CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21029

STATISTICAL REVIEW(S)

Mr. Gunn

Statistical Review and Evaluation

DEC 1 1 1998

NDA#: 21-029

Applicant: Schering Corporation

Name of Drug: Temozolomide (TMZ) Capsules

Indication: Treatment of adult patients with anaplastic astrocytoma at first relapse

Document Reviewed: Vol. 245-259, Submission received on 09-17-1998

Medical Officer: Martin Cohen, M.D.

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I. BACKGROUND

Temozolomide (TMZ) is an alkylating agent. It is rapidly and completely absorbed following oral administration and undergoes spontaneous hydrolysis at physiologic pH to its active metabolite, MTIC. The cytotoxicity of MTIC is thought to be due to alkylation at the O 6 position of guanine with additional alkylation at the N 7 position. Study C/I94-123 was conducted to evaluate the efficacy and safety of temozolomide in patients with anaplastic astrocytoma at first relapse.

In this NDA, the sponsor seeks approval of Temozolomide (TMZ) in the indication of *treatment of adult patients with anaplastic astrocytoma at first relapse.*

The study submitted in this application is a single arm (uncontrolled), prospective, multicenter, open-label, phase II trial. This review will focus on the efficacy aspect of the study.

II. BRIEF DESCRIPTION OF STUDY

Study C/I94-123 is a single arm (uncontrolled), prospective, multicenter, open-label, phase II trial in treatment of patients with anaplastic astrocytoma (AA) at first relapse.

Progression-free survival at 6 month was used as the primary efficacy endpoint, as stated in the protocol. Secondary efficacy endpoints were overall survival and health related quality of life. The study was conducted in 32 participating centers.

A total of 162 patients were enrolled and 4 patients did not receive the study medication. All 162 patients were followed-up for a minimum of 6 months and were included in efficacy analyses. The sample size was determined by assuming that the true progression-free survival at 6 months for temozolomide is 20%. With sample size of 100, it will assured that the lower boundary of the 95% confidence interval for 6 month progression-free survival would remain above 10%.

The protocol specified primary efficacy analysis was based on progression-free survival. Progression-free survival included only progressive disease and death as an event and was measured from the date of treatment start to the date of an event (progressive disease or death) or last evaluation whichever was earlier. Overall survival was a secondary efficacy variable and was measured from the date of treatment start to the date of death or last follow-up.

III. SUMMARY OF EFFICACY RESULTS AND COMMENTS

This section will summarize the results of the intention to treat analysis for study C/I94-123. The intention to treat patient population included all patients (n=162) who were enrolled during the enrollment period.

Baseline Characteristics

The baseline demographic characteristics including age, race, gender and performance status were shown on appendix Table 1a. (sponsor's Table 9). The baseline tumor characteristics, including surgery at initial diagnosis, prior radiation or chemotherapy were also summarized by the sponsor.

Table 1. Patient's Baseline Characteristics

Baseline Disease Characteristics and Prior Therapies	Number (%) of Patients (N=162)
Surgery at Initial Diagnosis	
No	52 (32.1%)
Yes	110 (67.9)
Extent of Surgery at Initial Diagnosis	
Subtotal Resection	67 (41.4%)
Gross Total Resection	43 (26.5%)
Prior Radiation Therapy	162 (100.0%)
Time from End of Radiation Therapy to First Relapse	
<3 months	20 (12.3%)
3-6 months	40 (24.7%)
>6-9 months	10 (6.2%)
>9-12 months	10 (6.2%)
>12-18 months	20 (12.3%)
>18-24 months	14 (8.6%)
>24-36 months	18 (11.1%)
>36-48 months	11 (6.8%)
>48 months	19 (11.7%)
Median	12.1
Range	0.8-116.6
Prior Chemotherapy	
Yes	97 (59.9%)
No	65 (40.1%)
Time from Initial Diagnosis to First Relapse	
3 - 6 months	27 (16.7%)
>6 -9 months	32 (19.8%)
>9 -12 months	10 (6.2%)
>12-18 months	23 (14.2%)
>18-24 months	16 (9.9%)
>24-36 months	18 (11.1%)
>36-48 months	15 (9.3%)
>48 months	21 (13.0%)
Median	15.2
Range	3.1-122.3
Surgery at First Relapse	
No	132 (81.5%)
Yes	30 (18.5%)
Surgery at First Relapse	
Subtotal Resection	25 (15.4%)
Gross Total Resection	5 (3.1%)
Time from Surgery at First Relapse to Study Drug	
<1 month	12 (7.4%)
1-2 months	10 (6.2%)
>2-3 months	4 (2.5%)
>3-6 months	2 (1.2%)
>6 months	2 (1.2%)
Median	1.1
Range	0.3-15.8

Primary Efficacy Endpoint

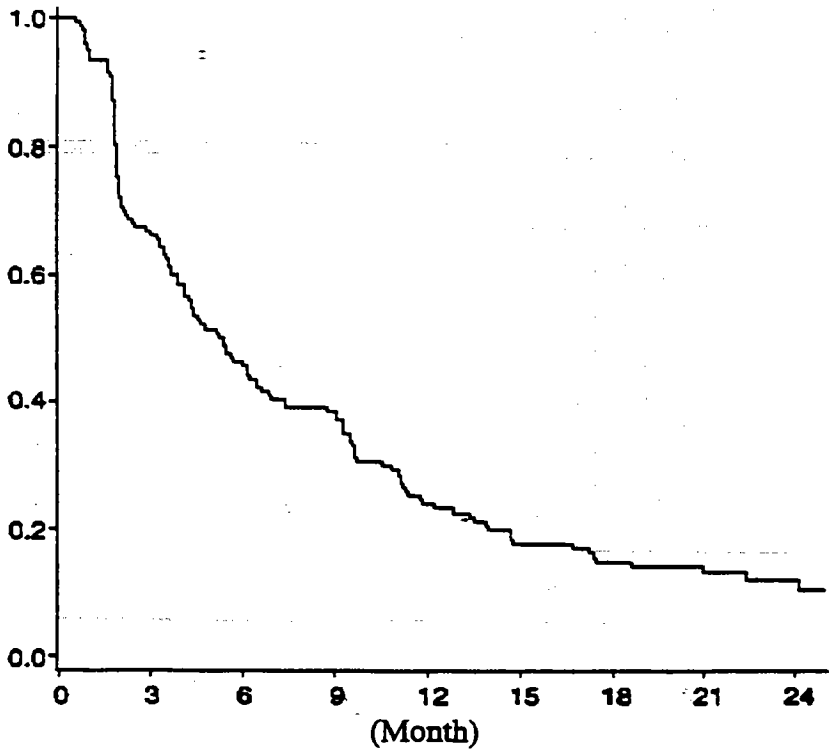
The primary efficacy endpoint for the study was the progression-free survival (PFS) at 6 month. The sponsor specified in the protocol that the efficacy threshold was 10% in terms of the 6 month progression-free survival. Secondary efficacy endpoints were the overall survival and health related quality of life.

The sponsor's results for the primary endpoint are summarized in Table 2. Figure 1 is the Kaplan-Meier curve for the study.

Table 2. Sponsor's Analysis for Progression Free Survival

ITT Population	Progressed Patients at 6 Month	PFS at 6 Month (%)	Median PFS (Month)	95% CI for Median PFS (Month)
n=162	84(51.9%)	46% (95% CI: 38%-54%)	5.43	4.14-6.64

Figure 1. Progression Free Survival



Reviewer's Comments:

1). The primary endpoint, progression free survival at 6 month, is 46% (95% CI: 38%-54%), which met the protocol objective (above 10%).

2). Given the uncontrolled nature of the study, the definitive conclusion can only be based on clinical judgment.

Secondary Efficacy Endpoints

Secondary efficacy endpoints were the overall survival, objective response rate and health related quality of life.

The results in Reviewer's Table 2 and Table 3 are based on the sponsor's analyses using the definitions described in the final medical report for these secondary endpoints.

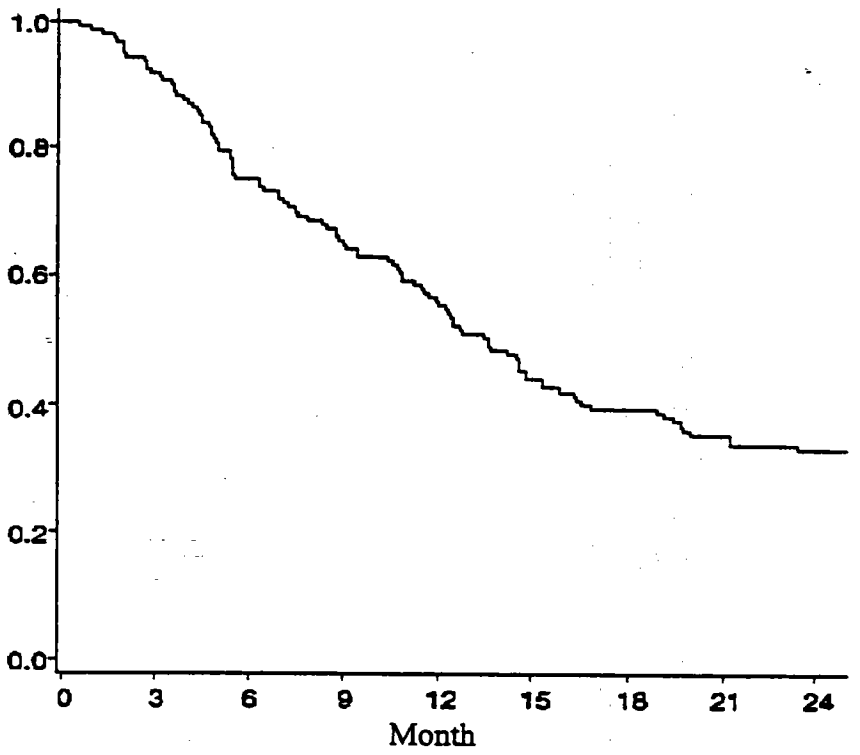
1. Overall Survival:

The sponsor's results for the overall survival are summarized in Table 3. Figure 2 is the Kaplan-Meier curve for the study.

Table 3. Sponsor's Analysis for Overall Survival

ITT Population	6 Month Survival Rate (95% CI)	12 Month Survival Rate (95% CI)	Median Survival Time (Month)	95% CI for Median Survival (Month)
n=162	75% (68-82%)	56.1% (48-64%)	13.58	11.58-15.86

Figure 2. Survival Curve for Study c/I94-123



2. Objective Response Rate:

The objective response (by neuroimaging) was defined as follow:

For measurable lesions,

Complete response (CR): Disappearance of all enhancing tumor.
Partial response (PR): .50% reduction in the sum of the products of the largest perpendicular diameters of contrast enhancement for all lesions; no new lesions.
Progressive Disease (PD): .25% increase in the product of the largest perpendicular diameters of contrast enhancement of any lesion or any new enhancing tumor.
Stable Disease (SD): All other situations.

For Non-measurable lesions:

Complete Response (CR): No enhancing tumor.

Partial Response (PR): Definitely better.
Stable Disease (SD): Possibly better or unchanged or possibly worse.
Progressive Disease (PD): Definitely worse.

Table 4 summarizes the results based on the sponsor's assessment.

Table 4. Objective Response: Sponsor's Assessment

Response Type	Number of Patients (n=162)	%
CR	13	8%
PR	44	27%
SD	44	27%
PD	61	38%

Reviewer's Comments:

1). Total number of response (CR+PR) was 35%. Due to the uncontrolled natural of the study, no definite conclusion can be made.

2). The objective response was not listed as the objective of this study.

3. Health Related Quality of Life (HQL)

HQL data were collected and the QLQ-C30 scoring method was used. In addition, an analysis of change from baseline was performed for patients who were progression free at 6 months. However, since the number of patients in the study was small, inferential statistical analyses were not performed for the HQL data. The sponsor claimed that the HQL results "showed maintenance if not notable improvement in the majority of HQL domain scores".

Reviewer's Comments:

1). Due to the uncontrolled natural of the study, claims regarding the HQL data are open to question.

2). Since missing data in the baseline measurement and the sample size for the study was small, no formal inferential statistical analyses can be undertaken for the HQL data. Any claims for "improvement" based on descriptive results should be interpreted with caution.

IV. CONCLUSIONS

The primary endpoint, progression free survival, is 46% (95% CI: 38%-54%), which met the protocol objective (lower limit of 95% CI > 10%). However, due to the uncontrolled natural of the study and the relative small sample size, no formal statistical testing can be conducted. Therefore, any claims of "improvement" or "no significant changes" need to be made cautiously. The definitive conclusion should only be based on clinical judgment.

/S/

Ning Li
Biostatistician

Concur:

/S/ 12/10/98

Dr. Chen

Dr. Chi /S/
12/11/98

cc:
Archival: NDA21-029
HFD-150/Dr. Williams
HFD-150/Dr. Cohen
HFD-150/Dr. Justice
HFD-150/Ms. Vaccari
HFD-150/Mr. Guinn, Project Manager
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Li
HFD-710/chron

This review consists of 9 pages of text.

LI/12/10/98 MSWD "C:/DATA/WORDFILES/NDA21029e1.DOC".

Statistical Review and Evaluation

JUL 19 1999

NDA#: 21-~~209~~ 029
Applicant: Schering Corporation
Name of Drug: Temozolomide
Indication: Newly Diagnosed Anaplastic Astrcytoma
Medical Officer: Martin Cohen, M.D.

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This review evaluates the sponsor's phase IV protocol entitled "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".

Study Design: This is a randomized, three arm phase I/III trial compare single agent BCNU, standard treatment for anaplastic astrocytoma, to both single agent Temozolomide and the combination of Temozolomide and BCNU.
Primary Objective: To provide an answer to which drug regimen might prolong overall survival.
Primary Endpoint: Overall Survival
Secondary Endpoint: Time to tumor progression, toxicity and molecular analysis
Sample Size Calculation: Assuming that the median survival time (MST) for RT+BCNU is 36 months and the best experimental arm has a MST of 54 months then a sample size of 156 evaluable patients per arm will provide overall statistical power of 85% with a one-sided significance level of 0.025 (with 36 months of accrual, 36 months of follow-up and a ratio of 1.272). Since it is expected that 5% of patients will be ineligible then a total of 492 patients will be required. The sample size may be adjusted based on the distribution of patients by RPA class.
Randomization: The randomization will be stratified by age (<50 vs. >50), KPS (60-80 vs. 90-100), and prior surgery (resection vs. biopsy). These stratification factors will ensure balance by RPA classes as well.
Analysis Plan: Survival will be analyzed using the method suggested by Chen and Simon (1994). RT+BCNU will be compared to RT+Tem. If the logrank does not surpass 0.05 then the arm with the best MST will be selected. The best arm will be compared to RT+Tem+BCNU.
Interim Analysis: Three interim analyses will be performed for survival endpoint. The stopping rules proposed by Hughes (1993) will be used.

Statistical Comments:

- Since the purpose of the study is to investigate which drug regimen might prolong overall survival, if one of the two Tem regimens demonstrates significant survival benefit, the sponsor may make conclusion. Therefore, an appropriate adjustment for multiplicity is needed.
- The duration of survival should be calculated from the date of randomization instead of initiation of treatment.

- All patients as randomized (ITT population) should be included in the survival analysis.
- Since the sample size may be adjusted based on the distribution of patients by RPA class, the sponsor needs to clarify when such a sample size reevaluation will be performed and whether the type I or type II error needs to be adjusted because of the sample size adjustification.
- The primary analysis for survival needs to be specified in the protocol (logrank or stratified logrank test).
- Results of analyses within RPA classes, or other prognostic groups should be considered as exploratory.
- Please submit the reference by Chen and Simon (1994).

/S/

Gang Chen, Ph.D.
Statistical Team Leader

Concur: Dr. Chi /S/

Cc:

Archival NDA 21-209
HFD-150/Dr. Cohen
HFD-150/Dr. Johnson
HFD-150/Mr. Guinn
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Chron

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21029

MICROBIOLOGY REVIEW(S)

P. Guinn

REVIEW FOR HFD-150

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 21-029
December 1, 1998

DEC 16 1998

A. 1. **APPLICATION NUMBER:** NDA 21-029

APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 740-2628

2. **PRODUCT NAME:** Temodal™

3. **DOSAGE FORM:** Temozolomide (5, 20, 100, and 250 mg) immediate release oral dosage capsules.

4. **METHOD OF STERILIZATION:** None (non-sterile product).

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** The proposed indication is for malignant glioma at first relapse and advanced metastatic melanoma.

6. **DRUG PRIORITY CLASSIFICATION:** P

B. 1. **DATE OF INITIAL SUBMISSION:** August 13, 1998

2. **DATE OF CONSULT:** September 19, 1998

3. **RELATED DOCUMENTS:** (none)

4. **ASSIGNED FOR REVIEW:** September 30, 1998

C. **REMARKS:** The consult request is for review of the microbiological specifications of the drug product. This review also considers the microbiology aspects of the proposed stability protocol.

D. CONCLUSIONS:

The application is recommended for approval for issues concerning microbial limits testing and acceptance criteria for the drug products.

/S/ 12/1/98
Neal Sweeney, Ph.D.

PAC 12/16/98

cc:
Original NDA 21-029
HFD-150/ Division File
HFD-150/L Zhou/C Liang/P Guinn
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, December 1, 1998
R/D initialed by P. Cooney December 1, 1998