6.0 Clinical Trials

6.1 Pivotal Trial C94091/I96058 – Relapsed GBM

The pivotal GBM trial was a multicenter, randomized, open-label, Phase II, reference agent trial designed to determine the efficacy and safety of TMZ in the treatment of patients with GBM at first relapse. Eligible histologies included GBM and gliosarcoma. The study period was January 1995 to April 1998. The primary objective was to compare progression-free survival (PFS) at 6 months and safety for temozolomide and procarbazine (active reference agent). Secondary objectives include overall survival; health-related quality of life (HQL) and population pharmacokinetics (TMZ patients only).

6.11 C94-091/I96-058 Investigators

Table 4 C94-091: List of Participating Investigators

C94-091-01 Victor Levin, MD/W.K. Alfred Yung, MD The University of Texas MD Anderson Cancer Center 1515 Holcombe Boulevard Houston, TX 77030	**C94-091-02** Michael Prados, MD University of California, San Francisco 350 Parnassus Avenue, Suite 805 San Francisco, CA 94143-0372
C94-091-04 Henry S. Friedman, MD Duke University Medical Center Department of Pediatric Hematology-Oncology Room 5418 Hospital North Erwin Road Durham, NC 27710	**C94-091-07** Robert E. Albright, MD University of Cincinnati Hospitals Barrett Cancer Center 231 Goodman Street Cincinnati, OH 45207
C94-091-06 William Shapiro, MD St. Joseph's Hospital & Medical Center 350 W. Thomas Road Phoenix, AZ 85013	**C94-091-08** Michael Glantz, MD Department of Neurology Memorial Hospital of Rhode Island 111 Brewster Road Pawtucket, RI 02860
C94-091-10 S. Clifford Schold, Jr., MD/Karen Fink, MD, PhD The University of Texas Southwestern Medical Center at Dallas 5323 Harry Hines Boulevard Dallas, TX 75235-9036	**C94-091-11** Harry Greenberg, MD University of Michigan Medical Center 1500 E. Medical Center Drive Ann Arbor, MI 48109
C94-091-14a Steven S. Rosenfeld, MD, PhD University of Alabama at Birmingham 625 South 19th Street Birmingham, AL 35233	**C94-091-15** Jeffrey Olson, MD Emory University School of Medicine 1364 Clifton Road, N.E. Atlanta, GA 30322
C94-091-16 James K. V. Willson, MD Case Western Reserve University 11100 Euclid Avenue Cleveland, OH 44106	**C94-091-17** Alex M. Spence, MD University of Washington 1959 NE Pacific Avenue Seattle, WA 98195
C94-091-18 Ruth K. Fredericks, MD Department of Neurology University of Mississippi Medical Center 2500 N. State Street Jackson, MS 39216-4505	**C94-091-20** Todd J. Janus, MD, PhD Division of Neuro-Oncology The University of Iowa 200 Hawkins Drive (2 RCP) Iowa City, IA 52242-1053

C94-091-21 John Gutheil, MD/L. Austin Doyle, MD Division of Maryland Cancer Center 22 South Greene Street Baltimore, MD 21201	**C94-091-23** Peter C. Phillips, MD The Hospital of the University of Pennsylvania 34th and Spruce Streets Philadelphia, PA 19104
C94-091-24 a Edward J. Dropcho, MD Indiana University Medical Center 541 Clinical Drive Indianapolis, IN 46202	**I96-058-01** Michael Brada, MD Institute of Cancer Research, Royal Marsden Hospital Downs Road, Sutton, Surrey, SM2 5PT UNITED KINGDOM
I96-058-02 R. Rampling, MD Beatson Oncology Centre Western Infimary Glasgow G11 6NT UNITED KINGDOM	

6.12 C94-091/I96-058 Patient Enrollment by Site

Table 5 C94-091: Enrollment by Site - ITT Population

		No. of Patients	
Investigator	Site	Temozolomide	Procarbazine
Dr. Levin	C94-091-01	21	13
Dr. Prados	-02	6	5
Dr. Friedman	-04	3	3
Dr. Shapiro	-06	3	6
Dr. Albright	-07	4	16
Dr. Glantz	-08	6	3
Dr. Fink	-10	9	7
Dr. Greenberg	-11	3	5
Dr. Vick	-12	5	2
Dr. Selker	-13	7	1
Dr. Rosenfeld	-14	2	3
Dr. Olson	-15	7	11
Dr. Willson	-16	2	1
Dr. Spence	-17	7	3
Dr. Fredericks	-18	8	10
Dr. Janus	-20	5	5
Dr. Gutheil	-21	4	1
Dr. Phillips	-23	2	4
Dr. Dropcho	-24	0	4
Dr. Brada	I96-058-01	4	7
Dr. Rampling	-02	4	3
TOTAL		112	113

6.2 Supporting Trial I94-122 – Relapsed GBM

This study was an open-label, multicenter (26 centers) Phase II trial designed to determine the efficacy and safety of temozolomide in the treatment of patients with supratentorial GBM at first relapse. Eligible histologies included GBM and gliosarcoma. At least one hundred evaluable patients were to be enrolled in the study. Study period encompassed March, 1995 to October, 1996.

6.21 Participating Investigators

Investigators participating in this trial are listed in table 6

Table 6 Investigators Participating in Trial I94-122

Center No.	Investigator(s)	Institution/Location
I94-122-01	Michael Brada, MD	The Royal Marsden Hospital, Sutton, Surrey, U.K.
I94-122-02	Prof. Dr. Herwig Kostron	Clinic Innsbruck, Innsbruck, Austria
I94-122-03	J. Cebon, MD	Austin and Repatriation Medical Centre, Heidelberg, Australia
I94-122-04	Dr. M. Findlay	Royal Prince Alfred Hospital, Camperdown, Australia
I94-122-05	Dr. L. Dirix	Universitair Ziekenhuis, Edegem, Belgium
I94-122-06	Dr. J.G. Villemure	Institut Neurologique de Montreal, Quebec, Canada
I94-122-07	D. Stewart, MD	Ottawa Regional Cancer Centre, Ottawa, Ontario, Canada
I94-122-08	Dr. David R. MacDonald	The London Regional Cancer Centre, London, Ontario, Canada
I94-122-09	H. Skovgaard Poulsen, MD	Rigshospitalet, Copenhagen, Denmark
I94-122-10	Dr. Olivier Chinot	Hopital de La Timone, Marseille, France
I94-122-11	Prof. M. Poisson	Hopital Pitie Salpetriere, Paris, France
I94-122-12	Dr. E. Bouffet	Centre Regional Leon Berard, Lyon, France
I94-122-13	Prof. Dr. med Michael Bamberg Dr. med. Wolfgang Hoffmann	Klinikum der Eberhardt-Karls-Universitaet, Tuebingen, Germany
I94-122-14	Privadozent Dr. med. J-C Tonn	Universitaet Wuerzburg, Wuerzburg, Germany
I94-122-15	Privadozent Dr. med Rita Engenhart-Cabillic	Klinikum der Ruprecht-Karls-Universitaet Heidelberg, Heidelberg, Germany
I94-122-16	B. Zonnenberg, MD	University Hospital Utrecht, Utrecht, The Netherlands
I94-122-17	B. Marques, MD	Instituto Portugues de Oncologia, Lisbon, Portugal
I94-122-19	M. Santos Ortega, MD	Sanatorio San Francisco de Asis, Madrid, Spain
I94-122-20	R. Henriksson, MD	Norrland University Hospital, Umea, Sweden
I94-122-21	A. Malmstrom, MD	University Hospital, Linkoping, Sweden
I94-122-22	Dr. Pierre-Yves Dietrich	Hospital Cantonal Universitaire, Geneva, Switzerland
I94-122-23	R. Herrmann, MD	Kantonsspital Basel, Basel, Switzerland
I94-122-24	Univ. Prof. Dr. Christoph Zielinski	University Clinic Vienna, Vienna, Austria
I94-122-25	R. Rampling, MD	Beatson Oncology Centre, Glasgow, United Kingdom
I94-122-26	J. Heimans, MD	Free University Hospital, Amsterdam, The Netherlands
I94-122-27	Dr. Luis Dávila Maldonado	Hospital Angeles, Mexico City, Mexico

A total of 138 patients comprised the intent to treat population. Enrollment by site is listed in **Table 7.**

Table 7 I94-122: Enrollment by Site

			Number of Patients	
Investigator(s)	Location	Center No.	ITT Population	Eligible Histology Population
Brada	Surrey, UK	I-01	11	11
Zwierzina/Kostron	Innsbruck, Austria	I-02	3	2
Cebon	Heidelberg, Australia	I-03	1	1
Findlay	Camperdown, Australia	I-04	4	4
Dirix	Wilrijkstraat, Belgium	I-05	8	5
Villemure	Quebec, Canada	I-06	5	5
Stewart	Ontario, Canada	I-07	5	5
MacDonald	Ontario, Canada	I-08	8	7
Poulsen/Kristjansen	Kobenhavn, Denmark	I-09	2	2
Chinot	Marseille, France	I-10	4	4
Poisson/Delattre	Paris, France	I-11	10	9
Bouffet	Lyon, France	I-12	5	5
Bamberg/Hoffmann	Tuebingen, Germany	I-13	5	5
Tonn	Wuerzburg, Germany	I-14	5	4
Engenhart-Cabillic/ Albert	Heidelberg, Germany	I-15	3	3
Krouwer/Zonnenberg	Utrecht, Netherlands	I-16	6	5
Marques/Salgado	Lisboa, Portugal	I-17	6	6
Santos Ortega	Madrid, Spain	I-19	1	0
Henriksson	Umea, Sweden	I-20	6	6
Malmstrom	Linköping, Sweden	I-21	4	4
Lejuene/Dietrich	Geneve, Switzerland	I-22	9	9
Herrmann	Basel, Switzerland	I-23	2	2
Zielinski	Vienna, Austria	I-24	3	3
Rampling	Glasgow, Scotland	I-25	10	9
Heimans	Amsterdam, Netherlands	I-26	7	7
Dávila Maldonado	Mexico City, Mexico	I-27	5	5
Totals			138	128

6.3 Pivotal Trial C/I94-123 – Anaplastic Astrocytoma

A multicenter open-label phase II study of temozolomide (SCH 52365) in the treatment of patients with anaplastic Astrocytoma at first relapse. Study period encompassed February 16, 1995 to April 1, 1998. The primary efficacy endpoint was progression-free survival (PFS) at 6 months, with an analysis of event-free survival (EFS) performed as a supplement. Secondary efficacy endpoints were overall survival, objective response and HQL. Adverse events (AEs) and changes in lab parameters from grades 0, 1, or 2 to grade 3 or 4 were also evaluated.

6.31 Participating Investigators

Investigators participating in this trial are listed in table 8.

Table 8 I94-123: Participating Investigators

I94-123-01 Michael Brada, MD The Royal Marsden Hospital Downs Road, Sutton Surrey, SM2 5 PT UNITED KINGDOM **I94-123-04** Dr. M. Findlay Royal Prince Alfred Hospital Missenden Road Camperdown, NSW 2050 AUSTRALIA **I94-123-05** Luc Yves Dirix, MD Universitair Ziekenhuis Antwerpen Wilrijkstraat 10 b-2650 Edegem BELGIUM **I94-123-06** Dr. J.G. Villemure Institut Neurologique de Montreal 3801 University Street Montreal, Quebec H3A 2B4 CANADA **I94-123-07** D. Stewart, MD Ottawa Regional Cancer Centre 190 Melrose Avenue Ottawa, Ontario K1Y 4K7 CANADA **I94-123-08** Dr. David R. MacDonald The London Regional Cancer Centre 790 Commissioners Road East London, Ontario N6A 4L6 CANADA **I94-123-09** H. Skovgaard Poulsen, MD Rigshospitalet Blegkamsvej 9 DK-2100 Kobenhavn O DENMARK **I94-123-10** Dr. Olivier Chinot Hopital de La Timone Service de Neurochirurgie Boulevard Jean Moulin 13385 Marseille Cedex FRANCE	**I94-123-11** Prof. M. Poisson Hopital Pitie Salpetriere 47-83, Boulevard de l'Hopital 75013 Paris FRANCE **I94-123-12** Dr. E. Bouffet Centre Regional Leon Berard 28, rue Laennec 69373 Lyon Cedex O8 FRANCE **I94-123-15** Priv. Doz. Dr. med Rita Engenhart-Cabillic Universitaetsklinikum Radiologische Klinik Im Neuenheimer Feld 400 69120 Heidelberg GERMANY **I94-123-16** B. Zonnenberg, MD University Hospital Utrecht Heidelberglaan 100 3584 CX Utrecht THE NETHERLANDS **I94-123-17** José Maria Bravo Marques, MD Servicio de Neurologia - Clinica 8, Piso 3 Instituto Portugues de Oncologia Rua Professor Lima Basto - 1093 Lisboa CODEX PORTUGAL **I94-123-19** M. Santos Ortega, MD Sanatorio San Francisco de Asis c/Joaquin Costa 28-28002 Madrid SPAIN **I94-123-22** Dr. F. Lejeune Division of Oncology Department of Medicine Kantonsspital Basel Petersgraben 4 4031 Basel SWITZERLAND
I94-123-24 Univ. Prof. Dr. Christoph Zielinski Medical University Clinical Dept. for Oncology University Clinic Vienna Währinger Straße 18-20 A-1090 Vienna AUSTRIA	**C94-123-11** Harry Greenberg, MD University of Michigan Medical Center 1500 East Medical Center Drive 1914 Taubman Center Box 0316 Ann Arbor, MI 48109

I94-123-27 Dr. Luis Dávila Hospital Angeles Office PB-4 Camino Santa Teresa No. 1055 Col. Heroes de Padierna Deleg. Magdalena Contreras Mexico City 17000 MEXICO **C94-123-01** Victor Levin, MD Alfred Yung, MD MD Anderson Cancer Center Professor of Neuro-Oncology Chairman, Department of Neuro- Oncology 1515 Holcombe Blvd. Houston, TX 77030 USA **C94-123-02** Michael Prados, MD University of California, San Francisco Director, Neuro-Oncology Service 350 Parnassus Avenue San Francisco, CA 94117 **C94-123-04** Henry Friedman, MD Dept. of Pediatric Hematology-Oncology Duke University Medical Center Duke North-Room 5418 Erwin Road Durham, NC 27710 **C94-123-06** William Shapiro, MD Barrow Neurological Institute 350 West Thomas Road Phoenix, AZ 85013 **C94-123-07** Robert E. Albright, Jr., MD Barrett Cancer Center 243 Goodman Street Cincinnati, OH 45267-0501 **C94-123-08** Michael Glantz, MD Chief of Neurology Memorial Hospital of Rhode Island 111 Brewster Street Pawtucket, RI 02860 **C94-123-10** Karen Fink, MD, PhD University of Texas Southwestern Medical School 5323 Harry Hines Blvd. Dallas, TX 75235-9036	**C94-123-12** Nicholas A. Vick, MD Nina A. Paleologos, MD Evanston Hospital 2650 Ridge Avenue Evanston, IL 60201-1782 **C94-123-13** Robert G. Selker,MD West Penn Hospital Center for Neuro-Oncology 4800 Friendship Avenue Pittsburgh, PA 15224 USA **C94-123-14** Steven Rosenfeld, MD, PhD Assistant Professor, Dept. of Neurology University of Alabama at Birmingham 1813 6th Avenue South Birmingham, AL 35294-3295 **C94-123-15** Jeffrey Olson, MD Dept. of Neurosurgery The Emory Clinic 1327 Clifton Road, NE Atlanta, GA 30322 **C94-123-17** Alex Spence, MD University of Washington Dept. of Neurology Mailstop RG-27 1959 N.E. Pacific Street Seattle, WA 98195 **C94-123-20** Todd J. Janus, PhD, MD University of Iowa College of Medicine Department of Neurology Iowa City, IA 52242 **C94-123-23** Peter Phillips, MD University of Pennsylvania Medical Center Hospital of the University of Pennsylvania Childrens Hospital of Philadelphia Dept. of Neuroscience, Abramson 516 3400 Civic Center Boulevard Philadelphia, PA 19104

6.32 Enrollment by Site

C/I 94-123 enrollment, by site, is listed in table 9.

Table 9 C/I94-123: Enrollment by Site

Investigator	Site	No. of Patients Enrolled
Dr. Levin/ Dr. Yung	C94-123-01	18
Dr. Prados	-02	15
Dr. Friedman	-04	7
Dr. Shapiro	-06	5
Dr. Albright	-07	7
Dr. Glantz	-08	4
Dr. Fink	-10	3
Dr. Greenberg	-11	2
Dr. Vick	-12	5
Dr. Selker	-13	4
Dr. Rosenfeld	-14	8
Dr. Olson	-15	7
Dr. Spence	-17	5
Dr. Janus	-20	1
Dr. Phillips	-23	1
Dr. Brada	I94-123-01	7
Dr. Findlay	-04	3
Dr. Dirix	-05	6
Dr. Villemure	-06	3
Dr. Stewart	-07	1
Dr. MacDonald	-08	3
Dr.Poulsen/Dr. Kristjansen	-09	1
Dr. Chinot	-10	6
Dr. Poisson/Dr. DeLattre	-11	8
Dr. Bouffet	-12	5
Dr. Engenhart-Cabillic/Dr. Albert	-15	2
Dr. Krouwer/Dr. Zonnenberg	-16	6
Dr. Marques/Dr. Salgado	-17	1
Dr. Santos	-19	2
Dr. LeJuene/ Dr. Dietrich	-22	6
Dr. Zielinski	-24	3
Dr. Davila	-27	7
TOTAL		162

7.0 Study Design - All Glioma Studies – per Sponsor

7.1 Central Pathology Review

An independent central pathology review of all qualifying histology samples was conducted by with the intention of standardizing histological categorization. Gliomas were classified as either astrocytoma, anaplastic astrocytoma (AA), or glioblastoma according to the system of Burger and Nelson. The reviewing pathologist was unaware of treatment assignment. Each patient was to have submitted at least one histologic specimen from each surgical procedure along with the appropriate institutional pathology reports. Specimens submitted must include the specimen obtained at the time of initial diagnosis and the specimen which documents the eligible histology for study enrollment. The most recent diagnosis prior to study enrollment must be used to determine eligibility.

7.2 Central Radiology Review

Central radiology review was performed by all members of the committee were unaware of treatment assignment. Pre- and post-treatment Gd-MRI scans for each patient were reviewed to evaluate objective tumor assessments, based on prospectively defined criteria.

7.3 Choice of Reference Agent for Study C94-091

Procarbazine, an active reference agent, was included to verify that objective responses for PCB could be seen within the definition of the protocol in a randomized group of patients using state-of-the-art techniques, and to allow a contrast of the reference agent to the literature. As there are no widely accepted standards for the treatment of recurrent glioblastoma multiforme (GBM) the choice of a control was based on discussions with leading experts and a thorough review of the literature.

7.4 Study Population

Adult patients, aged ≥18 years, with histologically proven supratentorial GBM (C94-091/I96-023, I94-122), or Anaplastic Astrocytoma (AA) (C94-123) with unequivocal evidence of tumor recurrence or progression at first relapse. Eligible histologies include GBM and gliosarcoma or AA, AA with necrosis, and Anaplastic mixed oligoastrocytoma (AOA)) were to be based on the most recent histology prior to study enrollment, unless GBM or gliosarcoma was diagnosed earlier.

7.5 Eligibility

7.51 Glioma Inclusion Criteria

- Patients with histologically proven supratentorial glioma, having the appropriate histology, at first relapse.

- Histologic specimens from each surgical procedure must have been forwarded for central review. This must have included the specimen obtained at the time of initial diagnosis and the specimen which documented the eligible histology for study enrollment. Patients in whom it had been previously documented that a histologic progression had occurred from anaplastic astrocytoma at the time of initial diagnosis to glioblastoma multiforme at relapse were eligible for GBM studies. In the original protocol, the most recent histology prior to study enrollment must have been used to determine eligibility. Per Protocol Amendment 1, the definition of the histology used for determination of study eligibility was changed to "The most recent histology at initial diagnosis was used to determine eligibility, unless there was a more current histology which documented glioblastoma multiforme."

- Patients must have shown unequivocal evidence for tumor recurrence or progression (first relapse) by Gd-MRI or contrast-enhanced computerized axial tomography (CT) scan after failing a conventional course of radiation therapy for initial disease AND no more than one prior regimen of chemotherapy either single agent or combination therapy. The two scans (pretreatment) obtained prior to study entry demonstrating tumor recurrence or progression must have been reviewed by the Principal Investigator. Both scans for a patient must be of similar type, either Gd-MRI or CT scan.

- Patients must have had evaluable (measurable or non-measurable) enhancing residual disease documented on a baseline Gd-MRI scan of the brain performed within 14 days prior to study drug administration, inclusive. Patients should have been on a non-decreasing dose of steroids for at least 7 days prior to obtaining the Gd-MRI scan of the brain except for post-surgical patients. Patients may have multifocal disease, however, central pathology review must be performed prior to randomization for any patient diagnosed with multifocal disease." Each patient should have had all of his/her Gd-MRI scans performed at the Principal Investigator's study location.

- Age greater than or equal to 18 years.

- Karnofsky performance status (KPS) of greater than or equal to 70.

- Laboratory values (performed within 14 days prior to study drug administration, inclusive) as follows:-absolute neutrophil count (ANC)

>1500/mm3 ; platelet count >100,000/mm3 ; hemoglobin >10 g/dL; BUN and serum creatinine <1.5 times upper limit of laboratory normal; total and direct serum bilirubin <1.5 times upper limit of laboratory normal; SGOT or SGPT <3 times upper limit of laboratory normal; alkaline phosphatase <2 times upper limit of laboratory normal.

- Patients may or may not have had prior chemotherapy as treatment for initial disease. If prior chemotherapy was given, then the regimen must have contained at least a nitrosourea. Patients treated with a chemotherapeutic agent concurrent with radiation therapy are eligible if this agent is not known to have any antitumor activity and either no subsequent chemotherapy was administered or if subsequent chemotherapy was administered, as treatment for initial disease, than that treatment regimen must have contained a nitrosourea. The patient who did not receive any further treatment must be discussed with the Project Director prior to enrollment of the patient onto the study. This defined one previous regimen of chemotherapy for this specific patient group.

- Patients who underwent surgical resection of tumor at first relapse were eligible if there was evaluable (measurable or non-measurable) enhancing residual disease documented by a baseline Gd-MRI obtained within 72 hours following that surgical procedure. Patients undergoing surgical resection of tumor at first relapse who do not have a post-operative Gd-MRI obtained within 72 hours following that procedure may be eligible, after discussion with the Schering-Plough Project Physician, if the patient has a Gd-MRI scan performed 8-12 weeks post-surgery and has received no further therapy since that surgery for the treatment of his/her disease prior to study enrollment The patient must have recovered from the acute effects of surgery.

- Patients must ~~have been on a non-increasing dose of steroids~~ for at least 72 hours prior to study drug administration. Patients who had debulking of tumor at time of first relapse could have their steroids tapered after surgery and prior to study drug administration.

- Patients must be registered to treatment within eight weeks, inclusive, after their date of diagnosis of first relapse (see patients undergoing surgical resection, second paragraph above, for only exception).

7.52 Glioma Exclusion Criteria

- Patients with more than one previous regimen of chemotherapy. Patients treated only with a chemotherapeutic agent concurrent with radiation therapy were eligible if the drug had unknown activity as a glioma treatment agent.

- Patients who had received prior chemotherapy with single agent procarbazine or dacarbazine (DTIC) or who have a history of previous rash to procarbazine.

- Chemotherapy (excluding nitrosourea, mitomycin C or vincristine) within four weeks prior to study drug administration, inclusive.

- Vincristine within two weeks prior to study drug administration, inclusive.

- Nitrosourea or mitomycin C administration within six weeks prior to study drug administration, inclusive.

- Patients with previous interstitial radiotherapy or stereotactic radiosurgery.

- Patients who were poor medical risks because of non-malignant systemic disease as well as those with acute infection treated with systemic antibiotics.

- Surgery, including biopsy, for first relapse within one week prior to study drug administration, inclusive.

- Completion of radiation therapy within twelve weeks prior to documented progression of disease at first relapse, inclusive.

- Patients who had not recovered from all acute toxicities of prior therapies.

- Previous or concurrent malignancies at other sites with the exception of carcinoma in-situ of the cervix and basal or squamous cell carcinoma of the skin.

- Known HIV positivity or AIDS-related illness.

- Pregnant or nursing women.

- Women of childbearing potential who were not using an effective method of contraception. Women of childbearing potential must have had a negative urine pregnancy test 24 hours prior to administration of study drug and must have been practicing medically approved contraceptive precautions.

7.6 *Removal of Patients from Therapy or Assessment*

Patients were permitted to discontinue the study prior to completion for any of the following reasons:

- A clinically significant adverse event as determined by the principal investigator;

- Request to be withdrawn from the study;

- Failure to comply with the requirements for study evaluations/visits;

- Development of circumstances which prevented study evaluations/visits;
- Other conditions for which, in the investigator's opinion, it was in the patient's best interest to be withdrawn from the study;
- Patient did not meet eligibility requirements;
- A total dose reduction of >50% of the starting dose for PCB or a total dose of <500 mg/m2 (100 mg/m2 /day) for TMZ.

Patients who discontinued prior to completion were to have the evaluations, including Gd-MRI scan, HQL questionnaire and Physician's Assessment, required at the end of treatment visit repeated on the last day of study or within one week of this day. A Gd-MRI scan including tumor assessment was to be performed whenever there was clinical evidence of progression. Patients who were removed from the study were not replaced.

7.7 Treatments

7.71 Treatments Administered

TMZ and PCB doses were calculated at each cycle based on body surface area (BSA). The patient's height obtained at the pretreatment visit and weight obtained at each study visit immediately prior to dosing were used to calculate BSA. Doses for both drugs were then rounded up to the nearest available capsule strength. If vomiting occurred during the course of treatment for either study drug, no re-dosing was allowed before the next scheduled dose.

Since PCB may cause a disulfiram-like action, patients were instructed to avoid alcohol consumption. Furthermore, since PCB and its metabolites also exhibit monoamine oxidase inhibitory (MAOI) activity, patients were instructed to avoid sympathomimetic amines, tricyclic anti-depressants, and other drugs and foods with known high tyramine content during and up to 14 days after the last dose. The investigator was to review the drugs and/or foods listed in Protocol Appendix I (that may result in AEs such as headache, tremor, excitation, cardiac arrhythmia, nausea, vomiting and visual disturbances when co-administered with PCB) and was to advise patients accordingly.

7.72 Temozolomide Dosing Guidelines

Patients were to receive the same dose orally once a day for 5 consecutive days (Days 1-5), in a fasting state. TMZ was administered as 150 mg/m2 /day (750 mg/m2 total dose per cycle) to patients who previously received chemotherapy or 200 mg/m2 /day (1000 mg/m2 total dose per cycle) to those who had not previously received chemotherapy. Subsequent treatment cycles could be repeated every 28 days. As per protocol, patients were allowed to continue treatment until unacceptable toxicity and/or disease progression occurred or until they received a maximum of 2 years of treatment.

7.73 Procarbazine Dosing Guidelines

PCB was administered orally, daily for 28 consecutive days (Days 1-28) at a starting dose of 150 mg/m 2 /day for patients who had not previously received any chemotherapy or 125 mg/m 2 /day for those who received previous chemotherapy.13-15,19 These doses and schedule are consistent with those reported in the literature. Treatment cycles could be repeated every 56 days. As per protocol, patients were allowed to continue treatment until unacceptable toxicity and/or disease progression occurred or until they received a maximum of 2 years of treatment.

7.74 Identity of Investigational Product(s)

TMZ was supplied as a white, hard gelatin capsule available in 5, 20, 100, and 250 mg strengths and containing the following excipients: anhydrous lactose, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. TMZ capsules were packaged in amber glass bottles and could be dispensed in these bottles or in light-resistant plastic containers. The following batch numbers were used: 5 mg capsules: 35923-030, 35923-080, 35923-098; 20 mg capsules: 33208-002, 33208-106, 35923-025, 35923-031, 35923-065, 35923-115; 100 mg capsules: 30451-125, 27925-129, 33208-107, 35923-026, 35923-028, 35923-081, 35923-116; and 250 mg capsules: 35923-082, 35923-027, 33208-105, and 35923-117.

PCB was provided by the sponsor and was labeled as an investigational drug by study personnel prior to dispensing to the patient. The principal investigator was referred to the PCB package insert for supply, packaging, storage and stability of PCB. The following batch numbers were used: 50 mg capsules: 33208-099, 33208-127, and 38101-071.

7.75 Method of Assigning Patients to Treatment Groups

Eligible patients were randomly assigned to receive TMZ or PCB upon enrollment and after completion of baseline evaluations using an outside consultant. Patients were balanced between treatment groups for prior exposure to chemotherapy (yes/no), for surgical resection at the time of first relapse (yes/no) and for age (<60/≥60 years). This was accomplished by generating 8 different sets of 100-patient treatment assignments based on randomly permuted blocks of size 2 corresponding to the 8 combinations resulting from 2 categories each of prior chemotherapy, surgical resection at the time of first relapse and age.

7.76 Selection of Doses in the Study

Starting TMZ or PCB doses were dependent upon whether or not the patient had prior chemotherapy as previously defined. TMZ doses were based on the results of previous Phase I and II studies which indicated these doses had meaningful clinical activity and were well tolerated. PCB doses were based on previous studies 13-15 and the package insert.

7.77 Selection and Timing of Dose for Each Patient

7.77.1 Temozolomide Starting Dose During Cycle 1

Dosing guidelines were used as described in **Section 7.7.2.** Subsequent treatment cycles could be repeated every 28 days. Patients were to fast for a minimum of 4 hours prior to administration of each TMZ dose and to continue fasting for 2 hours after dosing. An overnight fast was preferred with TMZ administered early the next morning. If a light meal had to be eaten 4 hours prior to the dosing period, it was to consist of juice, toast and jam. Water was allowed during the fasting period. TMZ was to be given with approximately 8 ounces of water. Patients were instructed to swallow capsules whole, in rapid succession and to not chew capsules.

7.77.2 Procarbazine Starting Dose During Cycle 1

Dosing guidelines were used as described in **Section 7.7.3.** Subsequent treatment cycles could be repeated every 56 days following the first daily dose of PCB.

7.78 Hematologic Criteria for Re-Treatment at Subsequent Cycles

The initiation of subsequent treatment cycles, either 28 days following the first daily dose of TMZ or 56 days following the first daily dose of PCB, was based upon complete blood counts (CBC) obtained within 72 hours prior to the

scheduled day of dosing. If the ANC was ≥1500/mm 3 and the platelet count was ≥100,000/mm3 , repeat cycles could be administered according to the dose adjustments outlined in **Section 7.79**; otherwise treatment was to be delayed. Growth factors could not be used to induce elevations in neutrophil counts for the purposes of administering study drug at the scheduled interval or to allow treatment with higher doses.

If study drug could not be administered on the scheduled day of dosing, the CBC was to be repeated weekly for up to 4 weeks until the ANC was ≥1500/mm3 and the platelet count was ≥100,000/mm3 . If the ANC was ≥1500/mm 3 and the platelet count was ≥100,000/mm3 , treatment could be administered according to the dose adjustments outlined in **Section 7.79**. If the ANC remained <1500/mm3 or the platelet count was <100,000/mm3 at 4 weeks, the principal Investigator was to immediately notify the SPRI Project Physician. In addition, the delay in dosing was to be considered a serious adverse event (SAE) and had to be reported to the trial monitor (or designee).

7.79 Criteria for Dose Adjustment

Dose adjustments based on hematologic criteria were determined according to nadir ANC or platelet counts during the previous cycle (**Table 10**). No dose reductions were required for Grade 2 or lesser non-hematologic toxicity. For Grades 3 and 4 non-hematologic toxicity, dosage for the subsequent cycle was to be reduced by 50% from the previous cycle for PCB and 2 dose levels for TMZ. If, however, in the investigator's opinion, a Grade 3 or 4 non-hematologic toxicity did not necessitate either a 50% reduction (for PCB) or 2 dose levels (for TMZ), a 25% reduction (for PCB) or one dose level reduction (for TMZ) could have been used. The reason was to be noted in the data collection form. Additionally, if in the investigator's opinion, a Grade 3 or 4 non-hematologic toxicity did not necessitate any reduction in dosage, the patient could continue at their current dose. The reason had to be recorded in the data collection form. If no further Grade 3 or 4 non-hematologic toxicity occurred with subsequent dosing, the total dose to be administered for the next cycle was to be determined by the criteria in **table 10.**

Table 10 Dose Adjustment Criteria

Nadir Toxicity Level	Nadir ANC/mm 3	Nadir Platelets/mm 3	Procarbazine Dose Modification	TMZ Dose Modification
0	>2000	>125,000	Increase by 10% up to a maximum of 110% of starting dose of procarbazine	Increase to next higher level for a maximum of 200 mg/m 2 /day
1	1500-1999	75,000-124,999	Increase by 10% up to a maximum of 110% of starting dose of procarbazine	Increase to next higher level a for a maximum of 200 mg/m 2 /day
2	1000-1499	50,000-74,999	Dose Unchanged	Dose Unchanged
3	500-999	25,000-49,999	Decrease Dose 25%	Decrease dose to next lower dose level a
4	<500	<25,000	Decrease Dose 25%	Decrease dose to next lower dose level a

a: Dose levels of TMZ: 200 mg/m 2 /day, 150 mg/m 2 /day, and 100 mg/m 2 /day.

If multiple hematologic or non-hematologic toxicities occurred, the dose was to be based on the reduction required for the most severe toxicity. Administration of subsequent cycles was dependent on resolution of nonhematologic Grade 2 toxicities to pretreatment levels and on resolution of nonhematologic Grade 3 or 4 toxicities to at least Grade 2. In the absence of grade 3 or 4 toxicities, TMZ patients started at 150 mg/m2/day could be increased to 200 mg/m2/day and PCB patients could be increased to a maximum of 110% of the starting dose at subsequent cycles.

7.80 Blinding

This was an open-label study. However, central pathology and radiology reviewers were blinded to the treatment assignment.

7.81 Prior and Concomitant Therapy

Prior therapy, including chemotherapy, biologic therapy, radiation, and surgeries were recorded in addition to other medications. All medications administered during the study and reasons for use were to be recorded. Prophylactic antiemetics were used at the discretion of the investigator. Patients were to be maintained on the lowest dose of steroids necessary for neurological stability. Colony-stimulating factors were not to be used, except in cases of Grade 4 neutropenia when the use of G-CSF was permitted. Other chemotherapy, radiation, biologic therapy or investigational medications were prohibited.

7.82 Treatment Compliance

Patients received a supply of TMZ or PCB capsules after a complete eval-uation by the treating physician on Day 1 of each cycle. Patients were instructed to return unused study medication to the investigative facility during each visit, and capsule counts were performed after dosing for each cycle.

7.83 Efficacy and Safety Variables Flow Chart

7.83.1 Efficacy and Safety Measurements Assessed and Flow Chart

The timing of efficacy and safety measurements is presented in **Table 11**. If multiple hematologic or non-hematologic toxicities occurred, the dose was to be based on the reduction required for the most severe toxicity. Administration of subsequent cycles was dependent on resolution of nonhematologic Grade 2 toxicities to pretreatment levels and on resolution of nonhematologic Grade 3 or 4 toxicities to at least Grade 2. In the absence of grade 3 or 4 toxicities, TMZ patients started at 150 mg/m2/day could be increased to 200 mg/m2/day and PCB patients could be increased to a maximum of 110% of the starting dose at subsequent cycles.

Table 11 Efficacy and Safety Determinations

Evaluation	Pre-treatment (≤14 days prior)	Day 1 Cycle 1 (both drugs)	Scheduled day of dosing (subsequent cycles)	TMZ Days 14 and 21(all cycles)	PCB every 2 weeks (all cycles)	PCB Day 29 Mid-cycle (all cycles)	6 months following Cycle 1 Day 1	End of Treatment Visit	Follow-up (every 8 wks)
Medical History	X								
Physical Examination	X	X	X			X	X	X	
Vital Signs/ Weight	X	X	X			X	X	X	
Neurologic Exam	X		X			X	X	X	
KPS	X		X			X	X	X	
Hematology	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X			X	X	X	
Urine Analysis	X								
ECG (12-lead)	X								
CXR (PA/lateral)	X								
Urine Pregnancy Test		X							
Pharmacokinetics		X	X						
Gd-MRI Tumor Assessment	X		X(a)				X	X	
Overall Response			X				X	X	
HQL		X	X			X	X	X	
Survival									X

a: Gd-MRI scans were done every other (even-numbered) cycle for TMZ.

7.84 Criteria for Objective Response by Neuroimaging

Objective tumor assessments were made from Gd-MRI scans according to standardized procedures. Scans were to have been performed at either the principal investigator's study institution or one designated radiology facility. Copies of all scans were to be made available for central review at

7.84.1 Measurable Lesions

For measurable lesions, the product of the largest perpendicular diameters of enhancement was recorded and radiologic response was determined by the following standardly accepted criteria:

7.84.11 Complete response (CR)

CR = Disappearance of all enhancing tumor.

7.84.12 Partial response (PR)

PR = ≥50% reduction in the sum of the products of the largest perpendicular diameters of contrast enhancement for all lesions; no new lesions.

7.84.13 Progressive Disease (PD)

PD = ≥25% increase in the product of the largest perpendicular diameters of contrast enhancement of any lesion or any new enhancing tumor.

7.84.14 Stable Disease (SD):

SD = all other situations.

7.84.2 Non-measurable lesions

Non-measurable lesions were assessed to approximate the definitions for measurable lesions:

7.84.21 Complete Response (CR):

CR = No enhancing tumor

7.84.22 Partial Response (PR):

PR = Definitely better

7.84.23 Stable Disease (SD):

SD = Possibly better or unchanged or possibly worse

7.84.24 Progressive Disease (PD):

PD = Definitely worse

7.85 Clinical Neurological Examination

A comprehensive neurological examination was performed at each study visit. Evaluation was based on changes in symptoms and signs from the previous examination deemed unrelated to postictal state or other unrelated events such as infection. Relative changes were graded as: definitely better (+2); possibly better (+1); unchanged (0); possibly worse (-1); or definitely worse (-2).

7.86 Criteria for Overall Response

Assessments of overall response by the investigator were based upon objective tumor assessments interpreted in light of steroid use and, to a lesser extent, neurologic status. Overall response was assessed as follows:

7.86.1 Complete response (CR):

CR = disappearance of all enhancing tumor (measurable or non-measurable) on consecutive MRI scans at least one month apart, off steroids except for physiologic doses which may have been required following prolonged therapy and neurologically stable or improved.

7.86.2 Partial response (PR):

PR = for patients with lesions which were either all measurable or all nonmeasurable, ≥50% reduction (<100%) in the sum of the products of the largest perpendicular diameters of contrast enhancement for all measurable lesions or definitely better for all non-measurable lesions on consecutive MRI scans at least one month apart, steroid use stable for 7 days prior to each scan at the same dose administered at the time of the previous scan or at a reduced dose, and neurologically stable or improved. No new lesions could arise. See the protocol for the definition of PR in patients with multifocal disease (measurable + nonmeasurable lesions).

7.86.3 Progressive disease (PD):

PD = ≥25% increase in size of the product of the largest perpendicular diameters of contrast enhancement for any measurable lesions or definitely worse for any non-measurable lesions or any new tumor on MRI scans, steroid use stable for 7 days prior to each scan at the same dose administered at the time of the previous scan or at an increased dose, with or without neurologic progression. Non-tumor-related causes of clinical or radiological worsening were excluded based on the investigator assessment.

7.86.4 Stable disease (SD):

SD = All other situations.

An algorithm that was prospectively-defined prior to data review was used by the sponsor (SPRI Project Physician) to verify the investigator-determined date of a progression event (progressive disease or death).

7.9 Safety Measurements

7.91 Adverse Events

Treatment-emergent adverse events were those that began during treatment or up to 30 days after treatment ended, or that began prior to the start of treatment and worsened in severity while on treatment regardless of relationship to treatment. For each adverse event, duration, severity (using the CTC grading system of toxicity as described in the protocol), consequence and investigator-assessed relationship to treatment was to be recorded **(Table12)**.

Table 12 Adverse Event Scoring

0 = unrelated - no temporal association, other etiologies very likely the cause. 1 = possibly related – less clear temporal association, other etiologies are also possible. 2 = probably related – clear-cut temporal association with improvement upon medication withdrawal, and not reasonably explained by the patient's known clinical state. 3 = related - clear-cut temporal association with laboratory confirmation or a positive recalling test.

Serious adverse events, whether or not deemed treatment-related or expected by the investigator, were to be reported by the principal investigator as defined in the protocol. Worsening of neurological deficits were not to be considered an adverse event within the context of this study but were to be considered physical findings associated with the neurological examination. Abnormal laboratory values were not to be recorded as adverse events unless they caused hospitalization, transfusion of blood products, or discontinuation of therapy.

Adverse events considered serious by the sponsor's Drug Safety Surveillance Department were defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may

jeopardize the patient or 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 dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

7.10 Laboratory Measurements

Complete blood counts, including differential and platelet counts, were to be obtained during each cycle to evaluate potential hematologic toxicity, to determine the timing of subsequent cycles, and the need for any dose adjustments. Blood samples and urine specimens were to be obtained at specified time points (indicated in **Table 11**).

7.11 Health-Related Quality of Life

Health-related quality of life (HQL) was assessed to evaluate the impact of therapy from the patient's perspective. A patient self-administered HQL instrument, comprised of the validated European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 (+3)20,21 (33 questions) and a validated malignant brain cancer module BCM20)22-29 (20 questions) was administered on Day 1 of Cycle 1 and at every visit throughout the study. The QLQ-C30 provides summary scores for 6 general HQL concepts or domains: Physical Functioning, Role Functioning, Cognitive Functioning, Emotional Functioning and Social Functioning, and Global HQL. For these 6 scale scores, higher values represent better functioning. In addition to these 6 functioning domains, the QLQ-C30 also provides information on 9 disease or treatment-related signs and symptoms or problems commonly experienced by cancer patients; these include Fatigue, Pain, Nausea/Vomiting, Dyspnea, Insomnia, Anorexia, Constipation, Diarrhea, and Financial Impact. For these 9 symptom scores, higher values represent a greater degree of symptom severity.

The disease-specific HQL concepts included in the BCM20 are Visual Disorder, Motor Dysfunction, Communication Deficit, Headaches, Seizures, Drowsiness, Weakness of Both Legs, Trouble Controlling Bladder, Bothered by Hair Loss, Bothered by Itching Skin, and Future Uncertainty. Higher scores on these 11 brain cancer specific domains correspond to worse disease symptomatology.

Administration of the HQL questionnaire followed the guidelines in the protocol.

7.12 Appropriateness of Measurements

The sponsor states that 1) the efficacy and safety measurements employed in this study are well-established in the oncology and clinical research literature and are well accepted by oncologists and 2) that The HQL measurements were appropriately validated. The QLQ-C30 is widely employed by oncology research groups and the BCM20 is a newly validated instrument for brain cancer patients. The endpoint based on imaging was stated to have been defined after discussion with clinical experts and was prospectively specified in the protocol as the primary efficacy parameter. The validity of imaging as an endpoint of progression was additionally assured by two protocol-defined activities: defined conditions for use and objective central review. In order to capture tumor growth by scan and clinical deterioration that might precede detectable tumor growth, the protocol required investigators to consider all available neurologic and clinical data in addition to radiologic evidence when making an assessment of progression. As with other oncologic diseases, scan-based progression generally occurred prior to evidence of clinical deterioration. Therefore, in the majority of patients, progression was image-based; progression was based on a clinical event (including death) in less than 20% of patients. Thus, PFS defined primarily by image-based progression on regular MRI scans, and taking into account clinical parameters, is the most objective and rigorous endpoint of disease progression. As applied in this trial, these criteria represent the most stringent criteria for evaluating efficacy of chemotherapy in recurrent malignant glioma. A review of the literature, as presented in this report, fails to support progression free survival at six months as a primary study endpoint.

7.13 Data Quality Assurance

The quality of data collected at study sites was assured by the procedures specified in SPRI standard operating procedures, which are consistent with Good Clinical Practice guidelines. Subject data were entered into a database using RDE data collection forms. RDE data entries were compared by the study monitor against information in source documents, including patient files, hospital records and charts, original recordings, laboratory notes and slips, and raw data for clinical and laboratory findings. All applicable source documents for 20% of patients were compared with RDE entries. In addition, the accuracy of prospectively identified, key efficacy variables, was 100% verified for all patients, as were the recording and reporting of AEs.

The sponsor's Worldwide Research Quality Assurance (WRQA) group conducted audits at selected centers according to WRQA's written standard operating procedures. The following 4 centers were audited: -02, Dr. Prados; -07, Dr. Albright; -10, Dr. Fink; -15, Dr. Olson.

7.14 Statistical Methods Planned in the Protocol and Determination of Sample Size

7.14.1 Baseline Evaluations

The parameters summarized at baseline were: age; gender; race; previous treatment with chemotherapy; surgery and extent of surgery at initial diagnosis; surgery and extent of surgery at first relapse; time from initial diagnosis to first relapse; time from end of radiation therapy at initial diagnosis to first relapse; and KPS.

7.14.2 Evaluation of Efficacy

The primary efficacy analysis was based on PFS. PFS included only progressive disease and death as an event and was measured from the date of randomization to the date of an event or last evaluation, whichever was earliest. Overall survival, a secondary efficacy variable, was measured from the date of randomization to the date of death or last evaluation. The product limit method (Kaplan-Meier [K-M])30 was used to estimate PFS and overall survival. Median PFS and overall survival along with the distribution of follow-up duration and K-M estimates were provided. For PFS, the proportion of patients progression-free at 6 months based on K-M estimates, with a 95% confidence interval was provided. Objective response (as defined in **Section 7.86**) was also a secondary efficacy variable and was based on the central reviewer assessment.

The FDA disagreed with death as a progression event. If there was no objective evidence of progressive disease at the last patient exam or visit prior to death the patient was censored for progression on that date by the FDA.

The sponsor stated that this study was not planned as a comparative trial of TMZ and PCB. PCB, was included as a reference control. However, as TMZ demonstrated meaningful improvement in the sponsor's primary endpoint of PFS at 6 months relative to PCB, a retrospective statistical comparison of the two treatments was carried out using the log-rank test.

All efficacy analyses were carried out on the intent-to-treat (ITT) population which included all randomized patients. An "eligible histology" subgroup was defined as including only those with GBM or gliosarcoma by central reviewer assessment. Patients who had surgical resection at the time of first relapse (ie, study entry), had to have either GBM or gliosarcoma. The eligible histology subgroup also included patients who had the following: i) surgical resection at enrollment who either did not have histologic review of the initial diagnosis specimen or ii) central review identified a histology other than GBM or gliosarcoma but the initial diagnosis was GBM or gliosarcoma. Patients who had a histological specimen only at initial diagnosis had to have GBM or gliosarcoma.

Supplementary analyses were performed for the eligible histology subgroup for PFS and overall survival.

In order to assess the potential influence of baseline characteristics on treatment effect for PFS and overall survival, Cox's regression model 31 was used by including the following potential prognostic variables in the model in addition to treatment: age; sex; prior chemotherapy; surgery at initial diagnosis; time from initial diagnosis to first relapse; time from end of radiation therapy to first relapse; baseline KPS. Subgroup analyses were performed for PFS and overall survival based on all prognostic variables used in Cox's model. Subgroups based on age, time from initial diagnosis to first relapse, time from end of radiation treatment to first relapse and baseline KPS were selected so that approximately 50% of the patients were in each category.

7.14.3 Evaluation of Safety

AEs, laboratory data and neurological examination data were listed. The incidence of AEs and dropout rates for AEs were tabulated by treatment group. Changes in neurological data were also tabulated.

7.14.4 Evaluation of Health-Related Quality of Life

Scoring of the HQL instruments was consistent with the EORTC scoring instruction.

Since 70% of PCB patients dropped out of the study by the end of the third month (compared to 35% of TMZ patients), a limited number of descriptive HQL analyses were carried out as follows to explore whether TMZ provided HQL benefit to patients compared to PCB:

- HQL of the subgroup of patients progression-free at 6 months (the primary endpoint) was compared between groups
- at fixed time points (month 3 and 6) the number and percent of patients improving their HQL or maintaining high functioning were compared between groups.
- Defining an HQL response as a 10-point improvement from baseline in an HQL domain maintained for at least 2 consecutive months, the percentage of patients achieving such a response was compared between groups.

7.14.5 Quality-Adjusted Survival Analysis

A retrospective quality-adjusted survival analysis is a different approach for accounting for HQL when comparing treatments. The Q-TWiST (Quality-adjusted Time Without Symptoms and Toxicity) methodology,33 which integrates both quantity and quantity of life into a single endpoint, was used to

provide such a treatment comparison. This methodology has also been applied to trials in breast cancer, melanoma and other life-threatening diseases.

7.14.6 Determination of Sample Size

The objective of this study, as stated in the protocol, was estimation of PFS at 6 months. The study was targeted to enroll a total of 200 evaluable patients. The study was not planned as a hypothesis testing study, since the sample size requirement to show equivalence or to show a clinically meaningful difference from a control group would be extremely high (ie, if the true control rate was 20%, to show equivalence, defined as within 5%, the sample size requirement would be 1092 per group and to detect a 10% improvement from the control the sample size needed would be 298 per group) making it difficult to do the study in view of a relatively low incidence of the disease.

With 100 patients per group, assuming the true 6-month PFS rate for TMZ to be 20%, the 95% confidence interval ranges from 12.2% to 27.8%. This assured with confidence that the lower boundary of the 95% confidence interval for the 6-month PFS rate for TMZ would stay above 10%, with 10% assumed to be the threshold of non-effectiveness.

7.14.7 Changes in the Conduct of the Study or Planned Analyses

The protocol was amended on September 11, 1995 to clarify inclusion criteria, response definitions, safety reporting requirements, and administrative issues (Amendment No.1). The protocol was further amended on January 20, 1997 to allow for treatment to continue for up to two years in the absence of disease progression (Amendment No.2). In addition, for patients who discontinued for reasons other than disease progression, MRI or CT scans were to be performed every 2 to 3 months until disease progression occurred, or until the patient was treated with another chemotherapy or radiotherapy regimen.

8.0 Study Results

8.1 Study Execution

Four hundred twelve patients were treated with TMZ, and 113 with PCZ in three SPRI-sponsored glioma trials (C94-091, I94-122, and C/I94-123) **(Table 13)**. Adult patients, aged ≥18 years, with histologically proven evidence of tumor recurrence or progression at first relapse were eligible for participation; the inclusion and exclusion criteria (aside from histology) were the same for all three studies. These trials included 363 GBM patients and 162 AA patients. Among the total study population 32 had ineligible histology **(Table 14)** and 7 were unevaluable for response or survival **(Table 15)**.

Table 13 TMZ Clinical Studies in Relapsed Glioma Patients

TMZ	Number of Patients
C94-091/I96-058 - (GBM)	112
I94-122 - (GBM)	138
C/I94-123 - (AA)	162
Total	412

8.11 Ineligible/Non-evaluable Patients

8.11.1 Ineligible Histology per FDA

Table 14 Ineligible Histology

	Number of Patients
C94-091/I96-058 - (GBM)	9
I94-122 - (GBM)	5
C/I94-123 - (AA)	18
Total	32

8.11.2 Unevaluable patients per FDA

Table 15 Unevaluable Patients

	Number of Patients
C94-091/I96-058 - (GBM)	4
I94-122 - (GBM)	2
C/I94-123 - (AA)	1
Total	7

8.12 Patient Demographics

In the following tables patient demographics will be shown per sponsor and per FDA for each of the glioma studies.

8.12.1 Pivotal study C94-091/I96-058 - GBM

Sponsor's data on patient denographics and patient disease characteristics are recorded in **Tables 16 and 17.** FDA patient characteristics are recorded in **Table 18.**

Table 16 Pivotal Study C94-091. Patient Demographics per Sponsor

	Temozolomide (N=112)	Procarbazine (N=113)	p-Value
Age (years)			0.43 a
20-40	15 (13%)	24 (21%)	
>40-50	36 (32%)	31 (27%)	
>50-65	55 (49%)	44 (39%)	
>65	6 (5%)	14 (12%)	
Median	52	51	
Range	21-76	21-74	
Sex	77 (69%)	72 (64%)	0.48 b
Male	35 (31%)	41 (36%)	
Female			
Race			0.20 c
Caucasian	106 (95%)	99 (88%)	
Black	4 (4%)	7 (6%)	
Hispanic	2 (2%)	2 (2%)	
Asian	0	2 (2%)	
Other	0	3 (3%)	
Karnofsky Performance Status			0.19 c
100	3 (3%)	10 (9%)	
90	32 (29%)	30 (27%)	
80	43 (38%)	34 (30%)	
70	34 (30%)	38 (34%)	
Not recorded	0	1 (1%)	

a: Kruskal-Wallis test.
b: Fisher's exact test.
c: Chi-square test.

Table 17 Pivotal Study C94-091: Patient Characteristics per Sponsor

	Temozolomide (N=112)	Procarbazine (N=113)	p-Value
Surgery at Initial Diagnosis			0.30 b
Yes	97 (86.6%)	103 (91.2%)	
No	15 (13.4%)	10 (8.8%)	
Extent of Surgery at Initial Diagnosis	58 (51.8%)	55 (48.7%)	0.37 c
Subtotal Resection	39 (34.8%)	48 (42.5%)	
Gross Total Resection			
Prior Radiation	112 (100%)	113 (100%)	
Time fr Radiation Therapy to First Relapse			0.03 a
<3 months	21 (18.7%)	17 (15.0%)	
3-6 months	54 (48.2%)	42 (37.2%)	
>6-9 months	15 (13.4%)	14 (12.4%)	
>9-12 months	6 (5.4%)	14 (12.4%)	
>12-18 months	5 (4.5%)	19 (16.8%)	
>18-24	4 (3.6%)	0	
>24	7 (6.3%)	7 (6.2%)	
Median	4.6	5.8	
Range	0.6-63.6	0.1-92.3	
Prior Chemotherapy			0.67 b
Yes	73 (65.2%)	77 (68.1%)	
No	39 (34.8%)	36 (31.9%)	
Time fr Initial Diagnosis to First Relapse			0.02 a
<3 months	0	1 (0.9%)	
3-6 months	38 (33.9%)	21 (18.6%)	
>6-9 months	41 (36.6%)	40 (35.4%)	
>9-12 months	11 (9.8%)	17 (15.0%)	
>12-18 months	10 (8.9%)	22 (19.5%)	
>18-24 months	3 (2.7%)	5 (4.4%)	
>24 months	9 (8.0%)	7 (6.2%)	
Median	7.0	8.4	
Range	3.1-66.0	2.2-92.3	
Surgery at First Relapse			1.0 b
Yes	22 (19.6%)	22 (19.5%)	
No	90 (80.4%)	91 (80.5%)	
Extent of Surgery at First Relapse			1.0 c
Subtotal Resection	16 (14.3%)	16 (14.2%)	
Gross Total Resection	6 (5.4%)	6 (5.3%)	
Time fr Surgery at First Relapse to Study Drug			0.2 a
<1 months	8 (7.1%)	14 (12.4%)	
1-2 months	9 (8.0%)	6 (5.3%)	
>2-3 months	4 (3.6%)	1 (0.9%)	
>6 months	1 (0.9%)	1 (0.9%)	
Median	1.2	0.9	
Range	0.4-9.8	0.3-17.1	

a: Kruskal-Wallis test.
b: Fisher's exact test.
c: Chi-square test.

Table 18 Pivotal Study C94-091: Patient Characteristics per FDA

Characteristic	Temozolamide 112 Patients	Procarbazine 113 Patients	p value
Age			
18-30	4	8	
31-40	11	16	
41-50	36	31	
51-60	40	36	
61-70	19	19	
>70	2	3	0.47
Sex			
Female	35	41	
Male	77	72	0.48
Race			
White	106	99	
Black	4	7	
Other	2	7	0.14
Performance Status			
100	3	10	
90	32	31	
80	43	32	
70	34	38	
Not recorded		2	0.79
Initial Surgery			
Biopsy Only	15	13	
Subtotal Resection	51	55	
Gross Total Resection	39	44	0.62
Initial Radiation Therapy (Gy)			
≤50	4	6	
51-60	45	39	
61-70	57	58	
>70	6	9	
Unknown	0	1	0.48

Table 18 Continued

Characteristic	Temozolamide 112 Patients	Procarbazine 113 Patients	p value
Initial Chemotherapy			
None	29	34	
Nitrosoureas	75	82	
Procarbazine	28	21	0.27
Time From Initial Diagnosis to First Relapse (mo)			
≤3	0	1	
4-6	33	24	
7-9	45	34	
10-12	12	14	
13-18	8	26	
19-24	3	4	
>24	9	6	
Unknown	2	4	0.03
Time from First Relapse to Registration/Randomization (mo)			
≤1	91	89	
2-3	18	17	
>3	1	4	
Unknown	2	3	0.57
Did Not Meet Protocol Eligibility			
Ineligible Histology	6	3	
Unknown Histology	2	2	
Surgery at Relapse			
Subtotal Resection	6	6	
Gross Total Resection	16	16	>0.9
Measurable Tumor Area (cm2)			
≤1.0	4	3	
1.1-3.0	4	7	
3.1-6.0	18	22	
6.1-9.0	12	10	
9.1-12.0	13	10	
12.1-15.0	10	14	
15.1-20.0	18	13	
20.1-30.0	11	15	
>30	11	10	
Not measurable	11	9	0.58

Symptoms (Baseline)			
Yes	99	104	
No	13	9	0.37
Laboratory Values			
Albumin [median (range)]	4.1 (2.5-5.0)	4.2 (3.1-4.9)	
Hgb	12.9 (10.9-15.9)	12.9 (9.7-16.1)	

8.12.2 Pivotal Study C/I94-123 – Anaplastic Astrocytoma

Sponsor's data on patient demographics and patient disease characteristics for patients enrolled in supporting trial C/I94-123 are recorded in **Tables 19 and 20.** FDA patient characteristics are recorded in **Table 21.**

Table 19 AA: C/I94-123: Patient Demographics per Sponsor

Demographic Parameter	Number (%) of Patients (N=162)
Age (years)	
19-<20	2 (1.2%)
20-40	72 (44.4%)
>40-50	48 (29.6%)
>50-65	33 (20.4%)
>65	7 (4.3%)
Median	42.0
Range	19-76
Gender	
Male	93 (57.4%)
Female	69 (42.6%)
Race	
Caucasian	147 (90.7%)
Black	4 (2.5%)
Hispanic	9 (5.6%)
Other	2 (1.2%)
Karnofsky Performance Status	
100	25 (15.4%)
90	50 (30.9%)
80	33 (20.4%)
70	51 (31.5%)
60	2 (1.2%)
50	1 (0.6%)