and preparation, grocery shopping, completion of daily food diary and education related to management of potential adverse effects of the study diet.

6.1.1. Diet adherence: Diet adherence will be carefully monitored via daily patient/caregiver-generated food diary and ability to achieve and maintain ketosis. Weekly phone contact with RD will aid in ensuring compliance to the study diet by addressing any questions/concerns the patient and/or caregivers may have regarding any aspect of the study diet/processes. Body weight will be recorded each week for the first six weeks.

6.1.2. Diet-related adverse effects: Weight loss is common during the initiation period due to the diuretic effect of the diet. Electrolytes will be monitored weekly, oral hydration and adequate sodium intake encouraged, and caloric intake adjusted as needed. Constipation can be managed pharmaceutically with carbohydrate-free stool softeners and/or laxatives. Dietary modifications such as adequate oral liquid intake and increases in fiber-containing low carbohydrate vegetables may be necessary.

6.1.3. The patient will be educated on concomitant over-the-counter and prescription medications that could prevent the patient from attaining ketosis because of their carbohydrate content. See appendix VII

6.2. **Duration of Therapy**: In the absence of treatment delays due to adverse events, treatment may continue for 10-11 weeks or until one of the following criteria applies:

6.2.1. Intercurrent illness that prevents further administration of treatment

6.2.2. Unacceptable adverse treatment related toxicity, NCI CTC AE version 4.0. Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks

6.2.3. General or specific changes in the patient's condition that render the patient unable or unsuited for further participation in the judgment of the investigator,

6.2.4. Patient decision to withdraw from treatment (partial consent) or from the study (full consent),

6.2.5. Pregnancy during the course of the study for a childbearing participant.

6.2.6. Death.

6.3. **Duration of Follow Up**

6.3.1. Patients will be followed for toxicity for 14 days after treatment has been discontinued or until progression/death, whichever occurs first

7. DOSING DELAYS / DOSE MODIFICATIONS

7.1. If serum ketosis is not obtained (BHB ≥0.5 mM), the RD will review the daily food diary (Appendix II) to determine if the calculation of net carbohydrate intake is accurate and to modify the diet to obtain ketosis.

7.2. If patient develops Grade 3 or Grade 4 toxicity determined to be related to the diet then patient will be removed off diet. Toxicity can be determined by research coordinator, primary investigator or co-investigator.

7.3 If patient has a fasting glucose level >90 mg/dl, it will precipitate an evaluation of dietary intake and/or medical issues (i.e. infection).

7.4 If patient is admitted to the hospital while on study/diet, compliance with the diet will be up to the admitting physician and the patient. If the admission is secondary to the diet/protocol, this will be documented as a serious adverse event and the diet will be discontinued to till patient returns to Grade 1 level and then the diet can be resumed. If the patient has a second serious adverse event from the protocol, then the patient will be permanently removed from the diet. Please see section 6.2

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENT

8.1. Adverse Events and Potential Risks with Dose Modifications

8.2. Modified Atkins Diet

8.2.1. Immediate short-term potential adverse effects[xi]

8.2.1.1. Constipation
8.2.1.2. Exacerbation of gastroesophageal reflux disease
8.2.1.3. Fatigue
8.2.1.4. Food refusal
8.2.1.5 Dehydration
8.3.1.6 Nausea
8.4.1.7 Mild increase in total cholesterol

8.3. Definitions

8.4.1. **Adverse Event:** An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments. Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.4.2. **Serious Adverse Events:** A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

8.4.2.1. Results in **death.**

8.4.2.2. Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

8.4.2.3. Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:

8.4.2.3.1. The admission results in a hospital stay of less than 24 hours OR

8.4.2.3.2. The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR

8.4.2.3.3. The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

8.4.2.3.4. However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

8.4.2.4. Results in persistent or significant disability/incapacity. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.

8.4.2.5. Is a congenital anomaly/birth defect.

8.4.2.6. Is an important medical event. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.4.Adverse Event Evaluation: The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events. A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

8.5.1. The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

8.5.1.1. Event term (as per CTCAE)

8.5.1.2. Description of the event
8.5.1.3. Date of onset and resolution
8.5.1.4. Expectedness of the toxicity
8.5.1.5. Grade of toxicity
8.5.1.6. Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
8.5.1.7. Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action or other intervention, etc.

8.5.2. Descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting.

8.5.2.1. **An expected adverse event** is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

8.5.2.2. **An unexpected adverse event** is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.5.2.3. **Attribution** is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

8.5.2.3.1. Definite – The AE is clearly related to the study drug.
8.5.2.3.2. Probable – The AE is likely related to the study drug.
8.5.2.3.3. Possible – The AE may be related to the study drug.
8.5.2.3.4. Unlikely – The AE is doubtfully related to the study drug.
8.5.2.3.5. Unrelated – The AE is clearly NOT related to the study drug.

8.5.2.4. Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.5. ALL SAE attributed to the MAD will reported to the DSMB.

8.6 Data and Safety Monitoring Board: Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once being enrolled, will be provided a unique id from the study and their personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever necessary to the researchers. Data entry will be monitored regularly by the "Data Safety Monitoring Board" which is an independent group of experts who will advise the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. Membership consists of persons independent of the investigators and any conflict of interest with the trial. Written documentation attesting to absence of conflict of interest is required. The DSMB includes experts in or representatives of the fields of relevant clinical expertise, and biostatistics. The DSMB will be provided feedback on a regular basis, including findings from adverse-event reports, and recommendations derived from data and safety monitoring, and members of the DSMB will have no personal or financial stake in the study. Interim reports will be prepared at least twice each year by the PI with the help of the study coordinator 1 month prior to DSMB

meeting for DSMB review. These reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events. All serious adverse events will be reported by the PI to the DSMB and IRB within 24 hours of knowledge of the occurrence. HIPAA confidentiality will be maintained during the phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety. The DSMB will function in an advisory capacity and recommendations that emanate from monitoring activities will be reviewed by the responsible official (the principal investigator) and addressed.

8.6.2 Responsibility of the DSMB: To approve the initiation of this clinical trial. After this approval and at periodic intervals during the course of the trial, the DSMB responsibilities are to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and when appropriate, efficacy. Make recommendations to the study investigators and regulatory agencies (IRB, IBC, FDA, etc.) concerning the continuation, modification, or termination of the trial.

8.6.3 Responsibility of the PI: It is the responsibility of the study PI to ensure that the DSMB is apprised of all new safety information relevant to the study. This includes providing the DSMB with a copy of the study protocol in advance as well as providing all IRB/Regulatory Protocol revisions and all safety data reports.

8.6.4 Serious Adverse Events: (Please see section 8.4 for definitions of adverse events.) All serious and related adverse events will be reported immediately to the Chair and other members of the DSMB by the study sponsor or designee. The decision to meet by teleconference or on site to discuss the adverse event will be left to the discretion of the members of the DSMB. If the DSMB determines that the study procedures present a greater risk than expected, the board may recommend to the P.I. and the IRB that the study enrollment be suspended pending further evaluation.

8.6.4.1 Written Reports: Written reports should be sent to DSMB members prior to the meeting and should allow sufficient time for review. Written reports may consist of 2 separate parts:

8.6.4.2 Open Session Report: This report provides information on study conduct, such as accrual, appropriate demographic representation, baseline characteristics, protocol compliance, site performance, quality control, currency of follow-up. General (ungrouped) adverse events and toxicity issues will be included in the open report. Open Session reports will be distributed at least a week prior to a scheduled meeting to DSMB members, study investigators and other appropriate persons as directed by the DSMB.

8.6.4.3 Closed Session Report: This report may contain data on study outcomes, including safety data and efficacy data. Closed session reports are distributed on the same schedule, but only to DSMB members, the chairman of the IRB, and others as designated by the DSMB Chair. This report is confidential and marked accordingly.

8.6.4.4 Verbal Report: At the conclusion of the DSMB meeting, the DSMB should discuss its findings and recommendations with the study investigator and sponsor (or sponsor designee). The DSMB will issue a written summary report that identifies topics discussed by the DSMB and describes their individual findings, overall safety assessment and recommendations. The report should conclude with a recommendation to continue or terminate the study. The DSMB Chair or designee is responsible for drafting, circulating and obtaining approval from other DSMB members within 2 weeks of the meeting.

8.6.4.5 A final summary report: will be forwarded to the Study Sponsor and PI. The UCCI Regulatory Coordinator will forward the summary report to regulatory authorities as a part of the annual report unless immediate action is required.

8.6.4.6 Closed Session Report (optional):_The DSMB may also prepare confidential minutes that include details of closed session discussions. These meeting minutes are to be held in strict confidence and only accessible to DSMB members until such a time when the study is closed or the DSMB recommends early termination or in the event the minutes are requested by the FDA for participant safety reasons or for regulatory purposes.

8.6.4.7 Immediate Action Report: The DSMB Chair will notify the PI directly of any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial. The report will be submitted to UCCI Regulatory Coordinator for appropriate dissemination to regulatory authorities. This will be done in order to identify significant adverse event trends, missing and incorrect inputs, and other outliers. A log file will be created and record any change/modification of data inputs for purpose of future inspection. Data files will be safely stored in the server of the cancer clinical trials office, with authorized access to researchers and staffs only; and protected by double firewalls from both UC Health and the University of Cincinnati Information Technology (UCIT). All active study patients are reviewed at the weekly study team meeting. Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the Food and Drug Administration (FDA) or other authorized user, only under guidelines established by the Federal Privacy Act.

9. CORRELATIVE / SPECIAL STUDIES/ LABS

9.1. B-hydroxybutyrate: It is necessary to obtain measures of ketone bodies to determine that the diet is producing the desired biological effect. In addition, this is one method to assess patient compliance. Serum BHB is a quantitative measure of ketosis that is less dependent on hydration status than other measures. In addition, the level of serum ketosis will be correlated with treatment outcome. It is speculative if the level of

ketosis as based on low, moderate or high will correlate with the treatment outcomes of treatment response, PFS 6 and overall survival.

9.2. Blood glucose: Measurement of blood glucose is necessary in patients on a low carbohydrate diet in order to monitor for hypoglycemia (< 70mg/L) for patient safety. In addition, serum glucose is known to be a prognostic factor for survival in GBM. The level of blood glucose will be correlated with treatment outcome. Every attempt will be made to obtain glucose levels fasting.

9.3. Blood insulin: Insulin is expected to be inversely related to beta-hydroxybutyrate. Insulin also will be important to measure, as reductions of insulin, a proliferative hormone, may be important mechanistically in the benefit associated with the nutritional intervention. Further, in our preliminary studies with older adults with MCI, insulin level was inversely related to cognitive performance. Insulin levels have been important in in IGF-1 pathway and therefore are important in addition to the fasting glucose levels. Every attempt will be made to obtain insulin levels fasting.

9.4. Complete Metabolic Panel: This is already monitored weekly for treatment of gliomas with temozolomide and radiation. However will be important to monitor for hyponatremia and increased creatinine indicating dehydration. CO2 will also be measured on this test and will determine if lactate levels need to be drawn to check for acidosis.

9.5. Imaging: MRI tumor imaging will be performed before radiation as a pre-planning scan, and 4 weeks after completion of radiation. Then MRI's will be done as per treating physician recommendations. The treatment planning MRI will occur as clinically ordered. The prior diagnostic MRI examination with contrast and the concurrent imaging for treatment planning will be employed in selecting the two locations. For the two locations, we will interrogate a) the solid portion of the tumor and b) a control region without tumor, preferably within the thalamus (left hemisphere preference; right hemisphere if tumor involvement within the left).

9.6. Neurocognitive Assessment: We will administer measures of attention, working memory, long-term memory, speed of processing, depression and anxiety prior to initiation of intervention and at termination of intervention. This is to determine effect of intervention on cognition and mood.

9.7.Peripheral Platelet Mitochondrial function: Whole blood will be obtained pre-treatment visit #2, post-treatment visit #1 and post-treatment visit #2. Patients are already having blood drawn at these visits as standard of care. This sample will be transported within hours to the laboratory of Dr. Matthew Skelton at Cincinnati Children's Hospital Medical Center for assessment of mitochondrial respiration in the platelets. Our preliminary data has shown that this measure responds to the institution of nutritional ketosis, and we would expect to observe enhanced state III respiration and uncoupling at termination of the intervention

10. MEASUREMENT OF EFFECT

10.1. Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. In addition to a baseline scan, confirmatory scans will also be obtained. Response and progression will be

evaluated in this study using RANO (radiographic assessment in neuro-oncology) criteria. (http://neurooncology.ucla.edu/pub/20231676.pdf)

10.2. **Definitions**

10.2.1. Quality of Life (QOL): QOL will be assessed using the FACT-Br QOL tool. See Appendix I. QOL scores pre-intervention will be compared to post intervention-QOL score. QOL will also be obtained at the post-treatment visit #2 to assess if termination of intervention decreased QOL score. We understand that there are many variables that can affect QOL during this time other than the intervention.

10.2.2. Two-year survival (2YS): Duration of survival will be defined as the number of months from diagnosis to death due to any cause.

10.2.3. 6-month progression free survival (6moPFS): will be defined as the percentage of patients without progression (defined below) at 6 months.

10.2.4. Ketosis**:** Will be defined as serum BHB $\geq$ 0.5 mM

10.2.5. Compliance: Dietary adherence is assessed by review of the daily food diary (Appendix II) serum ketone levels.

10.3. **Methods for Evaluation of Measurable Disease:** All baseline evaluations should be performed as closely as possible to the beginning of treatment. MRI imaging techniques that can be used to determine progression are:

10.3.1. T2-weighted MRI, Fluid-attenuated, inversion-recovery (FLAIR) MRI

10.3.2. Diffusion-weighted imaging (DWI)

10.3.3. T1 pre-contrast MRI

10.3.4. Perfusion including dynamic-contrast-enhanced (DCE) followed by dynamic-susceptibility- contrast (DSC) MRI

10.3.5. T1 post-contrast axial and coronal images

10.4. **Response Criteria**

10.4.1. Evaluation of target lesions will use the Radiographic Assessment in Neuro-oncology (RANO) criteria. See Appendix V will be defined as by RANO criteria.

10.4.1.1. >5 mm increase in maximal diameter, as well as ≥ 25% increase in the sum of the products of the progressing

10.4.1.2. Significant increase in T2/FLAIR non-enhancing lesion compared with baseline (post-chemoradiation) or best response after initiation of therapy, not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects)

10.4.1.3. Clear progression of non-measurable disease

10.4.1.4. Any new lesion

10.5 **Statistics**

10.5.1 Ketosis will be defined as serum BHB > 0.05 mM throughout 6-week period of radiation and chemotherapy. We hope to find that in our given sample of 30 patients at least 50% will meet this criteria. We will compute a 95% confidence interval for this rate to estimate the likely range in the target population. A 10% increase in glutamate within the tumor on the post-RT MRI as compared to the pre-RT MRI will be considered evidence that the tumor is using ketones as fuel by the conversion to glutamate.

APPENDIX I: Hematology Oncology Quality of Life Survey – FACT-Br (Version 4)

Patient MRN: _____

Patient Name:_____

Date/Time of Visit: _____

Patient DOB: _____

Below is a list of statements that other people with your illness have said are important. Please circle one (1) number per line indicating your response as it applies to the **past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
	PHYSICAL WELL-BEING					
	I have a lack of energy	0	1	2	3	4
	I have nausea	0	1	2	3	4
	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
	I have pain	0	1	2	3	4
	I am bothered by side effects of treatment	0	1	2	3	4
	I feel ill	0	1	2	3	4

	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING					
	I feel close to my friends	0	1	2	3	4
	I get emotional support from my family	0	1	2	3	4
	I get support from my friends	0	1	2	3	4
	My family has accepted my illness	0	1	2	3	4
	I am satisfied with family communication about my illness	0	1	2	3	4
	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
	Regardless or you current level of sexual activity, please answer the following question, If you prefer not to answer it, please mark this box and go to the next section.					
	I am satisfied with my sex life	0	1	2	3	4
	EMOTIONAL WELL-BEING					
	I feel sad	0	1	2	3	4
	I am satisfied with how I am coping with my illness	0	1	2	3	4
	I am losing in the fight against my illness	0	1	2	3	4
	I feel nervous	0	1	2	3	4
	I worry about dying	0	1	2	3	4

	I worry that my function will get worse	0	1	2	3	4
	FUNCTIONAL WELL-BEING					
	I am able to work (include work from home)	0	1	2	3	4
	My work (include work at home) is fulfilling	0	1	2	3	4
	I am able to enjoy life	0	1	2	3	4
	I have accepted my illness	0	1	2	3	4
	I am sleeping well	0	1	2	3	4
	I am enjoying the things I usually do for fun	0	1	2	3	4
	I am content with the quality of my life right now	0	1	2	3	4
	ADDITIONAL CONCERNS					
	I am able to concentrate	0	1	2	3	4
	I have had seizures (convulsions)	0	1	2	3	4
	I can remember new things	0	1	2	3	4
	I get frustrated that I cannot do the things I used to	0	1	2	3	4
	I am afraid of having a seizure (convulsion)	0	1	2	3	4
	I have trouble with my eyesight	0	1	2	3	4

	I feel independent	0	1	2	3	4
	I have trouble hearing	0	1	2	3	4
	I am able to find the right word(s) to say what I mean	0	1	2	3	4
	I have difficulty expressing my thoughts	0	1	2	3	4
	I am bothered by the change in my personality	0	1	2	3	4
	I am able to make decisions and take responsibility	0	1	2	3	4
	I am bothered by my drop in my contribution to the family	0	1	2	3	4
	I am able to put my thoughts together	0	1	2	3	4
	I need help caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
	I am able to put my thoughts into action	0	1	2	3	4
	I am able to read like I used to	0	1	2	3	4
	I am able to write like I used to	0	1	2	3	4

	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
	I have weakness in my arms or legs	0	1	2	3	4
	I have trouble with coordination	0	1	2	3	4
	I get headaches	0	1	2	3	4

APPENDIX II: Food diary

Date:

Meal	Food and Beverage Description	Amount	Total Carb (grams)	_	Total Fiber (grams)	=	Net Carbs (grams)
						Total Net Carbs	

APPENDIX III: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX IV

	Pre-Treatment Visit #1	**Pre-Treatment Visit #2**	**Pre-Treatment Visit #3**	**Temodar plus radiation therapy (RT)**		**Temodar and RT completed**	**Post-Treatment Visit #1**	**Post-Treatment Visit #2**
	D-28 to day -7	**-28 to day -7**	**D-28 to day -7**	**Day 0-42**		**Day42**	**Appx. Day 70**	**2-3 months after PTV1**
				Weekly	Daily			
Informed Consent	X							
Medical History	X			X			X	X
Concomitant Medications / Treatments	X		X	X			X	X
Physical Exam	X			X			X	X
Vital Signs/Weight/ Waist Circumference	X	X		X			X	X
Lipid profile, CBC with diff, hemoglobin A1C,	X						X	
Serum BHB		X		X			X	X
Complete Metabolic Panel, fasting glucose, fasting insulin		X		X			X	X
Platelet Mitochondrial Labs		X					X	X
MRI		X					X	X
Food diary				X	X		X	
	Pre-Treatment Visit #1	**Pre-Treatment Visit #2**	**Pre-Treatm**	**Temodar plus radiation**		**Temodar and RT completed**	**Post-Treatment Visit #1**	**Post-Treatment Visit #2**

			ent Visit #3	therapy (RT)				
	D-28 to day -7	**-28 to day -7**	**D-28 to day -7**	**Day 0-42**		**Day42**	**Appx. Day 70**	**2-3 months after PTV1**
				Weekly	Daily			
Adverse Events				X			X	X
Performance Status	X			X			X	X
Quality of Life (FACT-BR)		X		X			X	X
Neurocognitive Testing		X					X	X
RD Consult (initial in person and then via phone)			X	X				
Treatment								
MAD			X	X	X	X		
Temodar and RT (Stupp)				X	X			

APPENDIX V

RANO Criteria for Response Assessment using MRI

From: Wen 2010.

Response	**Criteria**
Complete Response	Requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.
Partial Response	Requires all of the following:≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater that the dose at the time of baseline scan; and stable or improved clinically. Note: Patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease.
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging show that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progressive Disease	Defined by any of the following: ≥ 25% increase in the sum of the products of maximal perpendicular diameters of enhancing tumor(s) compared to the smaller of pre-SL-701 baseline or best response following initiation of SL-701; New measureable contrast-enhancing lesion(s) defined as lesion(s) that measure at least 1 cm in at least 2 planes; Significant clinical decline not attributable to co-morbid event or change in concurrently administered medication.

NOTE: All measurable and non-measurable lesions must be assessed using the same techniques as at baseline. Abbreviation: FLAIR, fluid-attenuated inversion recovery

APPENDIX VI

GBM cognitive protocol (repeated three times)

1) Demographic, personal information

- **a)** Academic and Medical History Questionnaire

2) Executive ability, working memory, attention

- **a)** Delis Kaplan Executive Function System, Trails subtest
- **b)** Porteus Maze Test [revised version]
- **c)** Verbal Primary Memory with Interference
- **d)** Auditory Verbal Sequencing Test
- **e)** Corsi Block-Tapping Task

3) Lexical Access

- **a)** Controlled Oral Word Production (phonological & categorical constraints)
- **b)** Boston Naming Test

4) Secondary (long-term) memory

- **a)** Memory Impairment Screen
- **b)** Verbal Paired Associate Learning
- **c)** California Verbal Learning Test-II
- **d)** Spatial Paired Associate Learning

5) Mood

- **a)** Beck Depression Inventory
- **b)** Beck Anxiety Inventory

6) Cognitive Symptoms

- **a)** Dysexecutive Questionnaire
- **b)** Everyday Memory Questionnaire

APPENDIX VII

FeverAll Acetamenaphen Suppositories (all strenghts) • Actavis

NOTE: Although glycerol is a main ingredient of this product, the colon converts it to fatty acids; it is not used as sugar therefore it is safe for ketogenic therapy.

ACTIVE INGREDIENTS: Acetamenaphen
INACTIVE INGREDIENTS: Glycerol Monostearate , Hydrogenated Vegetable Oil , Polyoxyethylene Stearate , Polysorbate 80

Sudafed Nasal Decongestant Maximum Strength, Non-Drowsy 30 mg Tablets • Pfizer
Contains 120mg carbohydrate per tablet
ACTIVE INGREDIENTS: Pseudoephedrine HCl - 30 mgNasal Decongestant
INACTIVE INGREDIENTS: Carnauba Wax, Colloidal Silicon Dioxide, D&C Yellow #10 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Iron Oxide, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Pregelatinized Starch, Shellac, Sodium Starch Glycolate, Talc, Titanium Dioxide

Sudafed PE Sinus & Allergy Maximun Strength Tablets • Pfizer
Contains 100mg carbohydrate per tablet
ACTIVE INGREDIENTS: (in each Tablet): Chlorpheniramine Maleate (4 mg), Phenylephrine HCl (10 mg).
INACTIVE INGREDIENTS: Colloidal Silicon Dioxide, Crospovidone, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, and Stearic Acid

Sudafed PE Sinus Headache Maximum Strength, Non-Drowsy • Pfizer
Contains less than 1000mg carbohydrate per caplet (NOTE: This is much higher than the above pain relievers). ACTIVE INGREDIENTS: Acetaminophen (325 mg), Phenylephrine HCl (5 mg)
INACTIVE INGREDIENTS: Candelilla Wax, Colloidal Silicon Dioxide, Crospovidone, FD&C Yellow No. 6 Aluminum Lake, Hypromellose, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Povidone, Pregelatinized Starch, Starch, Stearic Acid, and Titanium Dioxide

Afrin 12 Hour Nasal Spray Original • Schering-Plough HealthCare Products
INGREDIENTS: Oxymetazoline Hydrochloride (0.05%). Benzalkonium Chloride Solution, Benzyl Alcohol, Edetate Disodium, Polyethylene Glycol, Povidone, Propylene Glycol, Water Purified, Sodium Phosphate Dibasic, Sodium Phosphate Monobasic

Vicks VapoRub Vaporizing Ointment • Procter & Gamble
INGREDIENTS: Camphor (4.8%), Eucalyptus Oil (1.2%), Menthol (2.6%), Cedarleaf Oil, Nutmeg Oil, Special Petrolatum, Thymol, Turpentine Oil

Vicks VapoInhaler (Nasal Decongestant) • Procter & Gamble
INGREDIENTS: Levmetamfetamine, Bornyl Acetate, Camphor, Lavender Oil, Menthol, Methyl Salicylate

Ayr Mentholated Vapor Inhaler (Nasal Decongestant) • B.F. Ascher & Co., Inc
INGREDIENTS: Aromatic Eucalyptus Oil, Menthol and Lavender Oil

Breath Again with SinoMarin – All Natural Seawater Nasal Spray • P.N. GEROLYMATOS
INGREDIENTS: Sterilized Seawater 70%, Purified Water 30%. Equivalent to 2.3% of Salt

Neo-Synephrine Nasal Saline Moisturizer Spray • Bayer
INGREDIENTS: Water, Sodium Chloride, Disodium Phosphate, Sodium Phosphate, EDTA Disodium, Benzalkonium Chloride

NOTE: Breath Again and Neo-Synephrine are salt solutions for clearing nasal passageways. There are several similar products on the market that may also be used. Check to make sure the ingredients are comparable to these.

Antacids

Carbohydrate free Products that contain minimal carbohydrate

Zantac 150 Maximum Strength Tablets • Boehringer Ingelheim
131mg Carbohydrate in each tablet
INGREDIENTS: Ranitidine - 75 mg Acid Reducer Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Synthetic Red Iron Oxide, Titanium Dioxide, Triacetin

Zantac 75 Tablets • Boehringer Ingelheim
70mg carbohydrate in each tablet
INGREDIENTS: Ranitidine - 150 mgAcid Reducer Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Synthetic Red Iron Oxide, Titanium Dioxide, Triacetin

Pepto Bismol Liquid – Regular and Maximum Strength • Procter and Gamble
ACTIVE INGREDIENT: (per tablespoon): Bismuth Subsalicylate (262 mg). (Total Salicylate 130 mg)
INACTIVE INGREDIENTS: Benzoic Acid, D&C Red No. 22, D&C Red No. 28, Flavor, Magnesium Aluminum Silicate, Methylcellulose, Saccharin Sodium, Salicylic Acid, Sodium Salicylate, Sorbic Acid, and Water

Pepto Bismol Easy To Swallow Caplets Original • Procter and Gamble
Company reports less than 1gram of carbohydrate in 2 caplets
INGREDIENTS: Bismuth Subsalicylate, Calcium Carbonate, D&C Red No. 27 Aluminum Lake, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Povidone, Polysorbate 80, Silicon Dioxide, Sodium Starch

Mylanta
Mylanta antacid is no longer available in gel caps.
The liquid versions contain 700-900mg of carbohydrate per teaspoon. The chewable tablets are just under 1gm of carbohydrate per tablet.

Heather's Tummy Tea - Fennel
Herbal remedy: traditional digestive aid for colic, heartburn, indigestion, and stomachaches INGREDIENTS: Organic fennel

Warning: Fennel may cause an increase in seizures when used in combination with these drugs: phenytoin (Dilantin); carbamazepine (Tegretol, Carbatrol, Epitol) or oxcarbazepine (Trileptal); gabapentin (Neurontin);
valproic acid (Depakene) or divalproex sodium (Depakote); felbamate (Felbatol); tiagabine (Gabitril); levetiracetam (Keppra); topiramate (Topamax); lamotrigine (Lamictal); zonisamide (Zonegran); ethosuximide (Zarontin); and others.

Laxatives

Carbohydrate free Products that contain minimal carbohydrate

Dulcolax Laxative Suppositories
INGREDIENTS: Bisacodyl USP 10mg Stimulant Laxative, Hydrogenated Vegetable Oil

Fleet Enema Adult • CB Fleet Co, Inc
ACTIVE INGREDIENTS: Monobasic Sodium Phosphate (19g), Dibasis Sodium Phosphate (7g). Sodium Content: 4.4 g INACTIVE INGREDIENTS: Benzalkonian Chloride, Disodium EDTA, purified water

Mineral Oil – There are several brands
INGREDIENT: Mineral oil
This is an oil that our body does not digest and therefore acts as a laxative (lubricant) in the colon. It should not be taken within 1 hour of medications or vitamin supplements. As with any laxative, it should not be used daily.

Miralax • Schering-Plough HealthCare Products, Inc.
INGREDIENTS: Polyethylene Glycol 3350
IMPORTANT NOTE: This laxative is on the FDA's Watch List for complaints of "neuropsychiatric events". There have also been reports of ski rash (uticaria) with Miralax.

Senokot Tablets • Purdue Products
Senokot tablet: 1 tablet has 100mg of carbohydrate Senokot-S: 1 tablet has 110mg of carbohydrate

Carb / Non-Carb Ingredients

Carbohydrate Ingredients	Non-Carbohydrate Ingredients
Glycerin	Asulfamine potassium (AceK)
Maltodextrin	Aspartame
Magnasweet	Carboxymethylcellulose
Organic acids: ascorbic acid, citric acid, lactic acid	Cellulose
Propylene glycol	Hydroxymethylcellulose
Sugars: dextrose, fructose, glucose, lactose, sucrose, sugar, palm sugar, agave nectar, cane syrup, cane juice, corn syrup, honey	Magnesium stearate
Sugar alcohols: erythritol, isomalt, glycerol, manitol, maltitol, sorbitol, xylitol	Microcrystalline cellulose
Starches: cornstarch, hydrogenated starch hydrolysates (HSH), pregelatinized starch, sodium starch glycolate	Polyethylene glycol
	Saccharine
	Superose
	Stevia (rebiana)

APPENDIX VIII

Modified Ketogenic Diet Guidelines

The modified ketogenic diet (MKD) is a diet that reduces the amount of carbohydrates you eat so that your body will begin burning primarily fat, instead of carbs, for energy. This diet is very low in carbohydrates, high in fat and moderate in protein.

When your body breaks down the carbohydrates found in food it makes a product called glucose. Glucose, commonly known as blood sugar, is the main source of energy for the body. The focus of the ketogenic diet is to shift your metabolism to use fat as the main source of energy. When your body breaks down fat it makes products known as ketones. When your body is using ketones for energy it is said that you are in "ketosis".

The goal of this diet is to get your body into ketosis and keep it there. Your doctor will monitor your level of ketosis by checking your blood for ketones. This will help you and your team know if you are following the diet properly. You may also monitor yourself via urine Ketostix. Your dietitian will explain their use.

Some individuals lose weight when they start this diet. It will be important to monitor this because it can indicate loss of lean muscle mass as well as loss of crucial vitamins and minerals important to maintaining your energy throughout treatment.

The guidelines below are designed to help you be successful in acquiring and maintaining ketosis.

1. Eat either three regular-sized meals per day or four to five smaller meals. Do not skip meals or go more than six waking hours without eating.

2. Eat no more than 20 grams of NET carbs per day. Try to eat a wide variety of vegetables including lettuce-based salads. This will help you get more vitamins and minerals for overall health, but also fiber needed to feel full longer and aid in preventing constipation. Remember, carb counts of various vegetables are different so be sure to check them. Use measuring cups, measuring spoons, and food scales for measuring all foods to ensure accuracy.

3. At each meal, including breakfast, eat 4 to 6 ounces of protein foods, including poultry, beef, lamb, pork, veal, fish and shellfish, eggs, and cheese; you may count 1 egg as 1 ounce of protein. There is no need to trim fat from meat or the skin from poultry, but it is fine if you prefer to. Just add a splash of olive or avocado oil or a pat of butter to your meal to replace the fat.

4. There is no restriction on fat. Enjoy butter, olive and avocado oils, canola oil, and seed and nut oils and mayonnaise. Aim for 1 tablespoon of oil on a salad or other vegetables, or a pat of butter. Cook foods in just enough oil to ensure that they don't burn. Or spritz the pan with a mist of oil.

5. Use spices and herbs to flavor foods. Get creative with meals and snacks to keep interest in the food you are eating. You will be given resources to find recipes appropriate for your diet.

6. This diet can cause constipation. Make sure you drink plenty of water, eat all of the recommended salad greens and vegetables, and let your doctor and/or dietitian know if you are becoming constipated. Occasionally, a medication bowel regimen is necessary.

7. Cheese can be a good source of fat and protein; however, cheeses such as cottage and ricotta have higher net carbs, so please remember to measure these carefully. Also, cheese can cause constipation – limit your daily intake to 4 ounces or less.

8. Acceptable sweeteners include sucralose (Splenda), saccharine (Sweet'N Low), stevia (SweetLeaf or Truvia). Have no more than three packets a day and count each one as 1 gram of carbs. These sweeteners themselves contain no carbs; however, the fillers they are packaged with to prevent caking do contain a little bit of carbohydrates. If you purchase a bulk container of these sweeteners, check the nutrition facts label for net carb content; they are not all the same.

9. To satisfy your sweet tooth you can have sugar-free gelatin desserts. There are resources for recipes within this educational packet that will give you more ideas.

10. Each day, drink at least eight 8-ounce portions of approved beverages: water, club soda, herb teas, or coffee (caffeinated in moderation). This will prevent dehydration and electrolyte imbalances. In this count, you may include two cups of broth (not low sodium), one in the morning and one in the afternoon.

11. Don't starve yourself and don't skimp on fats.

12. Don't assume that any food is low in carbs. Always read the labels on packaged whole foods being certain to note the serving size.

13. When dining out, be on guard for hidden carbs. Gravies and sauces are usually made with flour or cornstarch. Sugar is found in many commercial salad dressings and may be in coleslaw and other deli salads. Avoid breaded foods. Some restaurant websites have nutritional information posted; you should consider looking at these ahead of time to better manage your carb intake.

Where Are Carbohydrates Found?

Carbohydrates (carbs) are found in many, but not all, of the foods that we eat. Carbohydrates are found in foods that contain both natural and added sugars. The following foods and food groups have carbohydrates in them:

Grains: Any food made from wheat, rice, oats, cornmeal, barley, or white and wheat flour. Examples include white and wheat bread, hot and cold breakfast cereals, most types of pasta noodles, couscous, quinoa, etc. These foods contain many carbs and should not be eaten while following the diet. Ask your dietitian for examples of substitutions of these foods that can be included in the diet.

Fruits: All fruits have a natural form of sugar. Some fruits are higher in carbs than others. For example, one banana has more carbohydrates than one serving of raspberries. Very small portions of some fruit can be included in the diet.

Dairy: Milk and some dairy products contain a natural form of sugar (carb) called lactose. Cow's milk, most yogurt brands, pudding, and ice cream are examples of dairy foods that contain too many carbs and should not be included in the diet. Most cheeses, heavy cream, whipped cream, plain Greek yogurt, sour cream, and cottage cheese have less carbs. Portions of unsweetened versions of soy milk, almond milk, and/or cashew milk can be included in the diet.

Vegetables: All vegetables contain carbohydrates. Some vegetables contain more than others. "Non-starchy" vegetables contain minimal carbs and should be included in the diet. Examples of non-starchy carbs include spinach, green beans, asparagus, and salad greens.

"Starchy" vegetables include dried beans, peas, corn, potatoes, and sweet potatoes. They contain many carbs and should not be included in the diet.

Desserts: Foods made with flour and sugar contain carbs and should not be eaten while on the diet. This includes cookies, cakes, pies, ice cream, candies, etc. Even foods labeled as "sugar free" have some carbs. Ask your dietitian how to satisfy your sweet tooth.

Common Carb Foods

Cheese/Dairy: You may have up to 4 oz cheese per day. Most cheeses will have approximately 1 gram of carb per ounce. An ounce is about the size of an individually wrapped slice of American cheese or string cheese.

Type	Serving Size	Net Carbs
Blue Cheese	1 oz	0.7
Cheddar	1 oz.	0.9
Cottage cheese, 4% milkfat	½ cup	3.6
Cream Cheese	1 oz	1.6
Feta	1 oz	1.2
Gouda	1 oz	0.6
Heavy cream	1 tbsp	0.4
Mozzarella, part skim	1 oz	1.6
Parmesan, grated	1 tbsp	0.7
Ricotta cheese, part skim	½ cup	6.4
Sour cream	1 tbsp	0.6
Swiss	1 oz	0.6

Salad Garnishes/herbs/spices: If topping your salad with cheese, see above net carb table. Below is a list of commonly used foods, herbs, and spices used on many types of salads. Salad dressings have a wide variation in carb content -always check the nutrition facts label for serving size and net carbs.

Type	Serving Size	Net Carbs
Basil	1 tbsp	0.0
Cayenne pepper	1 tbsp	0.0
Cilantro	1 tbsp	0.0
Dill	1 tbsp	0.0
Garlic	1 clove	0.9
Ginger	1 tbsp chopped root	1.0
Pepper	1 tbsp	0.0
Rosemary	1 tbsp	0.0
Sage	1 tbsp	0.0
Tarragon	1 tbsp	0.0
Oregano	1 tbsp	0.0

Vegetables: You should eat 12 to 15 net carbs a day of vegetables. This should be ~ 6 cups of salad greens and ~ 2 cups cooked vegetables (depending on net carb content). Choosing a wide

variety of vegetables will not only add variety to your diet but provide important vitamins and minerals needed for optimal health.

Type	Serving Size/Prep	Net Carbs
Acorn squash	½ cup, cooked	10.4
Alfalfa sprouts	½ cup	0.0
Artichoke, whole	½ medium, boiled	3.8
Arugula	½ cup	0.2
Asparagus	6 medium spears, cooked	1.9
Avocado, black skinned	½ raw	1.3
Bamboo shoots	½ cup, boiled	1.2
Beets	½ cup, cooked	6.8
Bok Choy	½ cup, cooked	0.7
Broccoli	½ cup cooked	3.0
Broccoli	½ cup raw	1.8
Brussels sprouts	½ cup cooked	3.5
Cabbage, green or red	½ cup cooked	2.7
Cabbage, green or red	½ cup raw	1.1
Carrots	1 raw, large (8”)	4.9
Carrots	½ cup, cooked	4.1
Cauliflower	½ cup cooked	1.2
Celery	1 stalk, med (8”)	0.6
Chard, Swiss	½ cup	1.8
Chicory greens	½ cup raw	0.1
Chives	1 tbsp	0.0
Collard greens	½ cup cooked	1.6
Cucumber	½ cup raw	0.9
Daikon radish	½ cup, cooked	1.3
Eggplant	½ cup, cooked	3.1
Endive	½ cup	0.0
Escarole	½ cup raw	0.2
Fennel	½ cup, raw	1.9
Green beans	½ cup, cooked	2.9
Jicama	½ cup, raw	2.5
Kale	½ cup, cooked	2.4
Kohlrabi	½ cup, cooked	4.6
Kohlrabi	½ cup, raw	1.8
Leeks	½ cup, raw	5.5
Lettuce, average	1 cup	1.0

Mushrooms	½ cup, raw	1.1
Okra	½ cup, cooked	1.6
Olives, green or black	5 each	0.1
Onion	¼ cup, chopped, raw	2.2
Peas, green	¼ cup, cooked	2.4
Peppers, green or red	½ cup, raw	1.8
Pepper, green or red	½ cup, cooked	3.8
Potato, white	1 baked, small (2 ½")	27.0
Pumpkin	¼ cup, cooked	2.3
Radicchio	½ cup, raw	0.7
Radish	1 each, medium (¾" to 1")	0.1
Rhubarb	½ cup, raw	1.7
Sauerkraut	½ cup, canned	0.9
Spaghetti squash	½ cup, cooked	3.9
Spinach	½ cup, cooked	1.2
Spinach	1 cup, raw	0.4
Summer squash	½ cup, cooked	2.4
Sweet potato	½ cup, cooked	17.4
Tomato	1 med (2 ½"), raw	3.3
Turnips	½ cup, cooked	2.4
Water chestnuts	½ cup, canned	6.8

Fruits: Fruits are a good source of vitamins, minerals, and fiber; however, they are also high in carbohydrates. Be sure to measure serving sizes accurately.

Type	Serving Size	Net Carbs
Apple	½ whole, small (2 ¾")	8.5
Banana	1 small	20.5
Blueberries	¼ cup	4.5
Cantaloupe	¼ cup	2.8

Cherries	¼ cup	4.8
Grapefruit	½ whole, medium (4”)	8.9
Grapes, red or green	¼ cup	6.5
Guava	1 medium	4.9
Kiwi	1 medium	9.0
Lemon juice	¼ cup	4.0
Lime juice	¼ cup	4.9
Mango	¼ cup	5.5
Peach	1 whole, medium (2 ½”)	12.1
Plum	1 whole, medium (2 ½”)	6.6
Raspberries	¼ cup	1.7
Strawberries	¼ cup	2.4
Watermelon	½ cup	5.4

Legumes: Legumes can be used minimally to add color and texture to a combination meal.

Type	Serving size/Prep	Net Carbs
Black beans	¼ cup, canned, drained	5.8
Garbanzo beans	¼ cup, canned, drained	10.3
Great northern beans	¼ cup, canned, drained	10.5
Kidney beans	¼ cup, canned drained	10.6
Lentils	¼ cup, cooked	6.1
Lima beans	¼ cup, cooked	7.8
Navy beans	¼ cup, cooked	7.1
Pinto beans	¼ cup, cooked	10.2

Nuts and seeds: Nuts and seeds have a healthy amount of fiber and fat. They can be used on salads, in recipes, and as an easy in-between meal snack. Nuts and seeds also contain important minerals as well as antioxidants.

Type	Serving size	Net Carbs
Almonds	1 oz (23 kernels)	2.6
Brazil nuts	1 oz (6 kernels)	1.2
Cashews	1 oz (18 kernels)	7.6
Sunflower seeds, shelled	1 oz	1.7
Macadamias	1 oz (10-12 kernels)	1.2
Pecans	1 oz (19 halves)	1.2
Pistachios, shelled	1 oz. (49 kernels)	5.1

Walnuts	1 oz (14 kernels)	2.0

Find Recipes:

http://www.charliefoundation.org/resources-tools/resources-2/find-recipes

http://www.atkins.com/recipes

Book: Modified Keto Cookbook: Quick, Convenient Great Tasting Recipes ISBN: 978-1-936303-77-9

Calculating Net Carbs

Keeping your net carb intake at or below 20 grams per day is vital to reaching and maintaining ketosis. Therefore, it is important that you understand how to determine how many net grams are in each serving of the foods you eat. You can calculate this by reading the nutrition facts labels present on packaged food containers. The label will tell you how many servings there are in the container and how many grams of total carbohydrates and fiber are in each serving. Subtract the grams of fiber from total carbs to get the net carb amount.

1. Find how many servings are in the container and what the serving size is.

2. Total Carbohydrate minus Dietary Fiber equals Net Carb per Serving:

8g – 3g = 5g Net Carbs per ½ cup

Nutrition Facts

3 servings per container

Serving size **1/2 cup (125g)**

Amount Per Serving

Calories **80**

	% Daily Values*
Total Fat 11g	**17%**
Saturated Fat 3.2g	**16%**
Trans Fat 0g	
Cholesterol 0.2mg	**0%**
Sodium 75mg	**3%**
Total Carbohydrate 8g	**3%**
Dietary Fiber 3g	**12%**
Total Sugars 4g	
Includes 0g Added Sugars	**0%**
Protein 3g	**6%**

*The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

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