

Appendix B: Karnofsky Performance Status

Score	Karnofsky Performance Status
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Deceased

Appendix C: Schedule of Events

Study Procedures	Screening	Cycle 1 - Chemoradiation										Cycle 2 - Recovery period ⁹		Cycles 3 to 8 Adjuvant TMZ Cycles ¹⁰					Follow up ¹¹		End of Study						
		Day: Day 0	Dose 1	Doses 2-5	Dose 6	Doses 7-10	Dose 11	Dose 12 - 15	Dose 16	Dose 17 - 20	Dose 21	Dose 22 - 25	Dose 26	Dose 27 -29	Dose 30	Phone follow up Day 3, 11, 18	Day 28: Prior to Cycle 3	Day 1 Cycle 3-8	Day 28: Cycles 3 & 7	Day 28: Cycle 5		Day 28: Cycle 4 & 6	Day 28 Cycle 8	Onsite Every 3 months	Remote Every 3 months	Remote Every 6 months	
Window (days)	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±14	±14	±30			
Informed consent	✓																										
Eligibility criteria	✓																										
Medical history	✓																										
Height	✓																										
Weight	✓	✓		✓		✓		✓		✓		✓		✓		✓			✓	✓	✓	✓	✓			✓	
Vital signs ¹	✓	✓	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓	✓	✓	✓	✓			✓	
Pulse Oximetry	✓	✓	✓	✓		✓		✓		✓		✓		✓		✓											
KPS	✓																					✓	✓		✓	✓	
Complete PE	✓																					✓				✓	
Abbreviated PE		✓		✓		✓		✓		✓		✓		✓		✓		✓	✓	✓	✓						
Concomitant medications	✓	✓		✓		✓		✓		✓		✓		✓		✓		✓	✓	✓	✓	✓				✓	
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Serum chemistry ^{2,3,12}	✓	✓						✓										✓	✓	✓	✓	✓	✓	✓	✓	✓	
Complete blood count ^{2,4,12}	✓	✓		✓		✓		✓		✓		✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Serum pregnancy test ⁵	✓																										
Biomarkers on archived tumor	✓																										
FACT-Br questionnaire ⁶		✓						✓											✓		✓	✓				✓	
CQOLC questionnaire ⁶		✓						✓											✓		✓	✓				✓	
Gd-MRI scan ⁷	✓ ⁷																			✓	✓	✓					
TOLD ⁸		✓																									
NanO ₂ /placebo		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Radiation therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
TMZ 75 mg/m ² /day		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
TMZ 150-200 mg/m ²																		✓									
Survival Assessment																								✓	✓		

Footnotes

1. Supine heart rate, blood pressure, respiratory rate, temperature and oxygen saturation by pulse oximetry will be measured 10 minutes prior to each NanO₂ infusion and post-infusion. Pulse oximetry not required during cycles 3 – 8 or any follow up visits.
2. Clinical laboratory tests may be performed within 1 day prior to the scheduled visit, except for days 2 and 5 of chemoradiation.
3. Sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, albumin, and total protein.
4. Hemoglobin, hematocrit, red cell count, MCV, MCH, MCHC, white cell count with differential (neutrophils, basophils, eosinophils, lymphocytes and monocytes) and platelet count.
5. Women of child-bearing potential.
6. Functional Assessment of Cancer Therapy – Brain (FACT-Br) and Caregiver Quality of Life – Cancer (CQOLC) questionnaires will be collected on the same day as Doses 1 and 16 of Cycle 1-chemoradiation treatment, Day 28 of the Cycle 2-Recovery Period, Day 28 of Cycles 5 and 8 of the maintenance phase, through long-term study follow up, and at the end of study visit.
7. Standard diagnostic Gd-MRI, including T1- and T2-weighted images, axial flair and post-contrast gradient echo scans in all three planes will be performed post cycle 2, 4 and 6. Diffusion weighted images will also be obtained. Baseline Standard diagnostic Gd-MRI (only performed if radiation is scheduled to commence later than 28 days after surgical resection)
8. TOLD MRI performed on day 1, while breathing oxygen and repeated after administration of NanO₂/placebo and RT. Attempt to complete follow-up TOLD within 120 minutes of NanO₂/placebo infusion but under 180 minutes is acceptable. Gadolinium is not to be administered prior to any TOLD scans. TOLD scans are not to be interpreted by the study sites but by a central core lab. Note that if due to logistical issues the TOLD MRI cannot be performed on Day 1 it can be performed on any of the other days 2-5 during the first week of treatment. However, both TOLD MRI scans must be performed on the same day., or TOLD scans can be omitted and the study site may still participate in the trial. Site should have a discussion with the sponsor prior to study enrollment concerning scanning capabilities.
9. Duration of recovery period is 28 calendar days.
10. Duration of each adjuvant TMZ cycle is 28 calendar days.
11. Onsite follow up visits start 3 months after the last adjuvant TMZ treatment or after a subject discontinues study therapy. The onsite visits will continue until disease progression. Remote follow up visits will start after disease progression for a total of 3 years after the last administration of study drug. Remote follow up visits will be made every 6 months for two additional years. Remote visits can be made by telephone call, clinic visit, through another physician or via registry search.
12. S = standard of care assessments of serum chemistry and complete blood count. Blood tests during the recovery period and each cycle of adjuvant TMZ treatment are to be performed between days 22 and 28.

Appendix D: FACT-Br Questionnaire

FACT-Br (Version 4)

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

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
CP1	I have a lack of energy	0	1	2	3	4
CP2	I have nausea	0	1	2	3	4
CP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
CP4	I have pain	0	1	2	3	4
CP5	I am bothered by side effects of treatment	0	1	2	3	4
CP6	I feel ill	0	1	2	3	4
CP7	I am forced to spend time in bed	0	1	2	3	4
 <u>SOCIAL/FAMILY WELL-BEING</u>						
CS1	I feel close to my friends	0	1	2	3	4
CS2	I get emotional support from my family	0	1	2	3	4
CS3	I get support from my friends	0	1	2	3	4
CS4	My family has accepted my illness	0	1	2	3	4
CS5	I am satisfied with family communication about my illness	0	1	2	3	4
CS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
CS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.



<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
Hr1	I am able to concentrate	0	1	2	3	4
Hr2	I have had seizures (convulsions)	0	1	2	3	4
Hr3	I can remember new things	0	1	2	3	4
Hr4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Hr5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Hr6	I have trouble with my eyesight	0	1	2	3	4
Hr7	I feel independent	0	1	2	3	4
NTX8	I have trouble hearing	0	1	2	3	4
Hr8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Hr9	I have difficulty expressing my thoughts	0	1	2	3	4
Hr10	I am bothered by the change in my personality	0	1	2	3	4
Hr11	I am able to make decisions and take responsibility	0	1	2	3	4
Hr12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Hr13	I am able to put my thoughts together	0	1	2	3	4
Hr14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Hr15	I am able to put my thoughts into action	0	1	2	3	4
Hr16	I am able to read like I used to	0	1	2	3	4
Hr17	I am able to write like I used to	0	1	2	3	4
Hr18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Hr19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Hr20	I have weakness in my arms or legs	0	1	2	3	4
Hr21	I have trouble with coordination	0	1	2	3	4
An09	I get headaches	0	1	2	3	4



CAREGIVER QUALITY OF LIFE- CANCER

Below is a list of statements that other people caring for loved ones with cancer have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

0	=	Not at all	2	=	Somewhat
1	=	A little bit	3	=	Quite a bit
		4	=		Very much

During the past 7 days:

1.	It bothers me that my daily routine is altered.	0	1	2	3	4
2.	My sleep is less restful.	0	1	2	3	4
3.	My daily life is imposed upon.	0	1	2	3	4
4.	I am satisfied with my sex life.	0	1	2	3	4
5.	It is a challenge to maintain my outside interests.	0	1	2	3	4
6.	I am under a financial strain.	0	1	2	3	4
7.	I am concerned about our insurance coverage.	0	1	2	3	4
8.	My economic future is uncertain.	0	1	2	3	4
9.	I fear my loved one will die.	0	1	2	3	4
10.	I have more of a positive outlook on life since my loved one's illness.	0	1	2	3	4
11.	My level of stress and worries has increased.	0	1	2	3	4
12.	My sense of spirituality has increased.	0	1	2	3	4
13.	It bothers me, limiting my focus to day-to-day.	0	1	2	3	4
14.	I feel sad.	0	1	2	3	4
15.	I feel under increased mental strain.	0	1	2	3	4
16.	I get support from my friends and neighbors.	0	1	2	3	4
17.	I feel guilty.	0	1	2	3	4
18.	I feel frustrated.	0	1	2	3	4

Appendix E: CQOLC Questionnaire

0 = Not at all
 1 = A little bit
 2 = Somewhat
 3 = Quite a bit
 4 = Very much

19.	I feel nervous.	0	1	2	3	4
20.	I worry about the impact my loved one's illness has had on my children or other family members.	0	1	2	3	4
21.	I have difficulty dealing with my loved one's changing eating habits.	0	1	2	3	4
22.	I have developed a closer relationship with my loved one.	0	1	2	3	4
23.	I feel adequately informed about my loved one's illness.	0	1	2	3	4
24.	It bothers me that I need to be available to chauffeur my loved one to appointments.	0	1	2	3	4
25.	I fear the adverse effects of treatment on my loved one.	0	1	2	3	4
26.	The responsibility I have for my loved one's care at home is overwhelming.	0	1	2	3	4
27.	I am glad that my focus is on getting my loved one well.	0	1	2	3	4
28.	Family communication has increased.	0	1	2	3	4
29.	It bothers me that my priorities have changed.	0	1	2	3	4
30.	The need to protect my loved one bothers me.	0	1	2	3	4
31.	It upsets me to see my loved one deteriorate.	0	1	2	3	4
32.	The need to manage my loved one's pain is overwhelming.	0	1	2	3	4
33.	I am discouraged about the future.	0	1	2	3	4
34.	I am satisfied with the support I get from my family.	0	1	2	3	4
35.	It bothers me that other family members have not shown interest in taking care of my loved one.	0	1	2	3	4