BRIEFING BOOK FOR THE MARCH 13, 2003 ODAC MEETING REGARDING ACCELERATED APPROVAL CLINICAL PHASE 4 COMMITMENTS NDA 21-029 TEMODAR® (temozolomide) SCHERING-PLOUGH CORPORATION

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NDA 21-029 TEMODAR® (temozolomide)
SCHERING-PLOUGH CORPORATION

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I. GENERAL INFORMATION:

A. Drug Name: TEMODAR® (temozolomide)

B. Indication: For the treatment of adult patients with refractory anaplastic astrocytoma (AA), i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

C. Accelerated Approval Date: August 11, 1999

D. Outline of the Summary Basis of Approval:

The TEMODAR® clinical development program for malignant gliomas focused on GBM and AA from 1993 to 1998. The New Drug Application (NDA) for temozolomide capsules for the treatment of recurrent malignant GBM (glioblastoma multiforme) and AA was submitted to the FDA on August 12, 1998.

During the NDA review process, the FDA agreed that there was no standard of care for relapsed AA in recurrent disease, and agreed to review the AA indication under the accelerated approval regulations with a Phase 4 commitment to confirm clinical benefit in an AA population in a randomized controlled study to be approved by the Agency.

The clinical section of the AA accelerated approval NDA was based upon a multicenter 32 institution open-label Phase 2 study of temozolomide in the treatment of adult patients with AA at first relapse (Study C/I94-123). The primary efficacy endpoint of this study was progression-free survival (PFS) at six months. Secondary efficacy endpoints were overall survival, objective response and HQL (Health-related Quality of Life). An analysis of event free survival was also included in the NDA.

The FDA clinical review for accelerated approval of temozolomide in AA was completed January 29, 1999. According to FDA analysis of the results of study C/I94-123 (ITT population n=162), the response rate was 5% CR and 28% PR; median PFS was 6.18 months; PFS at 6 months was 51% (95% CI 43-59%); median

OS was 13.6 months; and survival rate at 6 months was 75% (95% CI 68-82%); the safety profile was acceptable.

In AA patients who were refractory to both a nitrosourea and procarbazine, the FDA analysis indicated that the overall response rate (CR + PR) was 22% with 9% complete response and the median duration of all response was 50 weeks (16-114 week range) with median duration of complete response of 64 weeks (range 52 to 114 weeks); the median PFS was 4.4 months and median OS was 15.9 months.

The Oncologic Drugs Advisory Committee (ODAC) in its 1/12/1999 meeting unanimously agreed (12-Yes, 0-No) that:

- The patients with relapsed AA who have received both nitorsourea and procarbazine could be considered unresponsive to other therapies.
- The AA Phase 2 study 94-123 shows that temozolomide capsules are effective for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitorsourea and procarbazine.
- The safety of temozolomide capsules is acceptable for this indication.

In early February 1999, the sponsor submitted a protocol concept sheet (PCS) for a proposed post-approval study in newly diagnosed AA patients to be conducted by the cooperative group Radiation Therapy Oncology Group (RTOG). At that time the proposal was for a two-arm study comparing radiation with BCNU to radiation with BCNU followed by temozolomide. There was no need for a Phase 1 safety program prior to this Phase 3 study.

On February 12, 1999, the FDA issued an approvable letter for TEMODAR® for the indication "treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine drug regimen".

The PCS of the RTOG study in newly diagnosed AA patients (Study 98-13) was reviewed by the FDA and initial comments were communicated to Schering Corporation on March 5, 1999. The protocol was revised in collaboration with RTOG to incorporate the FDA comments and was re-submitted to the Agency on June 24, 1999. The revised protocol included a third arm to study the doublet of BCNU/temozolomide. This revised protocol required a Phase 1-safety assessment of the doublet and the FDA required submission of the safety data prior to initiating the study with the BCNU/temozolomide combination. Additional FDA comments were received on July 8, July 30 and August 3, 1999.

On August 11, 1999, FDA approved TEMODAR® capsules under 21 CFR §314 Subpart H for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

The FDA approval was based on a surrogate endpoint (response rate) with a post-approval commitment to conduct a study entitled: "A Phase 1/3 randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma". The commitment further stipulated that safety data from a Phase 1 segment of the study would be submitted to the FDA with agreement that initiation of the combination arm (BCNU/temozolomide) would be contingent on FDA approval to proceed. Furthermore, Schering Corporation committed to completing the two monotherapy arms of the study in the event that the combination arm was stopped for any reason.

Two GBM studies were submitted in the original NDA. The first study, C/I94-091, compared temozolomide (112 patients) to procarbazine (113 patients). The primary endpoint of this study was progression free survival (PFS) with overall survival (OS) as a secondary endpoint. PFS at 6 months was 21% (95% CI 13-29%) for temozolomide versus 9% (95% CI 4-15%) for procarbazine (p=0.016). Median overall survival in this study showed a trend favoring temozolomide (7.34 vs 5.82 months; p=0.067).

The second study (C/I94-122) was a single arm study of 138 GBM patients in which 6-month PFS was reported as 19%.

The GBM claim from the August 12, 1998 NDA was determined not to be eligible for standard or accelerated approval.

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II. DESCRIPTION OF COMMITMENTS INCLUDING TITLES OF INDIVIDUAL STUDIES:

1. A Phase 1/3 randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma.

    1.1. In addition, Schering-Plough Research Institute (SPRI) will provide Phase 1/2 safety data of the above study to support the dosing schedule in the combination arm of the trial, and agree that initiation of the combination arm will be contingent on FDA approval to proceed.

1.2. Furthermore, SPRI committed to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason.

[Reference FDA Fax dated January 25, 2001 (Attachment #1) and FDA letter dated August 30, 2001 (Attachment #2)]

2. Other TEMODAR® Commitments: On January 25, 2001, the FDA issued a Pediatric Written Request and SPRI submitted the required studies on September 12, 2002. As a result of this, pediatric exclusivity was granted on November 12, 2002 and this commitment is now completed.

III. INFORMATION CONCERNING THE COMMITMENT STUDY:

A. Essentials of the Study Design

1. Summary of the Study Sites (Geography, Number).

There are 103 RTOG investigative sites (US and Canada) and additional sites as part of the Intergroup network participating in this study which is identified as RTOG 98-13. See Attachment 3 for the geographic location of sites.

The initial Phase 1 safety study was conducted at the sites listed in Attachment 4.

2. Patient Population (Eligibility/Exclusion Criteria)

The Radiation Therapy Oncology Group (RTOG) Protocol 98-13 has been reviewed by the FDA on several occasions and in response to FDA guidance, has been amended three times. The date(s) entered between parentheses next to section headings refer to the dates of the protocol amendment.

Eligibility Criteria (8/17/01)

- The protocol defined eligible patient population consists of histologically-confirmed unifocal anaplastic astrocytoma as determined by central review, or mixed oligodendroglial/astrocytic tumors where the oligodendroglial component is less than 25% of the tumor mass. Patients with prior biopsy-proven low grade astrocytoma who now have a biopsy-proven anaplastic astrocytoma and have not been previously treated with either radiation or chemotherapy are eligible.
- Karnofsky performance status (KPS) $\geq$ 60.
- Adequate bone marrow reserve hemoglobin $\geq$10 grams, absolute neutrophil count $\geq$ 1500/mm^3, platelets $\geq$ 150,000mm^3; liver function tests (AST/SGOT, alkaline phosphatase, total bilirubin) <2 x upper limit of normal; serum creatinine <1.5 x normal.
- Therapy must begin within 5 weeks after tissue diagnosis.
- Diffusion Lung Capacity Oxygen (DLCO) $\geq$ 70%.
- Pre- and post-op contrast-enhanced Magnetic Resonance Imaging (MRI).
- If patient had only a stereotactic biopsy, then a post biopsy scan is not necessary.
- Patient must sign a study-specific informed consent form prior to randomization.

Exclusion Criteria (8/17/01, 2/18/02)

- Major medical illnesses or psychiatric impairments, which in the investigator's opinion will prevent administration or completion of the protocol therapy and /or interfere with follow-up.

- Any oligodendroglial component > 25%.
- Tumor predominately located in the posterior fossa *(i.e. brainstem or cerebellum).*
- Spinal cord tumors.
- Evidence of spinal drop metastases or spread to non-contiguous meninges *(MRI of the spine not required in asymptomatic patient; patients will not be excluded based on pathologic evidence of local meningeal infiltration by underlying tumor)*.
- Prior malignancy *(excluding in situ carcinoma of the cervix or non-melanomatous skin cancer)* unless disease free for at least 5 years.
- Prior radiation to the brain or head/neck.
- Prior chemotherapy.
- Active infectious process.
- Pregnant or nursing. The effects of protocol agents in the fetus are unknown.
- Inability or unwillingness to use effective contraception. This applies to both female and male patients.
- Known or suspected by hypersensitivity to one of the components of BCNU or temozolomide or to any other nitrosourea or Dacarbazine.

3. Endpoints (8/15/02)

- Overall Survival.
- Time to tumor progression.
- Relative toxicities of the two regimens.
- Correlate molecular analysis with overall survival and time to tumor progression.

4. Treatment Schema (8/15/02)

STRATIFY

Age
1. <50
2. ≥50

KPS
1. 60-80
2. 90-100

Surgery
1. Biopsy only
2. Resection

RANDOMIZE

Arm 1: Radiation Therapy: 59.4 Gy (*1.8 Gy x 33 fractions, 5 days a week x 6 weeks)* plus Temozolomide 200 mg/m^2 daily on days 1-5 of the first week of radiotherapy. Repeat Temozolomide every 28 days for a total of 12 cycles.

Arm 2: Radiation Therapy: 59.4 Gy (*1.8 Gy x 33 fractions, 5 days a week x 6 weeks*) plus BCNU (*80 mg/m^2*) on days 1, 2 and 3 of the first week of radiotherapy and on days 56, 57, and 58, then every eight weeks for four cycles for a total of six cycles (*maximum BCNU dose 1440 mg/m^2*).

The following 2 arms have been closed:
Pilot#1, Arm 4, 15 patients: Radiation Therapy: 59.4 *(1.8 Gy x 33 fractions, 5 days a week x 6 weeks*) plus BCNU 200 mg/ m2 on day 1 of radiotherapy and Temozolomide 150 mg/m2 on days 1-5 of the first

week of radiotherapy. Repeat every six weeks for a total of six cycles (*maximum BCNU dose 1200 mg/m^2*). *(closed 3/15/01)*

Pilot#2, Arm 5, 14 patients: Radiation Therapy: 59.4 *(1.8 Gy x 33 fractions, 5 days a week x 6 weeks*) plus BCNU 150 mg/m^2 on day 5 of radiotherapy and Temozolomide 150 mg/m^2 on days 1-5 of the first week of radiotherapy. Repeat every eight weeks for a total of six cycles; BCNU will be given on day 5 of Temozolomide in these cycles. *(maximum BCNU dose 900 mg/m^2). (closed 5/2/02)*

5. Efficacy and Safety Monitoring

In accordance with the protocol, the case report form is designed to capture data related to study efficacy endpoints (survival, time to progression) and relevant safety information. Patients are monitored for progression and survival every three months from study start for one year, then every 6 months for 2 years and thereafter annually.

The dates of death, recurrence or progression are completed in the case report forms.

Toxicities are captured monthly using the Common Toxicity Criteria (CTC) 2.0, and for each toxicity, severity grade and attribution is captured. For each toxicity ≥ grade 3, a date of onset, a description and treatment given is also captured.

The table below depicts the toxicities observed in the Phase 1 safety assessment of the BCNU/temozolomide doublet arms (arms 4 and 5 from the above schema).

	Pilot #1, Arm 4 (n=15) Grades					Pilot #2, Arm 5 (n=12) Grades				
	1	2	3	4	5	1	2	3	4	5
Auditory/Hearing	0	1	0	0	0	0	0	0	0	0
Blood/Bone Marrow	3	3	1	5	0	3	1	2	3	0
Thrombocytopenia	2	3	4	2	0	1	2	6	0	0
Cardiovascular (General)	0	0	0	0	1*	0	0	0	0	0
Constitutional Symptoms	5	4	0	0	0	1	1	0	0	0
Dermatology/Skin	4	4	1*	0	0	3	1	0	0	0
Gastrointestinal	5	4	0	0	0	4	1	0	0	0
Hepatic	4	1	0	0	0	1	0	0	0	0
Infection/Febrile Neutropenia	0	0	3	2	0	0	0	0	0	0
Metabolic/Laboratory	3	1	1	0	0	2	1	0	0	0
Musculoskeletal	0	1	0	0	0	0	0	0	0	0
Neurology	1	2	2*	0	0	1	0	0	0	0
Ocular/Visual	1	1	0	0	0	0	0	0	0	0
Pain	1	1	0	0	0	1	1	0	0	0
Pulmonary	1	3	1*	0	0	1	1	0	0	0
Renal/Genitourinary	4	0	0	0	0	0	0	0	0	0
Maximum Toxicity per Patient	0	5	3	5	1	3	1	4	3	0
Maximum Non-Hema Tox per Patient	1	6	4	2	1	5	3	0	0	0

*Case number	Arm	Toxicity	Grade	Most recent cycle of chemotherapy	Days from Start of RT
3	Pilot #1, Arm 4	Pulmonary: Dyspnea	3	1	28
7	Pilot #1, Arm 4	Dermatology: rash/desquamation	3	2	45
13	Pilot #1, Arm 4	Neurology: confusion	3	6	259
14	Pilot #1, Arm 4	Cardiovascular (General): thrombosis/embolism	5	2	Unk
15	Pilot #1, Arm 4	Neurology: vertigo	3	6	199

As per the second annual report by the RTOG, which was submitted to the FDA on July 11, 2002, there have been no IND safety reports issued by SPRI.

There were 8 deaths reported during the first year of the study. Seven deaths were attributed to disease. One death was a pulmonary embolism.

6. Statistical Design

- *Sample Size*

  The primary endpoint of RTOG 98-13 is survival. The standard arm is radiotherapy *(RT)* plus BCNU. The experimental arm is RT and temozolomide. Assuming that the Median Survival Time (MST) for RT+BCNU is 36 months and the RT and temozolomide arm has a MST of 54 months, then a sample size of 216 evaluable patients per arm will provide overall statistical power of 90% with a one-sided significance level of 0.05. Since it is expected that 5% of the patients will be ineligible, then a total of 454 randomized patients will be required. The primary analysis method will be Kaplan-Meier with a stratified log rank test.

  According to Scott et al.[59] and Curran et al.[9] [superscript numbers indicate references in the protocol] the recursive partitioning analysis (RPA) classes are prognostically important. Based upon eligibility criteria, patients may be in RPA classes I-IV which have decreasing estimated MST from 58.6 to 11.1. The distribution of patients by RPA class will affect the expected number of deaths during the study. It is assumed that 67% of the patients will be in class I, 25% in class III, and 8% in classes II and IV combined. If the percentage of RPA class II patients in the study sample is substantially higher than 25%, then the MST will be lower than 36 months, or if the percentage of RPA class I patients is higher than 75%, then the MST will be higher than 36 months. In either case the sample size may need to be adjusted. (8/17/01, 2/18/02)

- Phase 1 Arm *(8/17/01)*

  Initially, fifteen patients were accrued to the RT+temozolomide+BCNU arm and the specified number of dose limiting toxicities was not exceeded ($\geq$ 2 patients with grade $\geq$ 3 pulmonary toxicity or $\geq$ 5 patients with grade $\geq$ 4 thrombocytopenia or neutropenia). However, a sufficient number of patients had dose reductions resulting

in protocol changes, notably a reduction in the BCNU dose from 200mg/m^2 to 150mg/m^2. In addition, the eligibility criteria were also changed (patients with oligodendrogial/astrocytic tumors are eligible if the oligodendrogial component is less than 25%; pre-study liver and renal function limits added; eligible DLCO increased from ≥ 60% to ≥ 70%).

- Patient Accrual (Arm 5; 8/15/02)
  An additional 14 patients were accrued to assess further the combination of the RT+temozolomide+BCNU. The dose of temozolomide was 150 mg/m^2 p.o. daily on days 1-5 with BCNU 150 mg/m^2 i.v. on day 5. Accrual was suspended for 3 months to assess safety. Based on the high proportion of dose reductions seen and the toxicities encountered, the outcome of this safety assessment was that the phase 3 component of this study will consist only of Arms 1 and 2 (see Treatment Schema).
  An additional 454 patients are to be randomized to these two treatment arms discussed in Section 13.2 of the protocol.

- Randomization
  Patients are to be randomized according to a permuted block design, balancing by institution within strata. The randomization is stratified by age (*<50 vs ≥50*), KPS (*60-80 vs. 90-100*), and prior surgery (*resection vs. biopsy*). These stratification factors ensure balance by RPA classes as well.

- Analyses Plans

  Interim Analyses of Endpoints (8/15/02)
  Three interim analyses of the primary study endpoint (survival) are scheduled as per the following table:

Cumulative Events	Significance Level
63	0.0041
126	0.0158
188	0.0285

If a significance level is smaller than the H_0 values, then the null hypothesis will be rejected. These significance levels were calculated to ensure an overall significance level of 0.05. There will be two stochastic analyses: at 50% accrual and 75% accrual. If the stochastic analysis indicates less than 15% power to observe the alternative hypothesis, then the study will be recommended to be closed. The results of these interim analyses will only be reported in a blinded fashion to the RTOG Data Monitoring Committee *(DMC)*. A report with recommendations will be given to the

study chairman. Any problems or recommendations identified by the DMC, not results, will be reported to the Brain Committee, which is responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

Analysis for Reporting the Initial Treatment Results (8/15/02)

This analysis is planned at the point where all patients have been followed for a minimum of 36 months, or a maximum of 251 deaths have occurred. The anticipated components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;

b) reporting institutional accrual;

c) distribution of important prognostic baseline variables by treatment arms;

d) observed results with respect to the endpoints described in (need correct reference)

Survival (8/15/02)

Survival is the primary endpoint. RT+BCNU will be compared to RT+temozolomide. A significance level of 0.0405 (*one-sided*) will be used, adjusting for prior analyses. Analyses within RPA classes, or other prognostic groups, may be performed if there are sufficient numbers of patients.

Tumor Progression (8/15/02)

Time to tumor progression will be evaluated. Subgroup analyses within RPA classes, or other prognostic groups, selecting the best treatment, may be performed if there are sufficient numbers of patients.

Toxicity

Overall toxicity will be compared across treatments. The comparison will be performed using the Pearson chi-square test.

Molecular Analyses

Pathologic samples will be analyzed for chromosomes 1p and 19q and CDKN2A. The distribution of the outcome of molecular analyses will be examined by treatment arm to identify any imbalance. If there is no imbalance then the treatment arms will be collapsed and survival and time to tumor progression will be compared by the groups identified by Cairncross et al. These groups will also be correlated with other pretreatment characteristics.

B. Date of Initiation

Following protocol review and approval within RTOG and NCI, the Phase 1 component of the study was initiated June 16, 2000. Enrollment was suspended on March 15, 2001 for evaluation of the safety profile of the combination arm in this cohort. This evaluation was completed by RTOG in June 2001 and it was decided that additional safety data for the combination of BCNU/temozolomide was needed before commencing the Phase 3 study. An additional cohort of 15 patients was added to the Phase 1 plan. The Phase 1 study re-opened on August 17, 2001 and closed to enrollment on January 25, 2002.

The safety results from the two cohorts of Phase 1 did not support starting Phase 3 portion of the study with the combination arm. Consequently, the third arm (BCNU/temozolomide doublet) was dropped, the amended protocol submitted to the FDA on October 8, 2002 and the Phase 3 study was submitted to IRBs beginning on October 16, 2002. The Phase III portion of the study was initiated in January, 2003.

C. Accrual

The study completed accrual to initial cohort of the Phase 1 study (15 patients) on March 15, 2001 and the second cohort completed enrollment (14 patients) on January 25, 2002 whereupon enrollment was suspended. Following review of the safety data and the decision to drop the doublet arm, enrollment was opened to the Phase 3 portion of the study on January 10, 2003.

As of January 30, 2003, 5 patients have been accrued in the Phase 3 study. The total accrual is targeted to be 454 patients. The patient accrual was originally projected to be 12 cases per month based upon accrual rates to study RTOG 94-04. At this rate, it will take approximately 38 months to reach the required total accrual of 454 cases. Several initiatives are being taken to increase the accrual rate in order to decrease the time needed to achieve the target study size.

D. Estimated Timelines for Study Completion

At the time the Phase 3 study was designed, the anticipated patient accrual was 12 patients per month for 38 months. Based on the study status as of January 2003 the last patient would be enrolled in December 2006**.** If the accrual rate can be at least doubled through current initiatives, it is estimated that the last patient would be enrolled by the end of 2004. The primary endpoint of the study is survival and the presumed median survival time for the treated AA patient population is 36 months.

If the target of last patient enrollment by the end of 2004 is achieved, and the event rate occurs as predicted, an analysis of survival could be available by late 2007.

E. Estimated Timelines for Submission of Study Results

The final study protocol has scheduled interim analyses based on a prespecified number of events which may allow study results to be shared with the Agency in advanced of June 2007.

A report of the survival analysis, assuming the current initiatives to achieve accelerated enrollment are successful, may be available by late 2007.

IV. OTHER ISSUES:

A. Difficulties encountered in conduct/accrual/completion of trial

1. Changes in Medical Practice

Temozolomide is approved for patients with relapsed anaplastic astrocytoma (AA). There is no standard chemotherapy for the treatment of patients with newly diagnosed AA. However, from a survey of how temozolomide is being used in clinical practice in the United States, it appears that there is about equal use in recurrent AA and newly diagnosed AA. While it is impossible to precisely predict the effect of current clinical practice for AA on enrollment in the current RTOG study, the significant and growing use of temozolomide in first line treatment of AA may well be an impediment to accrual to this trial.

2. Natural History of the Disease

Patients diagnosed with anaplastic astrocytoma have a median survival of approximately 36 months. As a consequence, any randomized survival study in this population can be projected to require at least 3 years (and longer if temozolomide extends survival) after completion of enrollment to reach maturity. The current RTOG study with its targeted enrollment of 454 patients into two arms will be the largest randomized comparative study ever conducted for first line anaplastic astrocytoma. Given these circumstances, the original target of initiating and completing first a Phase 1-safety evaluation and then a phase III study within 7 years was ambitious at the outset. Furthermore, the necessity for a more extensive than envisaged safety evaluation of the combination of temozolomide and BCNU, and the resulting time required in this evaluation, make the June, 2007 deadline even more ambitious.

3. Safety Considerations

As noted, the need to conduct sequential safety assessments of the BCNU and temozolomide arms (Pilot #1, Arm 4, and Pilot #2, Arm 5), resulted in RTOG extending the Phase 1 segment of this study until January 2002. The outcome of this assessment led to the decision to discontinue one of the planned arms of the Phase 3 portion (BCNU/temozolomide plus radiation therapy) of the current study.

4. Timelines

As a result of the review the Phase 1 safety data before allowing initiation of Phase 3 (consistent with FDA guidance on the phase 4 commitment), the Phase 3 portion of this study was initiated in October, 2002.

The below table summarizes the key milestones.

Initiation first Phase 1 study	June 16, 2000
Completion of Accrual	March 14, 2001
Safety data sent to FDA	July 27, 2001
Initiation 2nd Phase 1 study	August 17, 2001
Completion of Accrual	January 25, 2002
Safety data sent to FDA	July 11, 2002
Revised Phase 3 protocol to FDA	October 8, 2002
Initiation of Phase 3	October 16, 2002
First Patient enrolled in Phase 3	January 10, 2003

Initiatives are being taken to increase accrual to the Phase 3 study to about twice the original estimates. Accordingly, it is estimated that the last patient could be enrolled by the end of 2004. If the target of last patient enrollment by the end of 2004 is achieved, an analysis of survival is anticipated by November of 2007. It would be possible to issue a summary report on survival by the end of 2007. The RTOG protocol has scheduled interim analysis, which may allow study results to be shared with the Agency prior to June of 2007.

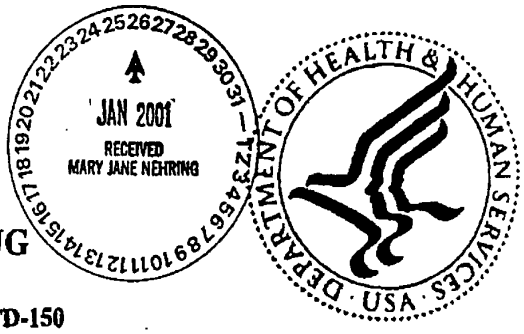
B. Other Applicant Concerns

Alternative Approaches

The sponsor would like to explore with the Agency possible alternative means to meet the post-approval commitment (confirmation of clinical benefit), foremost among them submission of the results of an EORTC randomized study in first line GBM comparing radiotherapy with temozolomide to radiotherapy alone.

Attachment 1

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Mary Jane Nehring	**From:** Sean Bradley
Fax: 908-740-2243	**Fax:** 310-827-4580
Phone: 908-740-6713	**Phone:** 301-594-5750
Pages, including cover sheet: 2	**Date:** January 26, 2001
Re: NDA 21-209, Post approval comments	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Please refer to your January 16, 2001 submission regarding your drug product Temodar® (temozolomide) Capsules.

Per your request, here are the post approval comments, which were included with the August 11, 1999 approval letter for Temodar Capsules.

Schering will conduct a study according to the following protocol:

"A phase I/III randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma". The statistical analysis plan for this study will be performed according to your submission dated July 19, 1999.

In addition, as agreed upon in your letter dated August 2, 1999, you will provide the Phase I/II safety data to support the dosing schedule in the combination arm of the trial and agree that initiation of the combination arm will be contingent on FDA approval to proceed. Furthermore,

Attachment 1 (cont)

you committed to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R.Ph.
Sean X. Bradley
Regulatory Project Manager

Attachment 2

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-029

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Mary Jane Nehring
Senior Director
Marketed Products Support

Dear Ms. Nehring:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Temodar (temozolomide) capsules.

We have received your submission dated May 9, 2001, regarding the following postmarketing study commitments.

1. A commitment for a Phase I/II randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma. The statistical analysis plan for this study will be performed according to firm's submission dated July 19, 1999.

   STATUS: Study ongoing; scheduled completion is June 30, 2007.

2. A commitment to provide the Phase I/II safety data to support the dosing schedule in the combination arm of the trial and agree that initiation of the combination arm will be contingent on FDA approval to proceed. Furthermore, the Firm commits to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason.

   STATUS: Study ongoing; scheduled completion is June 30, 2001.

3. Pediatric - 120 day commitment

   STATUS: FDA issued Pediatric Written Request January 25, 2001. Applicant requested revision on April 27, 2001; "granted" letter issued August 24, 2001.

Attachment 2 (cont)

Two studies ongoing (I93-125 and CCGA09701); scheduled completion is June 29, 2001.

If you have any questions, call Sean Bradley, Project Manager, at (301) 594-5750.

Sincerely, /s/

{See appe Richard Pazdur
8/30/01 04:31:01 PM

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment 3: Geographic location of sites (Study 98-13)

Group Name	City	State/Country
Kansas City CCOP	Kansas City	MO
Virginia Mason Medical Center	Seattle	WA
West Michigan Cancer Center CCOP	Kalamazoo	MI
Metro-MN CCOP	Minneapolis	MN
Cancer Research for the Ozarks	Springfield	MO
Mt. Sinai Comprehensive Cancer Center CCOP	Miami	FL
Mayo Clinic	Rochester	MN
Oncology Institute of Greater Lafayette	Lafayette	LA
The Wendt Regional Cancer Center of the Finley Hospital	Dubuque	IA
Yakima Valley Memorial Hosp	Yakima	WA
Providence Cancer Therapy Center	Anchorage	AK
Sutter Health Western Division Cancer Research Group	Greenbrae	CA
Peninsula Hospital & Medical Center	Burlingame	CA
University of Rochester	Rochester	NY
Finger Lakes Radiation Oncology PC	Clifton Springs	NY
University of Kentucky Hospital	Lexington	KY
Southeast Cancer Control Consortium, Inc. CCOP	Winston-Salem	NC
Thomas Jefferson University Hospital	Philadelphia	PA
Lutheran General Hospital	Park Ridge	IL
University of Wisconsin Hospital	Madison	WI
Marshfield Clinic	Marshfield	WI
Columbia Hospital-St. Mary's	Milwaukee	WI
Virtua Memorial Hospital Burlington County	Mount Holly	NJ
Halifax Hospital ROC	Dayton Beach	FL
McGill University	Montreal	Canada
Notre Dame Hospital/University of Montreal	Montreal	Canada
Wyoming Valley Health Care System - Hospital	Wilkes Barre	PA
Montefiore Medical Center	Bronx	NY
Akron City Hospital	Akron	OH
Emory University Affiliated Hospitals	Atlanta	GA
Beth Israel Medical Center	New York	NY
21st Century Oncology, Inc.	Ft. Myers	FL
University of Louisville	Louisville	KY
Vanderbilt University Medical Center	Nashville	TN
University of Miami	Miami	FL
Washington University	St. Louis	MO
University of Alabama at Birmingham Medical Center	Birmingham	AL
University of Cincinnati	Cincinnati	OH
St Louis University Hospitals	St. Louis	MO
Upstate Carolina CCOP	Spartansburg	SC
McLaren Regional Cancer Center	Flint	MI
University Hospitals of Cleveland	Cleveland	OH
Fox Chase Cancer Center	Philadelphia	PA
Mercy Hospital	Scranton	PA
Florida Radiation Oncology Group	Jacksonville	FL
St Mary Regional Cancer Center	Langhorne	PA
Reading Hospital and Medical Center	Reading	PA
Delaware County Memorial Hospital	Drexel Hill	PA
St. Elizabeth Medical Center	Edgewood	KY
South Jersey Hospital Systems	Camden	NJ
Monmouth Medical Center	Long Branch	NJ

Group Name	City	State/Country
University of California San Francisco	San Francisco	CA
University of California Davis Medical Center	Sacramento	CA
Mt. Diablo Medical Center	Concord	CA
Joe Arrington Cancer Research & Treatment Center	Lubbock	TX
LDS Hospital	Salt Lake City	UT
Foundation for Cancer Research and Education	Phoenix	AZ
Dixie Medical Cancer Center	East St. George	UT
Memorial Hospital	Colorado Springs	CO
Northwest Community Clinical Oncology Program	Tacoma	WA
John F Kennedy Medical Center	Edison	NJ
Albert Einstein Medical Center	Philadelphia	PA
Wake Forest University Baptist Medical Center	Winston-Salem	NC
Ingalls Memorial Hospital	Harvey	IL
Central Illinois CCOP	Decatur	IL
The Schiffler Cancer Center	Wheeling	WV
Lehigh Valley Hospital	Allentown	PA
Anne Arundel Medical Center	Annapolis	MD
University of Texas-MD Anderson Cancer Center	Houston	TX
Gulf Coast MBCCOP	Mobile	AL
St. Anthony Cancer Care Institute at St. Anthony Hospital	Oklahoma City	OK
The Christ Hospital	Cincinnati	OH
MD Anderson Cancer Center - Orlando	Orlando	FL
Mary Bird Perkins Cancer Center	Baton Rouge	LA
Cleveland Clinic Foundation	Cleveland	OH
Natalie Warren Bryant Cancer Center at St. Francis Hospital	Tulsa	OK
University of Texas Medical Branch	Galveston	TX
Medical College of Wisconsin	Milwaukee	WI
Community Memorial Hospital	Menomoee Falls	WI
Gunderson Clinic	Lacrosse	WI
Methodist Cancer Center	Omaha	NE
Western Pennsylvania Hospital	Pittsburgh	PA
St. Vincent Regional Cancer Center CCOP	Green Bay	WI
Cross Cancer Institute - University of Alberta	Alberta	Canada
Henry Ford Hospital	Detroit	MI
Wayne State University	Detroit	MI
Northwest Community Hospital	Arlington Heights	IL
Michigan Cancer Research Consortium CCOP	Ann Arbor	MI
University of Utah Health Science Center	Salt Lake City	UT
Green Mountain Oncology Group	Bennington	VT
University of South Alabama Cancer Center CCOP	Mobile	AL
Dartmouth Hitchcock Medical Center	Hanover	NH
Baptist Hospital of Miami	Miami	FL
Christiana Care Health Services, Inc.	Christiana	DE
Dayton CCOP	Dayton	OH
Bay Area Tumor Institute CCOP	Oakland	CA
University of Western Ontario	London, Ontario	Canada
Alta Bates Hospital Comprehensive Cancer Center	Oakland	CA
California Pacific Medical Center	San Francisco	CA
Cancer Care Center, Inc	Salem	OH
Mayo Radiation Oncology Center	Jacksonville	FL
Cancer Treatment Center	Wooster	OH
Cottonwood Hospital	Murray	UT

Attachment 4: Sites participating in the safety assessment (Study 98-13)

Group Name	City	State
Kansas City CCOP	Kansas City	MO
Metro-MN CCOP	Minneapolis	MN
Cancer Research for the Ozarks	Springfield	MO
Southeast Cancer Control Consortium, Inc. CCOP	Winston-Salem	NC
Thomas Jefferson University Hospital	Philadelphia	PA
Lutheran General Hospital	Park Ridge	IL
Rochester General Hospital	Rochester	NY
University of Wisconsin Hospital	Madison	WI
Vanderbilt University Medical Center	Nashville	TN
University of California Davis Medical Center	Sacramento	CA
Joe Arrington Cancer Research & Treatment Center	Lubbock	TX
Foundation for Cancer Research and Education	Phoenix	AZ
Dixie Medical Cancer Center	East St. George	UT
Wake Forest University Baptist Medical Center	Winston-Salem	NC
Ingalls Memorial Hospital	Harvey	IL
Central Illinois CCOP	Decatur	IL
Cleveland Clinic Foundation	Cleveland	OH
Natalie Warren Bryant Cancer Center at St. Francis Hospital	Tulsa	OK
University of Texas Medical Branch	Galveston	TX
University of Utah Health Science Center	Salt Lake City	UT
Dayton CCOP	Dayton	OH