10.11 Relapsed Glioblastoma Multiforme Trials

Table 64 Literature- Relapsed GBM per FDA

	Patient Characteristics			Endpoints				
GM # of Pts	Age Median	P.S. Karnof or ECOG Median	Prior Chemo (%)	GM CR+PR (%)	GM Median Survival (w)	GM Median Progr Free Surv(w)	Reference (yr)	Drug
24	50*	3*	58*	8	23*	-	1 (91)	Acivicin
15	40	>80	0	7	31+	-	2 (91)	CBDCA
17	49	1	33	52	20	14	3 (90)	NM,Vcr, Pcz
5	40-60	0-1	0	0	-	-	4 (95)	Ifn,BCNU
8	35	75	100	12	-	-	5 (95)	Taxol
13	43	80	14	-	41	-	6 (91)	Hyperther
21	39	0-2	0	-	28	-	7 (92)	BCNU ia Vcr,Pcz
31	42	80	37	7	33	13	8 (94)	6 drugs
12	41	67	100	-	-	-	9 (90)	Pcz
72	48	77	53	-	66% @ 26 weeks	-	10 (95)	Gliadel
73	47	86	48	-	36% @ 26 weeks	-	10 (95)	Gliadel control
17	47	86	100	2	35	12	11 (94)	CBDCA
29	48	65	83	-	17	-	12 (92)	Tam
6	38	60	18	33	26	-	13 (93)	Tam
37	39	82	43	-		31*	14 (92)	8 drugs
37	37	70	96	14	-	30	15 (89)	Pcz
23	49	1	50	4	19	11	NCCG (98)	CBDCA
112	**52**	**80**	**74**	**5§**	**32**	**13**	**C94-091**	**TMZ**
138	**54**	**80**	**34**	**6§**	**23**	**9**	**I94122**	**TMZ**
113	**51**	**80**	**70**	**3§**	**25**	**9**	**C94091**	**PCZ**

Continued on next page

	Patient Characteristics			Endpoints				
GM # of Pts	Age Median	P.S. Karnof or ECOG Median	Prior Chemo (%)	GM CR+PR (%)	GM Median Survival (w)	GM Median Progr Free Surv(w)	Reference (yr)	Drug
5	42*	1*	65*	0	-	-	16 (96)	Taxol
20	47	80	46	2	40	-	17 (97)	Crisnatol
42	48	67	-	-	44	-	18 (90)	Autol. Lymphs
14	48	70	42	14	32	18	19 (97)	CBDCA Ia (97)
47	45	90	-	13	27	11	20 (97)	BCNU Fluosol
13	53	70	100	8	20	-	21 (93)	Pcz, Vcr, Thio
10	49	60	100	0	26	26*	22 (91)	CBDCA
6	53	-	33	0	17	9	23 (97)	ATRA ± Ara C
14	49	70-80	-	13*	25	16	24 (97)	ATRA
8	41	85	100	0	30	-	25 (98)	Tam-Ifn
15	48	1	94	7	-	-	26 (96)	Topo
6	43	70	56	33	26	-	27 (92)	ACNU ia
26	55	70	0	12	26	-	28 (98)	DBD, BCNU, Pcz
112	**52**	**80**	**74**	**5§**	**32**	**13**	**C94-091**	**TMZ**
138	**54**	**80**	**34**	**6§**	**23**	**9**	**I94122**	**TMZ**
113	**51**	**80**	**70**	**3§**	**25**	**9**	**C94091**	**PCZ**

* = Approximate values as they summarize all study patients.

§ = Stricter response criteria than other studies. Required two consecutive determinations (2 month time span).

ATRA = all trans retinoic acid, CBDCA = carboplatin, DBD = dibromodulcitol, Hyperther = hyperthermia, ia = intraarterial, Ifn = interferon, Pcz = Procarbazine, Tam = tamoxifen, TMZ = temozolomide, Topo = topotecan, Vcr = vincristine

10.12 Relapsed Anaplastic Astrocytoma Trials

Table 65 Literature - Relapsed AA per FDA

	Patient Characteristics			Endpoints				
AA # of Pts	Age Median	P.S. Karnof or ECOG Median	Prior Chemo (%)	AA CR+PR (%)	AA Median Survival (w)	AA Median Progr Free Surv(w)	Reference (yr)	Drug
8	50*	3*	58*	25	23*	-	1 (91)	Acivicin
14	40	>80	0	21	32+	-	2 (91)	CBDCA
6	49	1	33	100	81	55	3 (90)	NM,Vcr, Pcz
10	40-60	0-1	0	20	-	-	4 (95)	Ifn,BCNU
123	35	75	100	25	-	-	5 (95)	Taxol
10	43	80	14	-	71+	-	6 (91)	Hyperther
9	39	0-2	0	-	87	-	7 (92)	BCNU ia Vcr,Pcz
20	42	80	37	5	79	32	8 (94)	6 drugs
16	41	67	100	-	-	-	9 (90)	Pcz
11	47	86	100	28	46	18	11 (94)	CBDCA
3	48	65	83	-	17*	-	12 (92)	Tam
5	38	60	18	20	35	-	13 (93)	Tam
38	39	82	43	-	-	50*	14 (92)	8 drugs
46	37	70	96	15	-	49	15 (89)	Pcz
17	49	1	50	18	53	16	NCCG (98)	CBDCA
164	42	80	62	33§	59	23.4	C/I94-123	TMZ

Continued on next page

	Patient Characteristics			Endpoints				
AA # of Pts	Age Median	P.S. Karnof or ECOG Median	Prior Chemo (%)	AA CR+PR (%)	AA Median Survival (w)	AA Median Progr Free Surv(w)	Study (yr)	Drug
12	42*	1*	65*	0	-	-	16 (96)	Taxol
6	47	80	46	23	40*	-	17 (97)	Crisnatol
33	48	67	-	-	88	-	18 (90)	Autol. Lymphs
5	48	70	42	20	96+	86	19 (97)	CBDCA Ia (97)
47	45	90	-	25	41	32	20 (97)	BCNU Fluosol
7	53	70	100	29	20*	-	21 (93)	Pcz, Vcr, Thio
9	49	60	100	22	26*	26*	22 (91)	CBDCA
3	53	-	33	33	65	52	23 (97)	ATRA ± Ara C
14	49	70-80	-	13*	25*	16*	24 (97)	ATRA
5	41	85	100	0	26	-	25 (98)	Tam-Ifn
16	48	1	94	6	-	-	26 (96)	Topo
12	43	70	56	50	52	-	27 (92)	ACNU ia
11	56	70	0	55	44*	-	28 (98)	DBD, Pcz, BCNU
164	**42**	**80**	**62**	**33§**	**59**	**23.4**	**C/I94-123**	**TMZ**

* = Approximate values as they summarize all study patients.

§ = Stricter response criteria than other studies. Required two consecutive determinations (2 month time span).

ATRA = all trans retinoic acid, CBDCA = carboplatin, DBD = dibromodulcitol, Hyperther = hyperthermia, ia = intraarterial, Ifn = interferon, NM = nitrogen mustard, Pcz = Procarbazine, Tam = tamoxifen, TMZ = temozolomide, Topo = topotecan, Vcr = vincristine

10.13 References

1. Taylor SA, Crowley J, Pollock TW, et al. Objective antitumor activity of Acivicin in patients with recurrent CNS malignancies. A SWOG trial. J Clin Oncol 1991;9:1476-9.

2. Yung WKA, Mechtler L, Gleason MJ. Intravenous carboplatin for recurrent malignant glioma. A phase II study. J Clin Oncol 1991;9:860-4.

3. Coyle T, Baptista J, Winfield J, et al. Mechlorethamine, vincristine and procarbazine chemotherapy for recurrent high-grade glioma in adults: A phase II study. J Clin Oncol 1990;8:2014-8.

4. Buckner JC, Brown LD, Kugler JW, et al. Phase II evaluation of recombinant interferon alpha and BCNU in recurrent glioma. J Neurosurg 199;82:430-5.

5. Chamberlain MC, Kormanik P. Salvage chemotherapy with paclitaxel for recurrent primary brain tumors. J Clin Oncol 1995;13:2066-71.

6. Sneed PK, Stauffer PR, Gutin PH, et al. Interstitial irradiation and hyperthermia for the treatment of recurrent malignant brain tumors. Neurosurgery 1991:28:206-15.

7. Watne K, Hannisdal E, Nome O, et al. Combined intra-arterial and systemic chemotherapy for recurrent malignant brain tumors. Neurosurgery 1992;30:223-7.

8. Rostomily RC, Spence AM, Duong D, et al. Multimodality management of recurrent adult malignant gliomas: Results of a phase II multiagent chemotherapy study and analysis of cytoreductive surgery. Neurosurgery 1994;35:378-88.

9. Newton HB, Junck L, Bromberg J, et al. Procarbazine chemotherapy in the treatment of recurrent malignant astrocytomas after radiation and nitrosourea failure. Neurology 1990;40:1743-6.

10. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. Lancet 1995;345:1008-12.

11. Warnick RE, Prados MD, Mack EE, et al. A phaseII study of intravenous carboplatin for the treatment of recurrent gliomas. J Neuro-Oncol 1994;19:69-74.

12. Vertosick FT, Selker RG, Pollack IF, Arena V. The treatment of intracranial malignant gliomas using orally administered tamoxifen therapy. Preliminary results in a series of "failed" patients. Neurosurgery 1992;30:897-903.

13. Couldwell WT, Weiss MH, DeGiorgio CM, et al. Clinical and radiographic response in a minority of patients treated with high dose tamoxifen. Neurosurgery 1993;32:485-90.

14. Levin VA, Prados MD. Treatment of recurrent gliomas and metastatic brain tumors with a polydrug protocol designed to combat nitrosourea resistance. J Clin Oncol 1992;10:766-71.

15. Rodriguez LA, Prados M, Silver P, Levin VA. Reevaluation of procarbazine for the treatment of recurrent malignant central nervous system tumors. Cancer 1989;64:2420-3.

16. Forsyth P, Cairncross G, Stewart D, et al. Phase II trial of docetaxel in patients with recurrent malignant glioma: a study of the NCI-C clinical trials group. Invest New Drugs 1996;14:203-6.

17. New P, Vokes E, Rogers L, et al. Long-term response to crisnatol mesylate in patients with glioma. Invest New Drugs 1997;15:343-52.

18. Ingram M, Buckwalter JG, Jacques DB, et al.Immunotherapy for recurrent malignant glioma: an interim report on survival Neurological Res 1990;12:265-73.

19. Cloughesy TF, Gobin YP, Black KL, et al. Intra-arterial carboplatin chemotherapy for brain tumors: A dose escalation study based on cerebral blood flow. J NeuroOncol 1997;35:121-31.

20. Hochberg f, Prados M, Russell C, et al. Treatment of recurrent malignant glioma with BCNU-fluosol and oxygen inhalation. A phase I-II study. J Neurooncol 1997;32:45-55.

21. Ameri A, Poisson M, Chen QM, Delattre JY. Treatment of recurrent malignant supratentorial gliomas with the association of procarbazine, thiotepa, and vincristine: a phase II study. J Neurooncol 1993;17:43-6.

22. Poisson M, Pereon Y, Chiras J, Delattre JY. Treatment of recurrent supratentorial gliomas with carboplatin (CBDCA). J Neurooncol 1991;10:139-144.

23. Defer GL, Adle-Biassette H, Ricolfi F, et al All transretinoic acid in relapsing malignant gliomas: clinical and radiological stabilization associated with the appearance of intratumoral calcifications. J Neurooncol 1997;34:169-177.

24. Phuphanich S, Scott C, Fishbach AJ, et al. All-trans-retinoic acid; a phase II RTOG study (RTOG 91-13) in patients with recurrent malignant astrocytoma. J Neurooncol 1997;34:193-200.

25. Chang SM, Barker FG 2nd, Huhn SL, et al. High dose oral tamoxifen and subcutaneous interferon alpha-2a for recurrent glioma. J Neurooncol 1998;37:169-176.

26. Macdonald D, Cairncross G, Stewart D, et al. Phase II study of topotecan in patients with recurrent malignant glioma. Annals Oncol 1996;7:205-7.

27. Vega F, Davila L, Chatellier G, et al. Treatment of malignant gliomas with surgery, intraarterial chemotherapy with ACNU and radiation therapy. J Neurooncol 1992;13:131-135.

28. Hildebrand J, De Witte O, Sahmoud T. Response of recurrent glioblastoma and anaplastic astrocytoma to dibromodulcitol, BCNU and procarbazine. J Neurooncol 1998;37:155-160.

10.2 Accuracy of MRI Determination of Tumor Margins

Two studies providing information on this issue were reviewed. The fist, which correlated postmortem MR imaging and neuropathologic findings evaluated 9 cases of recurrent GBM, 2 cases of cerebral untreated GBM, 2 cases of GBM in remission and 2 cases of untreated AA. In the 9 recurrent GBM cases the 20 T2-weighted images underestimated lesion size (6 images), overestimated tumor size (5 images) or correctly identified lesion size (9 images). Of the 4 images of untreated GBM 2 were correct and two underestimated. Of the 5 images of GBM in remission all were underestimated. Accuracy was better for untreated AA where 7 of 8 images were accurate and one was underestimated (Johnson PC, Hunt SJ, Drayer BP Human Cerebral Gliomas: Correlation of Postmortem MR imaging and Neuropathologic Findings. Radiology 1989;170:211-7).

The second study correlated Gadolinium enhanced MR with stereotactic biopsy in six glioma patients, 4 with GBM two with Grade 2 astrocytoma. Five of the 6 had not yet undergone surgery or radiation therapy and all were on steroids. In the 4 patients with GBM tumor cells were obtained from biopsies taken in white matter outsode of the margtins of MR image contrast enhancement (Earnest F, 4th, Kelly PJ, Scheithauer BW, et al. Cerebral astrocytomas: Histopathologic correlation of MR and CT contrast enhancement with stereotactic biopsy. Radiology 1988;166:823-27).

11.0 Summary

11.1 Sponsor's Proposed Basis for Marketing Approval

The sponsor's minutes of the October 8, 1996 Pre-NDA meeting state that at the November 17, 1994 meeting the endpoint of progression-free status at 6 months was accepted due to great difficulty in obtaining objective response data in this

disease. The Agency minutes of the November 17, 1994 meeting do not support this contention.

On October 7, 1997, in response to an interim report of trial C94-091 the Agency stated that the basis for approval in GBM, primary or recurrent, is significant improvement in overall survival. Gliadel was approved for use in recurrent brain cancer on the basis of a significant improvement in overall survival. The FDA and its outside experts do not believe that tumor shrinkage or increase can be adequately assessed in relapsed malignant gliomas because of their irregular configuration. Thus tumor response and tumor progression cannot be used as the principal basis for approval. Any new agent approved for the treatment of GBM would be expected to meet this standard. Three other pharmaceutical companies developing drugs for the treatment of recurrent GBM have been given this same advice and are proceeding with clinical trials on this basis.

11.2 Summary of Pivotal Relapsed GBM Trial C94091/l96058

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 primary objective, per sponsor, was to compare progression-free survival (PFS) at 6 months and safety for temozolomide (TMZ) and procarbazine (PCB) (active reference agent). Secondary objectives included response rates, overall survival and health-related quality of life (HQL).

The two treatment groups, in this study, did not differ significantly by any demographic, previous disease history or current tumor status variable that was evaluated with the exception that TMZ treated patients had a significantly shorter time from initial diagnosis to first relapse than did PCB treated patients. Both treatment groups generally received protocol prescribed treatment doses and tumor evaluations were generally performed as mandated by the protocol.

For both the intent-to-treat population and the population with eligible histology both the sponsor and the FDA analysis indicated that TMZ treatment was associated with a significant improvement in progression free survival (PFS). The median PFS for TMZ (sponsor's intent to treat analysis) was 2.99 mo. versus 1.97 mo for PCB (p=0.0065.) and the FDA's was 2.70 mo. versus 1.84 mo. p=0.0007. In both analyses the lower limit of the 95% confidence interval (CI) for 6 month PFS of TMZ treated patients was greater than 10%. For the eligible histology population the FDA analysis again demonstrated a significant improvement in PFS associated with TMZ treatment. In this analysis, the lower limit of the 95% CI for 6 month PFS of TMZ treated patients was 10%. As indicated above, the sponsor's definition of efficacy was a lower bound of the 95% CI of the 6-month progression-free survival for TMZ treatment that was greater than 10%.

Regarding overall survival there was no significant difference between treatment groups in either the sponsor's or the FDA's analysis. The median overall survival

(eligible histology population), in the FDA analysis, was 7.3 months for TMZ versus 5.86 months for PCB, p=0.61, and the 6 month survival rates with 95% CI's were 61% (51%-70%) versus 49% (39%-58%) for the two treatments.

Response rates were approximately 5% in both treatment groups. Health related quality of life assessments and quality adjusted survival (Q-TwiST) analysis (sponsor's results) generally favored TMZ treatment.

To place the results of this relapsed GBM trial in perspective the FDA reviewed the relapsed glioma literature. Of the 27 reviewed trials that reported any survival results, 13 reported only overall survival, 2 reported only progression free survival and 9 reported both. Six-month progression free survival (the primary outcome measure of C94091) was not reported in any study. Prognostic characteristics of patients entered into trial C94091 were generally similar to patients enrolled in the literature studies. Outcomes from C94091 and the literature were also relatively comparable. Median survivals in the literature studies ranged from 17 weeks to 44 weeks, compared to 32 weeks for TMZ in study C94091 and 23 weeks for TMZ in study I94122. The most frequently tested single agent, in the literature studies, was carboplatin (5 studies). Median survival in those 5 trials ranged from 19 to 35 weeks.

11.3 Summary of Supportive Relapsed GBM Trial I94122

The supportive trial I94122 was a phase II, open-label, multicenter study in relapsed GBM. All patients received TMZ therapy. Study patients generally received protocol prescribed treatment doses and tumor evaluations were generally performed as mandated by the protocol. The trial had similar efficacy endpoints and study design as the pivotal trial C94091.

In comparing survival differences of TMZ treated GBM patients on studies C94091 and I94122 the median survivals were 7.3 months versus 5.33 months and the percent survival at 6 months was 61% versus 44.5%, respectively. As indicated in Section 8.12.31 of this report the two populations were not entirely comparable, but prognostic factors seemed to favor C94091 patients in that they had a longer time from initial diagnosis to treatment and they had smaller tumors than did I94122 patients. Balancing this, however, was the fact that C94091 patients received higher doses of radiation therapy and were more likely to have received chemotherapy, as part of their initial disease treatment, than I94122 patients.

11.4 Summary of Pivotal Relapsed Anaplastic Astrocytoma Trial C/I94123

Pivotal study C/I94-123 was a multicenter open-label phase II study of temozolomide in the treatment of patients with anaplastic astrocytoma (AA) at first relapse. Thirty-two institutions, from the USA and abroad participated in this study. The study period was February 1995 to April 1998. The sponsor's primary

objectives of this study were to determine progression-free survival at 6 months and safety. Secondary objectives were to determine overall survival, objective response, health-related quality of life (HQL) and population pharmacokinetics.

The intent to treat group in this study included 162 patients. Nineteen of the 162 patients had ineligible or unknown histology so that the eligible histology group comprised 143 patients. Study patients generally received protocol prescribed treatment doses and tumor evaluations were generally performed as mandated by the protocol.

As expected, treatment outcomes were considerably better in AA patients than in GBM patients. Objective response rate to Temozolomide treatment was 33%, versus 5% for GBM, median progression free survival, per FDA analysis, for the eligible histology group, was 6.64 months with 52% (95% CI 44%-61% progression free at six months and overall survival, per FDA analysis of the eligible histology group, was 77% (95% CI 74%-84%).

In this trial , as in the other relapsed glioma studies reviewed in this document, Temozolomide was administered with few dose reductions or dose delays. The safety profile was acceptable. Most adverse events were mild to moderate in severity. and discontinuation of therapy because of adverse events was infrequent. Grade 3 or 4 myelosuppression was also infrequent.

To place the results of this relapsed GBM trial in perspective the FDA reviewed the relapsed glioma literature and selected reports providing AA data **(Table 50).** Like C/I94-123 all 27 of these studies were non-randomized, phase II trials. Further, only 5 of the trials included more than 20 patients. While it is impossible to directly compare treatment results because of differing patient populations and different response and progression criteria it appears that all results are in the same ball-park with some studies having better outcomes and some worse than C/I94-123. Thus, for example, median progression free survival, in the literature studies, ranged from 16 weeks to 86 weeks, compared to 23.4 weeks for TMZ and median survival, in the literature studies, ranged from 17 weeks to 96+ weeks, compared to 59 weeks for TMZ.

The sponsor indicated to the FDA that a relapsed AA RCT was not possible because almost all eligible patients would have previously received **all** active drugs, including nitrosoureas and procarbazine. In C/I94123, however, 63% of both the intent to treat and the eligible histology groups (102/162 patients and 89/143 patients, respectively) had not previously received nitrosourea and procarbazine therapy **(Table 30).** Further, 63 of 162 patients (39% ITT) or 57 of 143 patients (40% EH) had received **no** prior chemotherapy. Thus patients would have been available for a RCT.

The sponsor is requesting accelerated approval for treatment of relapsed AA based on tumor response rate. The eligible relapsed AA population for this indication are patients who previously received both a nitrosourea and

procarbazine. The Phase 2 study included only 54 such patients and their response rate (CR + PR) was 22% **(Tables 30 and 66)**. Five of the 54 patients achieved a long duration complete response. The median duration of these complete responses was 448 days with a range of 367 to 797 days **(Table 66)**.

11.4.1 Proposed Phase 4 Anaplastic Astrocytoma RCT if Accelerated Approval is Granted

The proposed trial is an intergroup study, led by RTOG and including ECOG and SWOG. Study patients would have newly diagnosed, histologically confirmed anaplastic astrocytoma. They would be stratified by age, performance status and extent of surgical resection. All patients would receive radiation therapy, delivered conventionally, to a total dose of 59.4 Gy. Patients would be randomized to receive either Temozolomide or PCV (Procarbazine/Lomustine [CCNU]/Vincristine) chemotherapy which would begin after completion of radiation therapy. The primary endpoint is survival. Sample size is 284 patients.

11.5 Summary of Quality of Life Data – All Relapsed Glioma Trials

The protocol specified quality of life analysis was to have been a longitudinal comparison of HQL of patients enrolled on each treatment arm. The sponsor, because of data censoring problems, was unable to perform this analysis. Instead, a variety of other kinds of analyses, not specified in the protocol and not of a kind accepted by the FDA, were performed. Thus any claims for improvement in HQL based on the sponsor's analyses that are included in this report must be interpreted with caution.

11.6 Response Rates All Relapsed Glioma Studies

Overall response rates the pivotlal (C94091) and supporting I94122 glioblastoma multiforme trials and for the pivotal anaplastic astrocytoma trial C/I94123 are summarized in **Table 66.** Only eligible histology patients are included in this table. As seen in the table, response rates are relatively comparable for the three glioblastoma multiforme treatment groups and anaplastic astrocytoma patients have a higher response rate.

Table 66 Response Rates and Response Duration - All Relapsed Glioma Patients

		Responders EH Population		Response Duration (days)	
Protocol	# of EH Patients	Number	Percent	Median	Range
C94091 (TMZ)	106	5	4.7	85	57-424
C94091 (PCZ)	111	3	3	99	77-201
I94122 (TMZ)	131	8	6	113	55-358
C94123 (TMZ) all	143	47	33	218	56+757
C94123 (TMZ) Prior NU+PCZ	54	12	22	348	112-797
C94123 (TMZ) Prior NU, No PCZ	30	11	37	190	91-667
Complete Responses					
C94123 (TMZ) Prior NU+PCZ	54	5	9	448	367-797
C94123 (TMZ) Prior NU, No PCZ	30	1	3	667	667
None	57	7	12	266	173-626

11.7 Survival (PFS & OS) All Relapsed Glioma Studies*

As summarized in **Table 67** both the sponsor's and the FDA analysis indicated that TMZ treatment produced a significant increase in progression free survival and 6-month progression free survival compared to PCZ treatment. In study C94091 (first relapse glioblastoma multiforme) there was no significant difference in overall survival and only a trend, favoring TMZ over PCZ in 6 month survival. Survival outcomes for TMZ treated glioblastoma multiforme patients in study I94122 were somewhat inferior to those of TMZ treated patients in C94091. As expected, anaplastic astrocytoma patients treated in study C/I94123 had better survival outcomes than did the glioblastoma multiforme patients enrolled in studies C94091 and I94122.

Table 67 Progression Free and Overall Survival - Summary of All Trials

					Median Survival (PFS or OS)		6 Month Survival (PFS or OS)		
Study	Data Source	# of Pts	Survival	Popu - lation	Months	p	%	95% CI - %	p
94091 GBM	SPRI	112 113	PFS	ITT	2.99 T 1.97 P	0.0065	21 T 9 P	13-29 4-15	0.016
94091	FDA	112 113	PFS	ITT	2.7 T 1.84 P	0.0007	19 T 7 P	11-27 2-12	0.012
94091	FDA	104 108	PFS	EH	2.7 T 1.88 P	0.003	17 T 7 P	10-25 2-15	0.04
94122 GBM	SPRI	138	PFS	ITT	2.1 T		19 T	12-26	
94122	FDA	138	PFS	ITT	2.24 T		21 T	14-28	
94122	FDA	131	PFS	EH	2.24 T		20 T	12-27	
94123 AA	SPRI	162	PFS	ITT	5.4 T		46 T	38-54	
94123	FDA	162	PFS	ITT	6.18 T		51 T	43-59	
94123	FDA	143	PFS	EH	6.64 T		52 T	44-61	
94123 prior N+P	FDA	54	PFS	EH	4.57		48	34-62	
94091 GBM	SPRI	112 113	OS	ITT	7.34 T 5.82 P	0.337	60 T 48 P	51-70 39-57	0.067
94091	FDA	104 108	OS	EH	7.3 T 5.86 P	0.61	61 T 48 P	51-70 39-58	0.07
94122 GBM	SPRI	138	OS	ITT	5.4 T		54 T	46-62	
94122	FDA	138	OS	ITT	5.39 T		45.8 T	38-54	
94122	FDA	131	OS	EH	5.33 T		44.5 T	36-53	
94123 AA	SPRI	162	OS	ITT	13.6 T		75 T	68-82	
94123	FDA	143	OS	EH	14.61 T		77 T	74-84	
94123 prior N+P	FDA	54	OS	EH	15.86		74 T	62-86	

* AA = Anaplastic Astrocytoma; EH = Eligible histology population; GBM = Glioblastoma Multiforme; ITT = Intent to treat population; OS = overall survival; PFS = Progression free survival; N = Nitrosourea; P = Procarbazine; T = Temazolomide

11.8 Safety

Among all malignant glioma patients treated with TMZ, the most common adverse events were nausea, vomiting, headache, fatigue, and constipation. In C94091, the incidence of AE's during the first 56 days of treatment were similar for the TMZ arm and the PCB arm. During this period, grade 3/4 AEs occurred in 35% of the PCB patients and in 26% of the TMZ patients. In TMZ patients almost all grade 4 adverse events occurred with a frequency of less than 1%. The most common hematologic Grade 4 AE was thrombocytopenia (5%) with other Grade 4 hematologic toxicities occurring in 2% or fewer patients. Recovery of blood counts tended to occur within 10 days.

Fifteen glioma patients treated with TMZ discontinued treatment due to adverse events; 8 because of hematologic toxicity. There were 30 deaths associated with TMZ treatment and 9 associated with PCB treatment. Most of these deaths appeared to be disease-related.

There were 10 glioma patients who developed pulmonary emboli, 8 TMZ (in all three malignant glioma studies) and 2 PCB treated (C94091). Two patients, both PCB treated, died of this complication. Venous thrombosis developed in an additional 10 patients, (all malignant glioma studies) all treated with TMZ. These numbers suggest that TMZ might induce hypercoagulability, at least in some patients.

11.9 Regulatory Issues

Temodal is not shown to improve survival in relapsed gliomas. Prolongation of life was the standard for approval of Gliadel for treatment of recurrent malignant gliomas. It is also the requirement for approval that the FDA has given to three other pharmaceutical companies that are developing new drugs for the treatment of malignant gliomas. One of the reasons for the requirement of prolongation of life is that the FDA and its outside expert advisors do not believe that tumor shrinkage or enlargement can be accurately measured in malignant gliomas because of the often irregular configuration of these tumors. Thus objective response rate and objective progression cannot be satisfactorily assessed. (See Section 10.2 for supporting information). This concern is even greater for relapsed malignant gliomas after prior surgery and/or radiation therapy.

11.10 Questions to the Oncology Drug Advisory Committee (1/12/99) re Glioma Trials and ODAC Response

11.10.1 Glioblastoma Multiforme – Trials C94091 and I94122

1. Is an improvement in 6-month progression-free survival or overall progression-free survival sufficient as the principal basis of regular approval for drugs indicated for the treatment of relapsed malignant gliomas or should an improvement in survival be required?

   Yes – 1 No – 11

2. Do the results of the randomized controlled trial (C94091) in patients with relapsed glioblastoma multiforme (Tables 1-3) provide evidence that Temodal is effective for this indication?

   Yes – 4 No – 8

3. Study C94122 is a single-arm, uncontrolled trial in patients with relapsed glioblastoma multiforme. Without a concurrent control it is difficult to attribute the progression-free survival and survival results to Temodal. While objective responses could potentially be attributed to drug effect, the observed response rate was low (6%) and the endpoint suffers from the previously mentioned concerns about the reliability of response assessments in this disease. Do the results of the phase 2 trial (C94122) in patients with relapsed glioblastoma multiforme provide confirmatory evidence that Temodal is effective for this indication?

   Yes – 0 No - 12

4. If so, is the safety of Temodal acceptable for this indication (Tables 6-8)?

   No vote was taken on Question 4.

5. Is Temodal approvable for treatment of relapsed glioblastoma multiforme?

   Yes – 0 No – 11 Abstain – 1

   The Committee had serious concerns about using a retrospectively chosen end-point (6-month progression-free survival) not validated by the literature. The data show no evidence of improvement in overall survival, a more important end-point and one that is less influenced by confounding factors such as delayed treatment effect, concomitant medications and investigator bias. Quality of life issues also need to be considered more thoroughly.

11.10.2 Anaplastic Astrocytoma – Trial C/I94123

1. The 54 patients with relapsed anaplastic astrocytoma who have received both a nitrosourea and procarbazine could be considered unresponsive to other therapies. Does the committee agree?

   Yes – 12 No – 0

2. Given the problems with determining objective responses in patients with recurrent gliomas, is objective response an adequate surrogate for clinical benefit for the purpose of accelerated approval of a drug in refractory malignant gliomas?

   The Committee felt that objective response could be an adequate surrogate for clinical benefit under the proper parameters. The response must be well-defined and of sufficient magnitude to overcome the noise level resulting from other variables. Both baseline and follow-up quality of life data should be included for all responders.

3. Does the phase 2 study in anaplastic astrocytoma (C94123) show that Temodal is effective for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine?

   Yes – 12 No – 0

4. If so, is the safety of Temodal acceptable for this indication?

   Yes – 12 No - 0

5. Should Temodal be given accelerated approval for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine?

   Yes – 12 No – 0

12.0 Summary

12.1 Glioblastoma multiforme.

Both the pivotal, controlled randomized trial and the supporting uncontrolled trial had low objective response rates (5% for each trials in the FDA intent to treat analysis). The pivotal trial, while demonstrating a significant difference in progression free survival and 6 month progression free survival rate favoring temozolomide over procarbazine, failed to demonstrate a significant difference in overall survival. The FDA reviewers did not believe that accurate tumor measurements could be obtained in relapsed glioma patients thus confounding determination of progression free survival. ODAC concurred with this assesssment. Moreover, median overall survival in the supporting uncontrolled trial (comprising a prognostically comparable or prognostically superior patient population to the pivotal RCT) was 5.33 months compared to 7.3 months for Temozolomide treatment and 5.86 months for Procarbazine treatment in the pivotal trial. Based on these considerations the FDA review team believed that Temozolomide should not be approved

for the treatment of relapsed Glioblastoma Multiforme patients. ODAC concurred. (See ODAC vote, page 98).

12.2 Anaplastic Astrocytoma

The applicant is requesting accelerated approval based on an objective tumor response rate in patients for whom there is no satisfactory available therapy, i.e. first relapse AA patients who have previously failed a nitrosourea and procarbazine containing drug regimen. There were 54 such patients in the sponsor's C/I94123 trial. With Temodal treatment there were 7 PR's and 5 CR's (overall response rate of 22% in this patient population). Responses were generally long-lasting. The median response duration for all responders was 348 days (range 112 to 797 days), and for the CR's the median response duration was 448 days (range 367 to 797 days. FDA reviewers felt that these response rates and response durations, in a chemotherapy refractory patient population, along with a satisfactory safety profile were sufficient to grant accelerated approval. ODAC concurred (See ODAC vote, page 99). The applicant has committed to conducting a satisfactory phase IV RCT (See section 11.4.1).

13.0 Labeling

The sponsor's labeling document is being revised by the FDA review team.

14.0 Recommendations

14.1 Glioblastoma Multiforme C94091 and I94122

Non-approval

14.2 Anaplastic Astrocytoma

Accelerated approval

/S/

Martin H. Cohen, M.D.
Medical Reviewer
January 29,1999

/S/

John R. Johnson, M.D.
Medical Team Leader
2-1-99

NDA's 21-050 and 21-029
Temozolomide Treatment of First Relapse High Grade Gliomas

One-Hundred Twenty Day Safety Review

The one-hundred twenty day safety review was submitted on December 10, 1998. The safety data in the original submission in August, 1998 included safety information up to the clinical cutoff of June 15, 1998. The current safety report includes 400 relapsing glioma patients, 151 metastatic melanoma patients and 479 patients (including 60 pediatric patients) enrolled in other completed or ongoing Phase 1 and 2 temozolomide studies. The cutoff date for new safety information in the 4 month report is October 31, 1998.

Safety information from the original submission is indicated in the following tables. Significant changes based on the one-hundred twenty day report are indicated in **boldface**. The revised tables contain safety data from all SPRI sponsored Temozolomide clinical studies.

Table 1 Adverse Events Reported in >2% of Temozolomide Treated Cancer Patients Modified From Sponsor

	All gliomas (cancers)		All gliomas (cancers) c
Adverse Event a	TMZ (N=400)(N=1030)	Adverse Event a	TMZ (N=400) (N=1030)
Number of Patients Reporting Any AE	97% (388) (95%)		
Nausea	46% (185) (49%)	Dyspnea	5% (19) (11%)
Headache	41% (162) (37%)	Petechiae	5% (18)
Vomiting	38% (151) (42%)	Weight increase	5% (18)
Fatigue	31% (122)	Alopecia	4% (17)
Constipation	24% (95) (28%)	Purpura	4% (17)
Convulsions	24% (94) (13%)	Vision abnormal	4% (17)
Hemiparesis	20% (78)	Candidiasis, oral	4% (16)
Pain	16% (62) (23%)	Diplopia	4% (16)
Somnolence	15% (59)	Myalgia	4% (16)
Amnesia	12% (47)	Leukopenia d	4% (15)
Diarrhea	12% (47)	Thrombophlebitis deep	4% (15)
Anorexia	12% (46) (18%)	Agitation	4% (14)
Fever	12% (46) (16%)	Micturition frequency	4% (14)
Ataxia	11% (45)	Neutropenia d	4% (14)
Asthenia	11% (44) (14%)	Pneumonia	4% (14)
Confusion	11% (43) (8%)	Thinking abnormal	4% (14)
Edema peripheral	11% (42)	Sinusitis	3% (13)
Gait abnormal	11% (42)	Moniliasis	3% (12)
Adrenal hypercorticism	10% (38)	Myopathy	3% (12)
Dysphasia	10% (38)	Papilledema	3% (12)
Paresis	10% (38)	Respiratory disorder	3% (12)
Insomnia	9% (36)	Vertigo	3% (12)
Thrombocytopenia	d 9% (35)	Anemia d	3% (11) (7%)
Urinary incontinence	9% (34)	Dysphagia	3% (11)
Coordination abnormal	8% (33)	Hypertension intracranial	3% (11)
Dizziness	8% (33) (10%)	Tremor	3% (11)
Paresthesia	8% (31)	Bronchitis	3% (10)
Rash	8% (31)	Concentration impaired	3% (10)
Depression	7% (27)	Conjunctivitis	3% (10)
Anxiety	7% (26)	Hypokinesia	3% (10)
Abdominal pain	6% (24)	Micturition disorder	3% (10)
Infection viral	6% (24)	Pulmonary infection	3% (10)
Urinary tract infection	6% (24)	Stomatitis	3% (10)
Aphasia)	6% (23)	Syncope	3% (10)
Back pain	6% (23)	Apathy	2% (9)
Upper respiratory tract infection	6% (23)	Earache	2% (9)
		Embolism pulmonary	2% (9)
Speech disorder	6% (22)	Erythema	2% (9)
Pharyngitis	5% (21)	Facial palsy	2% (9)
Convulsions local	5% (19)	Hypoesthesia	2% (9)
Dyspepsia	5% (19)	Malaise	2% (9)
Coughing	9%	Breast pain, female a	3% (4) (2%)

a: Numbers and percentages reflect all patients reporting any AE. Sex-specific AEs are based on the appropriate denominator.
b: For any individual adverse event (based on the all patients group) for all cycles - safety population
c: Equals all GBM (C94-091, 194-122) and AA (C/194-123).
d: Lab abnormalities that led to discontinuation, hospitalization or transfusion were reported as AEs.

Table 2 Grade 3 and Grade 4 Adverse Events Reported in Temozolomide Treated Cancer Patients Modified from Sponsor

Body System/ Adverse Event [a]					
All Gliomas [c] (Cancers) TMZ (N= 400) (N=1030)	Grade 3	Grade 4		Grade 3	Grade 4
Number of Patients Reporting Any AE	41% (163) **35% (1030)**	11% (45) **13% (1030)**			
Nausea	6% (25) (57)	0	Purpura	<1% (2)	0
Headache	7% (28) (57)	0	Vision abnormal	<1% (2)	0
Vomiting	5% (20)	<1% (1)	Myalgia	<1% (1)	0
Fatigue	4% (17)	1% (3)	Leukopenia [d]	2% (7)	2% (6)
Constipation	1% (5)	0	Thrombophlebitis deep	1% (3)	2% (6)
Convulsions	5% (18)	<1% (2)			
Hemiparesis	7% (27)	<1% (2)	Neutropenia [d]	2% (6)	2% (7)
Somnolence	4% (14)		Pneumonia	1% (5)	<1% (1)
Amnesia	4% (15)	<1% (1)	Thinking abnormal	<1% (2)	0
Diarrhea	1% (3)	0	Moniliasis	<1% (1)	0
Anorexia	<1% (2)	0	Myopathy	<1% (2)	0
Fever	1% (5)	<1% (1)	Papilledema	<1% (2)	0
Ataxia	3% (10)		Respiratory disorder	0	<1% (1)
Asthenia	4% (15)	1% (4)	Vertigo	<1% (1)	0
Confusion	3% (11)	0	Anemia [d]	1% (3)	<1% (2)
Edema peripheral	<1% (2)	0	Dysphagia	1% (3)	0
Gait abnormal	2% (8)	1% (3)	Hypertension intracranial	2% (7)	0
Adrenal hypercorticism	1% (3)	0			
Dysphasia	3% (10)	0	Concentration impaired	<1% (2)	0
Paresis	2% (9)	0			
Insomnia	<1% (1)	0	Hypokinesia	1% (3)	0
Thrombocytopenia [d]	3% (12)	5% (19)	Micturition disorder	<1% (1)	0
Urinary incontinence	3% (10)	0	Pulmonary infection	<1% (1)	<1% (1)
Coordination abnormal	1% (4)	0	Syncope	1% (3)	0
Dizziness	<1% (2)	0	Apathy	1% (4)	0
Paresthesia	<1% (2)	0	Embolism pulmonary	1% (5)	1% (3)
Depression	<1% (1)	0			
Anxiety	<1% (1)	0	Malaise	<1% (1)	0
Abdominal pain	1% (3)	0			
Aphasia	2% (7)	0			
Back pain	2% (7)	0			
Speech disorder	1% (4)	<1% (2)			
Convulsions local	<1% (2)	0			
Dyspnea	<1% (1)	0			
Petechiae	<1% (1)	0			

a: Numbers and percentages reflect all patients reporting any AE. Sex- specific AEs are based on the appropriate denominator.
b: For any individual adverse event (based on the all patients group) for all cycles - safety population
c: Equals all GBM (C94- 091, I94- 122) and AA (C/ I94- 123).
d: Lab abnormalities that led to discontinuation, hospitalization or transfusion were reported as AEs.

9.11.2 Temozolomide Hematologic Toxicity

TMZ treated patients who had an increase in hematologic toxicity from grade 0-2 at baseline to grade 3 0r 4 during treatment are reported below. There was no change in the percent of patients with a specific hematologic toxicity from the August, 1998 report.

Table 3 Changes in Hematology Laboratory Data from Grade 0-2 at Baseline to Grade 3-4 During Treatment (Patients Enrolled in SPRI Sponsored Temozolomide Clinical Studies)

	TMZ a
Hemoglobin	63/969 957 (7%)
Neutrophils	**154** 151/907 894 (17%)
Platelets	176/**950** 938 (19%)
White Blood Cells	**180** 114/**968** 956 (12%)
Lymphocytes	**461** 455/937925 (49%)b

a: Percents were based on the number of patients with data available at baseline and at least one subsequent visit for each parameter.
b: Not clinically significant; not associated with AEs or opportunistic infections.

9.12 Non-hematologic Laboratory Abnormalities

There were few non-hematologic laboratory abnormalities. Four percent of TMZ-treated patients had increased glucose, 2% had an increased SGOT, 2% had an increased SGPT, and 4% had increased total bilirubin (**Table 4**). Increased glucose was probably secondary to steroid use in these patients.

Table 4 Changes in Non-Hematology Laboratory Data from Grade 0-2 to Grade 3-4 During Treatment of Patients Enrolled in SPRI Sponsored Temozolomide Clinical Studies

	TMZ a
Alkaline Phosphatase	**11/683 2%**
Creatinine	**7/704 1%**
Glucose Increased	**37/862 4%**
SGOT	**12/636 2%**
SGPT	**12/621 2%**
Total Bilirubin	**27/675 4%**

a: Percents were based on the number of patients with data available at baseline and at following visits for each parameter.

/S/
Martin H. Cohen, M.D.
February 1, 1999

/S/
John R. Johnson, M.D.
February 1, 1999

1-GUINN

AUG - 3 1999

MEDICAL OFFICER REVIEW OF A NEW PROTOCOL FOLLOWING ACCELERATED APPROVAL OF TEMOZOLOMIDE FOR ANAPLASTIC ASTROCYTOMA

NDA: 21-029

DRUG: Temozolomide

SPONSOR: Schering Corporation

M.O.: Martin H. Cohen, M.D.

DATE RECEIVED: June 25, 1999

I. RESUME

Temozolomide was granted accelerated approvable status in January, 1999 for the treatment of refractory anaplastic astrocytoma (AA). Approvable status was based on a 22% response rate (12/54 patients) in AA patients who were refractory to both a nitrosourea and procarbazine. The complete response rate, in this group of patients, was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks). The median duration of complete response was 64 weeks (range of 52 to 114 weeks). Median progression free survival was 4.4 months and median overall survival was 15.9 months.

As part of the accelerated approval process the sponsor made a commitment to conduct a confirmatory study. The submitted protocol constitutes that confirmatory study.

II. GENERAL INFORMATION:

Related NDAs 21-050

Related INDs None

III. MANUFACTURING CONTROLS:

See Chemistry Review

IV. PHARMACOLOGY

See Pharmacology Review

V. CLINICAL BACKGROUND:

Nitrosoureas have been extensively evaluated as treatment for malignant high-grade astrocytomas. Usually they have been given as adjuvant therapy after radiation therapy

has been completed. A more recent trial has administered nitrosoureas concurrently with radiation therapy. Thus RTOG protocol 9305 administered BCNU 80 mg/m2 days 1,2,3 of radiation therapy (60 Gy/30 fractions) and then q 8 weeks for a total of 6 cycles. This is the same BCNU dose and schedule as is being proposed for the BCNU alone arm of the current study. The first BCNU dose is given on the first day of radiation therapy.

The proposed Temozolomide dose and schedule for this study (arm 2) is the standard dose used in chemotherapy naive patients, i.e. 200 mg/m2 P.O. days 1 through 5 q 28 days for 12 cycles. The first Temozolomide dose is given on the first day of radiation therapy.

The proposed combination BCNU/Temozolomide regimen (arm 3) consists of BCNU 200 mg/m2 iv administered on day 1 of radiation therapy. Temozolomide 150 mg/m2 po is administered on days 1 to 5 of the first week of radiation therapy. Cycles will be repeated every 6 weeks for a total of 6 cycles. Because there is no prior experience with this regimen administered concomitantly with radiation therapy the sponsor proposes to do a phase 1 trial in 15 protocol eligible patients to determine safety. If the toxicity profile is not acceptable, $\geq$2 patients with grade 3 or worse pulmonary toxicity **or** $\geq$ 5 patients with grade 4 or worse thrombocytopenia following one dose reduction, arm 3 will be terminated and subsequent patients will randomize to receive radiation therapy with either BCNU (arm 1) or Temozolomide (arm 2).

Limited volume irradiation will be used for this study. Total dose will be 59.4 Gy (1.8 Gy x 33 fractions, 5 days/week. The initial 50.4 Gy/28 fractions will include the initial target volume (T2-MR + 2 cm margin) or contrast enhancing lesion + 2.5 cm when no edema is present. The final 9 Gy/5 fractions will include the boost volume (T1 enhanced MR + 1 cm margin).

Cooperative groups participating in this trial include RTOG, ECOG, NCCTG and SWOG. RTOG is the lead group.

VI. PROTOCOL

The protocol is titled "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 study will include patients with a pathologically confirmed diagnosis of anaplastic astrocytoma. Patients will have received no prior chemotherapy and no prior radiation therapy to the head and neck. Karnofsky performance status must be $\geq$ 60. They must have adequate bone marrow function as defined in the protocol and therapy must begin within 5 weeks of tissue diagnosis. For additional inclusion and exclusion criteria see protocol.

The primary study endpoint is overall survival. Other endpoints include progression-free survival, safety, study of putative molecular predictors of survival (chromosome 1p, 10q and 19q loss, p53 mutations, RB, CDKN2A, EGFR status and Ki-67 proliferation rates)

and to correlate the pre-operative MRI with histopathological findings. Response rate is not mentioned as a study endpoint but it appears that it will be determined.

There will be central pathology review and central radiographic review.

Criteria for dose reduction based on nadir and day of treatment ANC and platelet counts are included. Treatment, in the absence of progression or significant toxicity, will continue for 48 weeks for arms 1 and 2 (monotherapy) and 36 weeks for the combined BCNU/Temozolomide arm..

The flow chart for follow-up studies is adequate.

Standard definitions for CR, PR and stable disease are employed. Progressive disease is defined, in part as "a radiographic increase in size of the lesion". There also is a separate category of *recurrence , which* appears to overlap the definition of progressive disease. Mental status will also be followed.

There will be 3 interim study analyses, when total accrual equals 25% 50% and 75% of the study population and minimal length of follow-up is 6 months. Final analysis will be undertaken when all patients have been potentially followed for a minimum of 36 months.

VII. SUMMARY STATEMENTS:

1. The risks of the proposed study are acceptable in view of its objectives.

2. The risks are adequately appreciated.

3. Adequate precautions are being taken.

4. A patient informed consent form is provided and is satisfactory except as detailed in section X below.

5. The study objectives are clear and are based on sound rationale.

6. The study protocol is adequate to provide data that will achieve the study objective.

VIII. REGULATORY ACTION:

The two monotherapy arms of the study may proceed. Phase I/II safety data must be provided before the combination therapy arm can proceed.

Schering Corporation, in its letter of August 2, 1999 "commits to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason". Schering also agrees that "initiation of the combination arm will be contingent on FDA approval to proceed".

IX. DEFICIENCIES:

None

X. SUGGESTIONS AND COMMENTS

1. Progressive disease should be defined as a specific percent increase in tumor size. Unless there is a specific reason progressive disease and recurrence should be combined.

2. Section 11.1 study parameters does not provide a schedule of follow-up neurologic exams and contrast head MRI's after chemotherapy is completed. Rather it references protocol section 12.1 where it appears that follow-up exams, after chemotherapy, will be performed q 6 months for 2 years and then annually. This examination schedule is too infrequent to accurately determine time to tumor progression (secondary study endpoint).

3. A precise definition of tumor progression by neurologic exam is not provided. The definition provided in protocol 11.3.2.4 states that "deterioration of the neurological examination" constitutes progression. How much deterioration is needed? Will assessors of neurologic progression be blinded to study treatment?

4. The timing of assessment of tumor progression during the first year on study will be different for each of the 3 study arms. This may impact on the time to tumor progression endpoint.

5. The informed consent has a wrong schedule of administration for the BCNU/ temozolomide arm i.e. every 4 weeks instead of every 6 weeks.

6. In section 11.0, item c, the last part of the sentence should be modified so that it is clear that a brain MRI should be obtained when radiation therapy is completed and before the next cycle of chemotherapy is initiated.

7. Pulmonary function tests and DLCO are required pre-therapy. Are there any test results that would preclude entry into this study?

8. If the answer to number 7 above is **no**, why are pulmonary function tests being done pre-treatment? They are never repeated.

/S/
Martin H. Cohen, M.D.
August 3, 1999

/S/
John R. Johnson, M.D.
August 3, 1999

cc NDA 21-029
Division File
[redacted]

Acting Director Comments on a New Drug Application

NDA: 21-029
Drug: Temodar (temozolamide) capsules
Applicant: Schering Corporation
Date: August 5, 1999

An approvable letter for the indication of "treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing drug regimen" was issued for this new drug application on February 12, 1999. The final piece of the complete response to the approvable letter was submitted on June 24, 1999.

The effectiveness of temozolamide in this indication is supported by Study C/I94123, a single arm, multicenter study conducted in 162 patients with anaplastic astrocytoma at first relapse. Eligibility was limited to patients with a baseline Karnofsky performance status of 70 or greater who had previously received radiation therapy and who may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). The median age of this subgroup of 54 patients was 42 years, 65% were male, and 72% had a KPS of ≥ 80. Sixty-three percent had surgery other than a biopsy at the time of initial diagnosis; 73% had a subtotal resection and 27% had a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2-75.4).

Temozolamide was given orally for the first 5 consecutive days of a 28 day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was $\geq 1.5 \times 10^9$/L and the nadir and day of dosing platelet count was $>100 \times 10^9$/L, the temozolamide dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28 day cycle.

In the refractory anaplastic astrocytoma population the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). The progression-free survival was 45% (95% C.I.: 31-58%) at 6 months and 29% (95% C.I.: 16-42%) at 12 months. The median progression-free survival was 4.4 months. Overall survival was 74% at 6 months (95% C.I.: 62-86%) and 65% at 12 months (95% C.I.: 52-78%). The median survival was 15.9 months.

In the 158 patients in the anaplastic astrocytoma study (C/I94123) with safety data, the most frequently occurring side effects (all grades) were nausea (53%), vomiting (42%),

headache (41%), and fatigue (34%). Adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity). The incidence of severe nausea and vomiting (CTC grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was dose-limiting, usually occurred within the first few cycles of therapy, and was not cumulative. Grade 3-4 neutropenia and thrombocytopenia occurred in 14% and 19%, respectively. Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets [range 21-40 days] and 28 days for neutrophils [range 1-44 days]. Fourteen percent (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion or discontinuation of therapy due to myelosuppression.

The application was presented to the Oncologic Drugs Advisory Committee on January 12, 1999. Since the application did not include evidence of clinical benefit, it was considered only for accelerated approval. The committee was asked whether the 54 patients with relapsed anaplastic astrocytoma who received both a nitrosourea and procarbazine could be considered unresponsive to other therapies. The committee's answer was yes (12 vs. 0). Objective response is usually considered an adequate surrogate for the purposes of accelerated approval. However, because of the problems with determining objective responses in patients with recurrent gliomas, the committee was asked whether objective response was an adequate surrogate for clinical benefit for the purpose of accelerated approval of a drug in refractory malignant gliomas. The committee felt that objective response could be an adequate surrogate for clinical benefit in this setting but that the response must be well-defined and of sufficient magnitude.

The committee was then asked whether the phase 2 study in anaplastic astrocytoma (C/I94123) demonstrated that temozoloamide is effective for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine. The committee again answered yes (12 vs. 0) and felt that the safety of temozolamide was acceptable for this indication. The committee then unanimously recommended that temozolamide be given accelerated approval for the treatment of relapsed anaplastic astrocytoma in patients who have had prior treatment with a nitrosourea and procarbazine.

Accelerated approval requires a post-marketing study to demonstrate clinical benefit. Schering submitted the proposed phase 4 study as the final piece to the complete response on June 24, 1999. Study RTOG 98-13 is entitled "A Phase I/III Randomized Study of Radiation Therapy and Temozolamide versus Radiation Therapy and BCNU versus Radiation Therapy and Temozolamide and BCNU for Anaplastic Astrocytoma. Although the study was developed by the RTOG and was approved by the NCI, it will be open to other cooperative groups (SWOG, ECOG, and NCCTG). It will start in the fall of 1999 and patient accrual is expected to be complete in early 2003. The final analysis will be done in the fall of 2006 and the final study report will be submitted in the fall of 2006.

The study will be conducted in patients with histologically confirmed anaplastic astrocytoma who have not previously received chemotherapy or radiation therapy to the head or neck. Although this population differs from the proposed indication, the results of the study will provide more useful information. After stratification by age, KPS, and extent of surgery, patients will be randomized to radiation therapy plus temozolamide 200 mg/m^2 orally on days 1-5 of a 28 day cycle for 12 cycles (Arm 1), to radiation therapy plus BCNU 80 mg/m^2 intravenously daily on days 1-3 every 8 weeks for 6 cycles (Arm 2), or to radiation therapy plus BCNU 200 mg/m^2 intravenously on day 1 and temozolamide 150 mg/m^2 orally on days 1-5 every 6 weeks for 6 cycles. All chemotherapy will start on day 1 of radiotherapy and all radiation therapy will consist of 59.4 Gy (1.8 Gy x 33 fractions, 5 days a week). Because the combination regimen in the third arm had not been studied previously, the investigators proposed to register the first 15 patients to this arm to assess safety before initiating randomization. An additional 492 patients will then be entered on the phase III arm. According to the protocol, survival is the primary endpoint of the study. The experimental arms of temozolamide plus radiotherapy and temozoloamide and BCNU plus radiotherapy will be compared to the standard BCNU plus radiotherapy arm. The RT+BCNU and RT+temozolamide arms will be first compared and the arm with the best median survival will then be compared with the RT+temozolamide+BCNU arm.

There are two major problems with this trial. First, there are concerns about evaluating the safety of Arm 3 in this relatively good prognosis patient population. There is preliminary data on a different schedule of these drugs in combination with radiation therapy and Schering agreed to provide safety data for FDA review before this arm is initiated. If the data do not confirm that the regimen is reasonably safe, Schering has committed to conducting the study with Arms 1 and 2 only. The second problem relates to the differences between the doses and schedules of BCNU in arms 2 and 3. Although the NCI argues that the differences in schedules are inconsequential and is unwilling to use the same BCNU schedule in both arms, there are no studies demonstrating that they are equivalent. These differences could confound interpretation of the comparison of arm 3 to arm 2. If arm 3 is superior to arm 2, the result could be due to the different dose and schedule of BCNU or to the addition of temozolamide. The only remaining comparison of regulatory interest is arm 1 vs. arm 2. To be interpretable as evidence of clinical benefit for temozolamide, the survival on arm 1 would have to be significantly better than that on arm 2. At a teleconference on July 8, 1999, Schering agreed that regardless of the planned analysis in the protocol, they will make the comparison of survival in these two arms their primary analysis.

Recommended Regulatory Action

Temozolamide should be given accelerated approved for the proposed indication.

/S/

Robert L. Justice, M.D.

cc:
Orig. NDA 21-029
Div. File
HFD-150/MCohen
HFD-150/JJohnson
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