

**Table 20 AA: C/I94-123: Patient Characteristics per Sponsor**

	Number (%) of Patients (N=162)
<b>Surgery at Initial Diagnosis</b>	
Yes	52 (32.1%)
No	110 (67.9)
<b>Extent of Surgery at Initial Diagnosis</b>	
Subtotal Resection	67 (41.4%)
Gross Total Resection	43 (26.5%)
<b>Prior Radiation</b>	162 (100%)
<b>Time fr Radiation Therapy to First Relapse</b>	
<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	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
<b>Prior Chemotherapy</b>	
Yes	97 (59.9%)
No	65 (40.1%)
<b>Time fr Initial Diagnosis to First Relapse</b>	
<3 months	27 (16.7%)
3-6 months	32 (19.8%)
>6-9 months	10 (6.2%)
>9-12 months	23 (14.2%)
>12-18 months	16 (9.9%)
>18-24 months	18 (11.1%)
>24-36 months	15 (9.3%)
>48 months	21 (13.0%)
Median	15.2
Range	3.1-122.3
<b>Surgery at First Relapse</b>	
No	132 (81.5%)
Yes	30 (18.5%)
<b>Extent of Surgery at First Relapse</b>	
Subtotal Resection	25 (15.4%)
Gross Total Resection	5 (3.1%)
<b>Time fr Surgery at First Relapse to Study Drug</b>	
<1 months	12 (7.4%)
1-2 months	10 (6.2%)
>2-3 months	4 (2.5%)
>6 months	2 (1.2%)
Median	2 (1.2%)
Range	1.1 0.3-15.8

**Table 21 AA: C/I94-123: Patient Characteristics per FDA**

<b>Characteristic</b>	<b>Temozolamide 164 Patients</b>
<b>Age</b>	
18-30	27
31-40	48
41-50	48
51-60	23
61-70	14
>70	4
<b>Sex</b>	
Female	70
Male	93
Not Recorded	1
<b>Race</b>	
White	148
Black	4
Other	11
Not Recorded	1
<b>Performance Status</b>	
100	26
90	51
80	34
70	53
<70	3
<b>Initial Surgery</b>	
Biopsy Only	54
Subtotal Resection	67
Gross Total Resection	43
<b>Initial Radiation Therapy (Gy)</b>	
<50	13
51-60	96
61-70	45
>70	7
Unknown	3

Table 21  
AA: 94123 Continued

Characteristic	Temozolamide 164 Patients
<b>Initial Chemotherapy</b>	
None	63
Nitrosoureas	98
Procarbazine	63
<b>Time From Initial Diagnosis to First Relapse (mo)</b>	
≤3	0
4-6	23
7-9	28
10-12	17
13-18	19
19-24	19
25-36	20
37-48	12
49-60	1
60-125	21
Not Recorded	4
<b>Time from First Relapse to Registration/Randomization (mo)</b>	
≤1	118
2-3	30
>3	14 (4-30)
Not Recorded	2
<b>Did Not Meet Protocol Eligibility</b>	
Ineligible Histology	18
Unknown Histology	1
<b>Surgery at Relapse</b>	
Subtotal Resection	24
Gross Total Resection	5

Table 21  
AA: C94123 Continued

Characteristic	Temozolamide 164 Patients
<b>Measurable Tumor Area (cm<sup>2</sup>)</b>	
≤1.0	8
1.1-3.0	15
3.1-6.0	21
6.1-9.0	19
9.1-12.0	13
12.1-15.0	10
15.1-20.0	14
20.1-30.0	16
>30	16 (31-58)
Non-measurable	32
<b>Symptoms (Baseline)</b>	
Yes	143
No	21
<b>Laboratory Values</b>	
Albumin [median (range)]	4.2 (3.5-6.0)
Hgb	13.5 (8.2-17.0)

### 8.12.3 Supporting Study I94-122

Sponsor's data on patient demographics and patient disease characteristics for patients enrolled in supporting trial I94-123 are recorded in Tables 22 and 23. FDA patient characteristics are recorded in Table 24.

**Table 22 GBM: I94-122: Patient Demographics per Sponsor**

Demographic Parameter	Number (%) of Patients (N=138)
Age (years)	
20-40	21 (15%)
>40-50	27 (20%)
>50-65	77 (56%)
>65	13 (9%)
Median	54.0
Range	24 - 77
Gender	
Male	85 (62%)
Female	53 (38%)
Race	
Caucasian	133 (96%)
Hispanic	5 (4%)
Karnofsky Performance Status	
100	7 (5%)
90	39 (28%)
80	33 (24%)
70	59 (43%)
Histology at Study Entry by Central Review	128 (93%)
GBM/Gliosarcoma	126
GBM	2
Gliosarcoma	6 (4%)
Other histologies	3
Anaplastic Astrocytoma	1
Anaplastic Oligoastrocytoma	2
Other Low-Grade Histologies	4 (3%)
Histology not available	

**Table 23 GBM: I94-122: Patient Characteristics per Sponsor**

<b>Baseline Disease Characteristics and Prior Therapies</b>	<b>Number (%) of Patients (N=138)</b>
<b>Prior Radiation Therapy</b>	
Yes	138 (100.0%)
<b>Radiation Dose (Gy) at Initial Diagnosis</b>	
<50	20 (14.5%)
50 - 65	115 (83.3%)
>65	2 (1.5%)
Unknown	1 (0.7%)
<b>Type of Radiation</b>	
Standard Dose	118 (85.5%)
Hyperfractionation	5 (3.6%)
Accelerated Fractionation	11 (8.0%)
Other	3 (2.2%)
Unknown	1 (0.7%)
<b>Time from End of Radiation Therapy to First Relapse</b>	
<3 months	24 (17.4%)
3-6 months	52 (37.7%)
>6-9 months	29 (21.0%)
>9-12 months	10 (7.2%)
>12-18 months	9 (6.5%)
>18-24 months	6 (4.3%)
>24 months	5 (3.6%)
Not known	3 (2.2%)
Median	5.6
Range	0.4 - 75.6
<b>Prior Chemotherapy</b>	
Yes	40 (29.0%)
No	98 (71.0%)
<b>Surgery at Initial Diagnosis</b>	
No Surgery	15 (10.9%)
Subtotal Resection	65 (47.1%)
Gross Total Resection	58 (42.0%)
<b>Surgery at First Relapse</b>	
No Surgery	120 (87.0%)
Subtotal Resection	9 (6.5%)
Gross Total Resection	9 (6.5%)

**Table 24 GBM: I94-122: Patient Characteristics per FDA**

Characteristic	Temozolamide 138 Patients
<b>Age</b>	
18-30	7
31-40	14
41-50	27
51-60	58
61-70	26
>70	6
<b>Sex</b>	
Female	53
Male	85
<b>Race</b>	
White	133
Black	0
Other	5
<b>Performance Status</b>	
100	7
90	39
80	33
70	59
<b>Initial Surgery</b>	
Biopsy Only	15
Subtotal Resection	65
Gross Total Resection	58
<b>Initial Radiation Therapy (Gy)</b>	
≤50	20
51-60	102
61-70	14
>70	1
Unknown	1

Table 24  
 GBM: I94122 Continued

Characteristic	Temozolamide 138 Patients
<b>Initial Chemotherapy</b>	
None	91
Nitrosoureas	41
Procarbazine	14
<b>Time From Initial Diagnosis to First Relapse (mo)</b>	
≤3	2
4-6	20
7-9	59
10-12	24
13-18	16
19-24	10
25-36	3
37-48	3
49-60	1
<b>Time from First Relapse to Registration/Randomization (mo)</b>	
≤1	107
2-3	23
>3	8 (4-15)
<b>Did Not Meet Protocol Eligibility</b>	
Ineligible Histology	5
Unknown Histology	3
<b>Surgery at Relapse</b>	
Subtotal Resection	9
Gross Total Resection	5

Table 24  
GBM: I94-122 Continued

Characteristic	Temozolamide 138 Patients
<b>Measurable Tumor Area (cm<sup>2</sup>)</b>	
≤1.0	2
1.1-3.0	6
3.1-6.0	11
6.1-9.0	15
9.1-12.0	10
12.1-15.0	10
15.1-20.0	18
20.1-30.0	33
>30	24 (31-87)
Non-Measurable	9
<b>Symptoms (Baseline)</b>	
Yes	120
No	18
<b>Laboratory Values</b>	
Albumin [median (range)]	3.9 (2.8-7.0)
Hgb	13.6 (6.6-17.8)

8.12.31 Prognostic Differences in TMZ Treated Study Patients in Trials C94091 and I94122

Tables 18 and 24 list characteristics of TMZ treated patients, FDA analysis, enrolled into the two GBM studies. By Kruskal-Wallis test C94091 TMZ patients received significantly higher doses of initial radiation therapy ( $p < 0.05$ ), were more likely to have received chemotherapy as part of initial treatment ( $p < 0.001$ ), had a longer time from initial diagnosis to first relapse ( $p = 0.04$ ), and had smaller measureable tumor area at the time of study enrollment ( $p = 0.023$ ). There were no significant difference in any other patient characteristic.

### 8.13 Treatment Delivery

The median number of cycles delivered in each of the three glioma trials is listed in table 25. The percent of cycles in which protocol specified drug doses were administered is depicted in table 26. In protocol C94-091 one hundred-ten TMZ patients received a total of 484 cycles of TMZ and 110 PCB patients received a total of 167 cycles of PCB. Ninety-six percent (463/484) of TMZ cycles were at the protocol-specified dose levels of 150 or 200 mg/m<sup>2</sup>/day. Similarly, 89% (149/167) of PCB cycles were at the protocol-specified dose levels of 125 or 150 mg/m<sup>2</sup>/day (Table 26). In protocol C/I 94-123 dose reductions occurred in only 4% (42/1168) of cycles. The primary reason for dose reductions (86%, 36/42) was hematologic toxicities. In protocol I94-122, 10% (39/406) of cycles were dose reduced. The majority (90%, 35/39) of dose reductions were due to hematologic toxicities, usually thrombocytopenia, with most dose reductions occurring during the first 2 to 4 cycles of treatment.

**Table 25 All Gliomas: Cycles of Treatment Received Modified from Sponsor**

Protocol	Cycles of Treatment	
	Median	Range
C94-091 TMZ	4	1 - >12
C94-091 PCB	1*	1 - 6
I94-122	4	1 - 14
C/I94-123	7	1 - >12
* cycle length for PCB is 56 days compared to 28 days for TMZ		

**Table 26 All Gliomas: Cycles with Protocol Specified Drug Doses per Sponsor**

Protocol Specified Drug Dose	C94-091 TMZ	C94-091 PCB	I94-122 TMZ	C/I94-123 TMZ
Yes (%)	96	89	96	90
No (%)	4	11	4	10

## 8.14 Treatment Response Rate

Treatment response rate, per sponsor, is indicated in Table 27 and response rate, per FDA, is indicated in Table 28. In the FDA analysis there were 69 documented responses in the three glioma studies. Sixty-two of the 69 responders had measurable disease. The median tumor area at baseline, for responders with measurable lesions, was 6.63 cm<sup>2</sup> (range 0.06 cm<sup>2</sup> to 40.0 cm<sup>2</sup>). Thus responders tended to have smaller tumors at baseline than did the total patient population. The median baseline tumor area for C94-091 patients receiving TMZ or PCB was 12.0 and 12.2 cm<sup>2</sup>, respectively. The median baseline tumor area for patients in trial I 94-122 was 18 cm<sup>2</sup> whereas patients in trial C/I94-123 had a median baseline tumor area of 10.0 cm<sup>2</sup>.

**Table 27 Response Rate per Sponsor**

Response	C94091 TMZ	C94091 PCZ	I94122 TMZ	C/I94123 TMZ
CR (%)	0	0	1	8
PR (%)	5.4	5.3	7	27

**Table 28 Response Rate per FDA**

Response	C94091 TMZ	C94091 PCZ	I94122 TMZ	C/I94123 TMZ
CR (%)	0	0	1	5
PR (%)	4.5	2.7	5	28

Characteristics of responding patients are indicated in Table 29. Included in this table are the numbers of responders in the intent to treat population (ITT), the number of responders with ineligible histology, the number of responders who had no prior chemotherapy, and the number of responders whose chemotherapy did not include a nitrosourea. As indicated in the table, all responding patients enrolled in C94091 had an eligible histology, and only 1 responding patient, randomized to Temozolomide, had not had prior chemotherapy. All 7 chemotherapy treated patients had received a nitrosourea. One of two procarbazine treated responders in C94091 had received prior procarbazine therapy. In I94122 one responder had an ineligible histology and an additional 5 responders had received no prior chemotherapy. In trial C/I94123 six of 53 responders had an ineligible histology. Of the 47 responders with eligible histology 22 had received no prior chemotherapy and two received a non-nitrosourea containing regimen. Thus for AA patients with eligible histology (19 of 162 patients had ineligible or non-evaluable histology) the response rate was 47/143 (33%). The response rate for eligible histology patients who had failed prior nitrosourea with or without concomitant procarbazine treatment was 8/55 (15%) and 15/29 (52%), respectively (Table 30).

**Table 29 Characteristics of Responding Patients per FDA**

	C94091	I94122	C/I94123
Number of Responders (ITT Population)	8	8	53
Ineligible Histology	0	1	6
No Prior Chemotherapy	1 (TMZ)	6*	23*
Chemo. But No Nitrosourea	0	0	3§

\* = 1 of these patients had ineligible histology

§ = 1 of these patients had ineligible histology

**Table 30 C/I94123 Eligible Histology Responders - Prior Chemotherapy per FDA**

Prior Chemotherapy*	Total Eligible Population (143)		Responders (47)		
	Number	(%)	Number	% of Responders	% of Corresponding Eligible Population
None	57	(40)	22	47	39
NU+PCZ+Others	55	(38)	8	17	15
NU-PCZ+Others	29	(20)	15	32	52
Other	2	(2)	2	4	100

\* NU = nitrosoureas, PCZ = procarbazine, + = with PCZ, - = without PCZ, + = with or without.

As indicated in Table 30, 39% of eligible histology patients who had not received chemotherapy as part of their original disease treatment responded to Temozolomide. Patients whose initial chemotherapy included both a nitrosourea and procarbazine had the lowest response rate (15%).

Response duration for C/I94123 histology eligible patients is recorded in Table 31. Whether or not the patient had prior chemotherapy did not seem to influence response duration.

**Table 31 C/I94123 Median Response Duration - Effect of Prior Chemotherapy**

Prior Chemotherapy	# of Patients	Median Response Duration (d)	Range (d)
No	22	191	56+ - 626
Yes	25	238	77 - 797

## 8.15 Time of Tumor Evaluation

Since the sponsor's primary study endpoint is progression free survival at 6 months the timing of tumor evaluations, especially brain MRI's, becomes important. If examinations are delayed that might falsely elevate progression-free survival estimates at various time points. Table 32, from the sponsor, indicates time to tumor evaluation for patients entered on trial C94-091. As indicated on that table during cycle 1 most patients were evaluated during the 30-60 day time period. Patients evaluated earlier were likely early progressors. The critical cycle for this study is cycle 3 which terminates at approximately 6 months into the study. As is evident from the table a total of 8 TMZ patients and 7 PCB patients had delayed evaluations. These delayed evaluations did not affect analysis of progression free survival as patients were censored by FDA, when appropriate, at the time of their last evaluation.

**Table 32 C94-0-91: Time to Tumor Evaluation**

Evaluation a		N	Median Days	Time to Tumor Evaluation (Days)							
				<30	30-60	61-90	91-120	121-150	151-180	181-210	>210
1	TMZ	105	57	7	70	27	1	0	0	0	0
	PCB	99	56	8	72	19	0	0	0	0	0
2	TMZ	60	114	0	6	5	32	15	2	0	0
	PCB	36	113	1	1	3	19	12	0	0	0
3	TMZ	37	170	0	0	1	2	1	25	8	0
	PCB	18	176	0	1	0	0	0	10	6	1
4	TMZ	23	231	0	0	0	0	0	0	2	21
	PCB	4	273	0	0	0	0	0	0	0	4

a: Evaluations were to be done every cycle for PCB (56 days) and every other cycle (56 days) for TMZ.

## 8.16 Survival

The sponsor's progression-free and overall survival analyses, summarized in the following tables and figures, include all study patients (Intent to treat [ITT] patient population). Because each of the trials had patients with ineligible or unknown histologies the FDA performed survival analyses both for the ITT population and the eligible histology population.

Because progression free survival was a primary endpoint of the pivotal trial C94091 the FDA analysis of responses and dates of progression for all three glioma studies were sent to SPRI to resolve, where possible, any disagreements concerning dates, or occurrence, of events. Based on their reply disagreements primarily focused on four areas;

- 1) Criteria of Progression- In the SPRI analysis radiologic progression generally took precedence over progression by neurologic examination so that progression was not

usually declared until an MRI scan was obtained. In the FDA analysis neurologic exam progression and MRI scan progression were weighted equally and whichever result was earliest was counted as the date of progression. The FDA did the analysis this way because the sponsor told the FDA, in response to FDA queries (Section 2.2 of this report) that Schering also used neurologic examination progression in their analysis.

- 2) Censoring- In the SPRI analysis date of death, in an individual without documented progression, was counted as the date of progression. In the FDA analysis individuals who died, without documented progression, were censored on the date of last evaluation for progression.
- 3) Delayed Evaluations- If MRI brain scans were delayed more than one month from the time the protocol stated that they should be obtained and, if that delayed scan demonstrated progression, the individual was censored on the date of the last prior scan.
- 4) Long Duration Response after Apparent Progression – In study C/194123 three patients; 02-076, 14-044 and 15-037, had long duration responses, 2 CR's, 1 PR after an early tumor measurement met the criteria for progressive disease. Because of the apparent beneficial effect of Temozolomide in these patients the early progression date was ignored.

8.161 Survival Pivotal Trial C94-091/196-058 (ITT Population) per Sponsor

Progression free survival (Table 33 and Figure 3) and overall survival (Table 34 and Figure 4) results are reported.

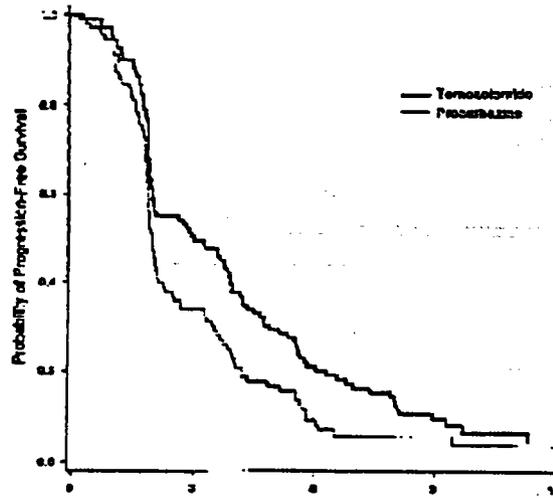
8.16.11 Progression Free Survival

Table 33 C94091/196058: Progression Free Survival (ITT Population) per Sponsor

	N	Median	p-value <sup>a</sup>	Hazard Ratio <sup>c</sup> (95% CI)	6-Month Rate (95% CI)	p-value <sup>b</sup>	Hazard Ratio <sup>c</sup> at 6 months
Temozolomide	112	2.99 mos		1.47	21% (13%-29%)		
Procarbazine	113	1.97 mos	0.0065	(1.11-1.95)	9% (4%-15%)	0.016	1.52

a: Log rank test.  
b: Chi-square test.  
c: Ratio of the log of the 6 month progression-free survival rate.

**Figure 3 C94-091: Progression Free Survival (ITT Population) per Sponsor**



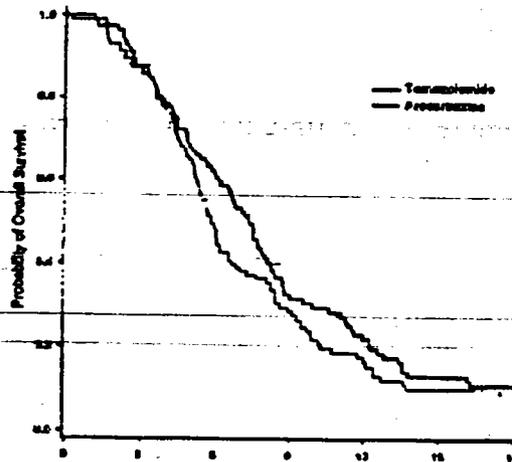
8.16.12 Overall Survival

**Table 34 C94-091: Overall Survival (ITT Population) per Sponsor**

	N	Median	p-value <sup>a</sup>	Hazard Ratio <sup>c</sup> (95% CI)	6-Month Rate (95% CI)	p-value <sup>b</sup>	Hazard Ratio <sup>c</sup> at 6 months
Temozolomide	112	7.34 mos		1.15	60% (51%-70%)		
Procarbazine	113	5.82 mos	0.337	(0.87-1.52)	48% (39%-57%)	0.067	1.46

a: Log rank test.  
 b: Chi-square test.  
 c: Ratio of the log of the 6 month progression-free survival rate.

**Figure 4 C94-091: Overall Survival (ITT Population) per Sponsor**



### 8.16.2 Survival C94-091/196-058 per FDA (ITT Population)

#### 8.16.21 Progression Free Survival

As indicated in Table 35 the FDA analysis also yielded a highly significant difference in median progression free survival in favor of the TMZ treatment group. The p values of the FDA and sponsor analyses were 0.0007 and 0.0065, respectively.

**Table 35 Progression Free Survival (ITT Population) per FDA**

	N	Median	p-value a	6-Month Rate (95% CI)	Difference 6-Month Rate (95% CI)	p-value b
Temozolomide	112	2.70	0.0007	19% (11%-27%)	8%	0.012
Procarbazine	113	mos 1.84 mos		7% (2%-12%)	3.3%-20.7%	

a: Log rank test.  
b Chi-square test.

#### 8.16.22 Overall Survival

No FDA analysis was performed. Results identical to those of the sponsor were expected. See Table 34 and Figure 4.

### 8.16.3 Survival C94-091/196-058 per FDA (Eligible Histology)

Nine patients had ineligible histology, 6 TMZ, 3 PCZ. Four patients had unknown histology, 2 TMZ, 2 PCZ.

#### 8.16.31 Progression Free Survival

As was noted for the ITT population, the median progression free survival of eligible histology patients was significantly longer for TMZ treated versus PCZ treated patients. The lower limit of the 95% CI for 6-month progression free survival decreased to 10%, however. The sponsor defined efficacy as a lower bound of the 95% CI greater than 10% (Table 36).

**Table 36 Progression Free Survival (Eligible Histology Population) per FDA**

	N	Median	p-value a	6-Month Rate (95% CI)	Difference 6-Month Rate (95% CI)	p-value b
Temozolomide	104	2.70 mos		17% (10%-25%)	10%	
Procarbazine	108	1.88 mos	0.003	7% (2%-12%)	1.3%-18.7%	0.04
a: Log rank test. b Chi-square test.						

8.16.32 Overall Survival

As with the ITT analysis there was no significant difference between eligible histology groups in overall survival (Table 37).

**Table 37 Overall Survival (Eligible Histology Population) per FDA**

	N	Median	p-value a	6-Month Rate (95% CI)	Difference 6-Month Rate (95% CI)	p-value b
Temozolomide	104	7.3 mos		61% (51%-70%)	13%	
Procarbazine	108	5.86 mos	0.61	48% (39%-58%)	-0.3%-26.3%	0.07
a: Log rank test. b Chi-square test.						

8.16.4 Survival I94-122 (ITT Population) per Sponsor

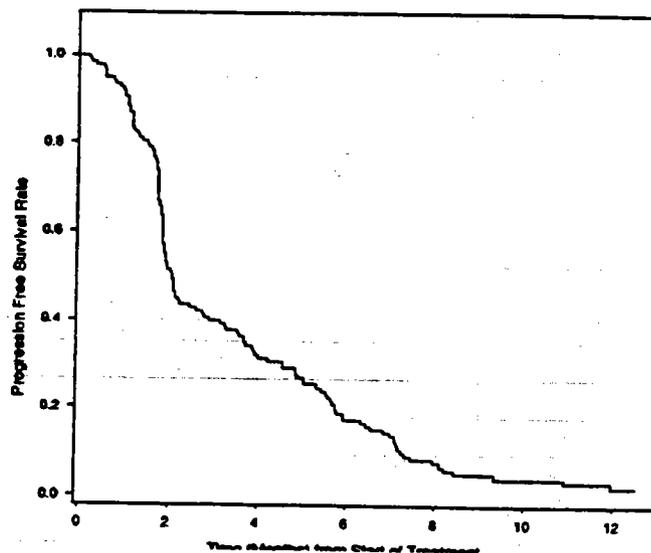
8.16.41 Progression Free Survival

Table 38 and Figure 5 indicates the sponsor's progression free survival analysis, ITT population, for patients with Glioblastoma Multiforme, study I94-122 and Table 40 indicates the FDA analysis.

**Table 38 I94-122 Progression Free Survival (ITT Population) per Sponsor**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression- Free Survival
Temozolomide	138	2.1	19%	(12%-26%)

**Figure 5 I94-122 Progression Free Survival (ITT Population) per Sponsor**



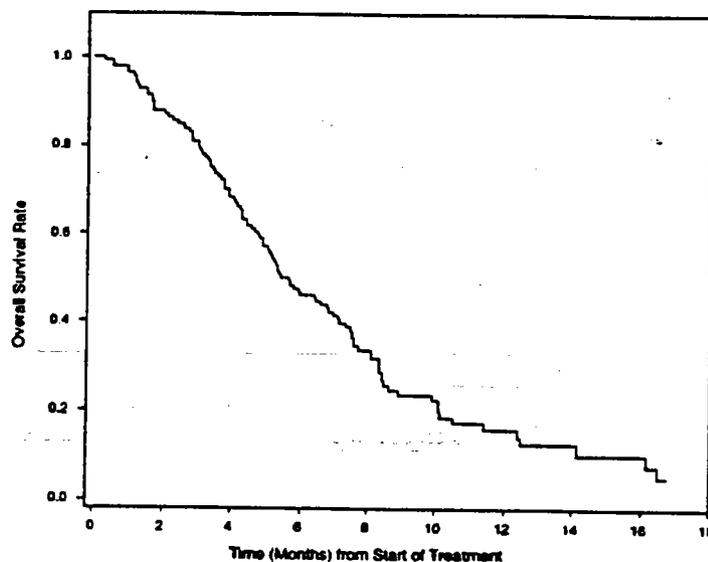
**8.16.42 Overall Survival per Sponsor**

Overall survival results, per sponsor, for study I94-122 are recorded in Table 39 and Figure 6.

**Table 39 I94-122 Overall Survival (ITT Population) per Sponsor**

Treatment	N	Median Overall Survival (months)	6 Month Death Rate (%)	95% CI for 6 month Death Rate
Temozolomide	138	5.4	54	(46%-62%)

**Figure 6 I94-122 Overall Survival (ITT Population) per Sponsor**



**8.16.5 Survival I94-122 (ITT Population) per FDA**

**8.16.51 Progression Free Survival**

**Table 40 I94122 - Progression Free Survival (ITT Population) per FDA**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression-Free Survival
Temozolomide	138	2.24	21	(14%-28%)

**8.16.52 Overall Survival**

Overall survival results for the ITT population were comparable in the analysis of the sponsor and the FDA (Tables 39 and 41). Note that the FDA table reports 6-month survival rate rather than 6-month death rate (Table 39).

**Table 41 I94122 Overall Survival (ITT Population) per FDA**

Treatment	N	Median Overall Survival (months)	6 Month Survival Rate (%)	95% CI for 6 month Survival Rate
Temozolomide	138	5.39	45.8	(37.5-54.1)

**8.16.6 Survival I94-122 (Eligible Histology Population) per FDA**

**8.16.61 Progression Free Survival**

Progression free survival, for eligible histology patients, (Table 42) was comparable to that in the intent to treat population (Tables 38, 40).

**Table 42 I94122 - Progression Free Survival (Eligible Histology Population) per FDA**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression-Free Survival
Temozolomide	131	2.24	20%	(12%-27%)

**8.16.62 Overall Survival**

There was a slight decrease in median survival and 6-month survival when the eligible histology population (Table 43) is compared to the ITT population (Tables 39 and 41).

**Table 43 I94122 - Survival (Eligible Histology Population) per FDA**

Treatment	N	Median Overall Survival (months)	6 Month Survival Rate (%)	95% CI for 6 month Survival Rate
Temozolomide	131	5.33	44.5	(36%-53%)

**8.16.7 C/I94-123 (ITT Population) per Sponsor**

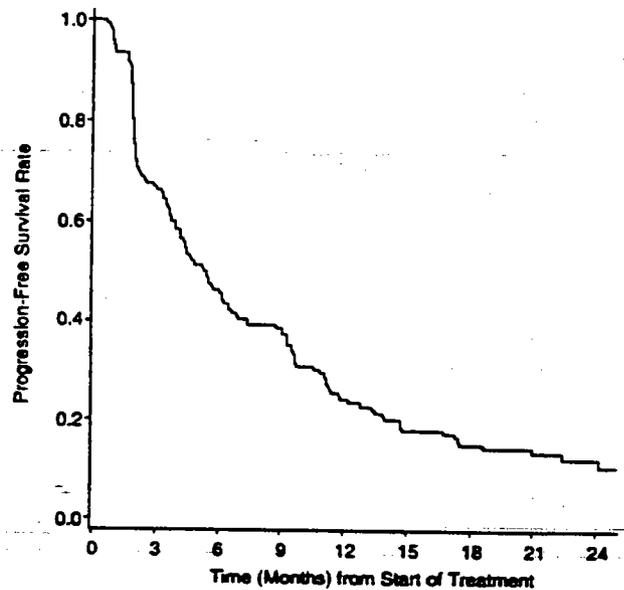
**8.16.71 Progression Free Survival**

Table 44 and Figure 7 indicates the sponsor's progression free survival analysis, ITT population, for patients with Anaplastic Astrocytoma, study C/I94-123. Table 45 and Figure 8 indicate the sponsor's overall survival results for the same patient population.

**Table 44 C/I94-123 Progression Free Survival (ITT Population) per Sponsor**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression-Free Survival
Temozolomide	162	5.4	46%	(38%-54%)

**Figure 7 C/I94123 Progression Free Survival (ITT Population) per Sponsor**

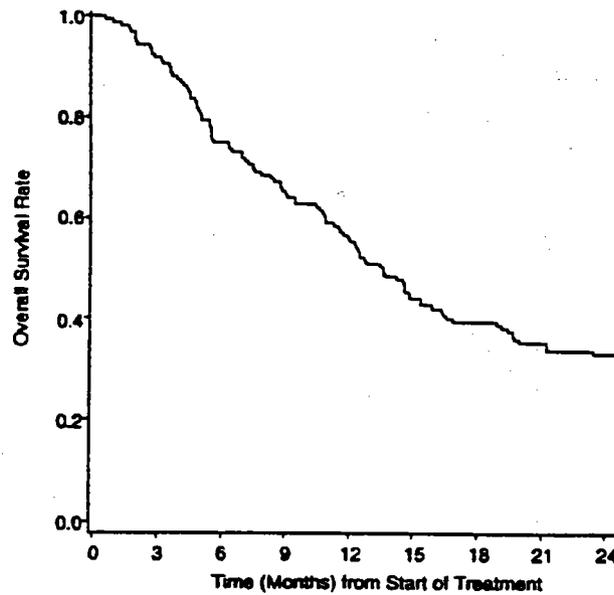


8.16.72 Overall Survival

**Table 45 C/I94123 Overall Survival (ITT Population) per Sponsor**

Treatment	N	Median Overall Survival (months)	6 Month Survival Rate	95% CI for 6 month Survival Rate	12 Month Survival Rate	95% CI for 12 month Survival Rate
Temozolomide	162	13.6	75%	(68%, 82%)	56.1%	(48%-64%)

**Figure 8 C/I94123 Overall Survival (ITT Population) per Sponsor**



**8.16.8 Survival C/I94-123 (ITT Population) per FDA**

**8.16.81 Progression Free Survival**

Progression free survival, ITT group, per FDA is indicated in Table 46. The median PFS was 0.78 months longer in the FDA analysis than in the sponsor's analysis (Table 44).

**Table 46 C/I94123 - Progression Free Survival (ITT Population) per FDA**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression-Free Survival
Temozolomide	162	6.18	51	(43%-59%)

**8.16.82 Overall Survival**

As expected, sponsor and FDA analysis for survival of ITT patients was identical. (Tables 45 and 47).

**Table 47 C/I94123 - Overall Survival (ITT Population) per FDA**

Treatment	N	Median Overall Survival (months)	6 Month Survival Rate (%)	95% CI for 6 month Survival Rate
Temozolomide	162	13.59	75	(68%-82%)

8.16.9 Survival C/I94123 (Eligible Histology Population) per FDA

8.16.91 Progression Free Survival

Comparing Tables 44, 46, and 48 there was a progressive increase in PFS from the sponsor's ITT analysis, to the FDA's and to the FDA eligible histology analysis. The sponsor's PFS (eligible histology population) was 5.53 months with 48% progression free at 6 months..

**Table 48 C/I94123 - Progression Free Survival (Eligible Histology Population) per FDA**

Treatment	N	Median Progression-Free Survival (months)	Progression-Free Survival at 6 months (%)	95% CI for 6 month Progression-Free Survival
Temozolomide	143	6.64	52%	(44%-61%)

8.16.92 Overall Survival

The eligible histology patients (Table 49) had improved overall survival and 6 month survival compared to the ITT population. This was expected as all ineligible histology patients had higher grade gliomas.

**Table 49 C/I94123 - Survival (Eligible Histology Population) per FDA**

Treatment	N	Median Overall Survival (months)	6 Month Survival Rate (%)	95% CI for 6 month Death Rate
Temozolomide	143	14.61	77.3	(74.4%-84.2%)

8.17 Prognostic Factor Analysis

The sponsor performed a Cox regression analysis to identify possible prognostic factors that may have impacted PFS and/or overall survival for each of the 3 glioma trials. Variables included in the model were treatment, age, sex, prior chemotherapy, surgery at initial diagnosis, time from initial diagnosis to first relapse, time from end of radiation therapy at initial diagnosis to first relapse, and baseline KPS. For PFS in trial C94091, baseline KPS was significant ( $p=0.0114$ ); for overall survival, age ( $p=0.0370$ ) and baseline KPS ( $p=0.0023$ ) were significant (Table 50). In the presence of the other factors, the effect associated with treatment remained virtually unchanged.

In trial I94122 no prognostic factors were significant for PFS but sex, time from initial diagnosis to first relapse, time from end of radiation therapy at initial diagnosis to first relapse, and baseline KPS were significant prognostic factors for overall survival.

In trial C/194123 only baseline KPS was a significant prognostic factor for PFS and overall survival..

**Table 50 C94-091 - Prognostic Factors by Cox Regression Analysis per Sponsor**

	PFS a	Overall Survival a
Treatment	0.0052	0.1873
Age	0.0572	0.0370
Sex	0.3027	0.2823
Prior Chemotherapy	0.4705	0.6147
Surgery at Initial Diagnosis	0.2405	0.9009
Time fr Initial Diagnosis to First Relapse	0.0651	0.9527
Time fr End of Radiation to First Relapse	0.6564	0.6582
Baseline KPS	0.0114	0.0023
a: Chi-square test.		

### 8.18 Health-Related Quality of Life (HQL)

The HQL analysis specified in the protocol (Section 11.3.5) was a longitudinal comparison of HQL between the two treatment arms. **This analysis has not been performed.** It was not possible to do a longitudinal analysis because of the large amount of censored and missing data. Instead, a variety of other analyses, not specified in the protocol, summarized below, were done including a Q-TWiST (Quality-adjusted Time Without Symptom or Toxicity) analysis. It must be emphasized, however, that FDA does not accept these types of HQL analyses and that any claims made on the basis of this data should be interpreted with caution.

The sponsor's HQL analyses focused on 7 HQL domains considered by a panel of clinical/HQL experts as having the most clinical relevance to patients with primary brain cancer. The 7 domains were Role, Social, and Global QOL from the EORTC QLQ-C30 (+3), and Visual disorder, Motor dysfunction, Communication deficit, and Drowsiness from the published brain cancer module (BCM20). In the analysis a 10-point improvement from baseline maintained for at least 2 consecutive months, was considered significant.

Forty-six of 225 C94091/196058 protocol patients (ITT population) had either no HQL data (16 patients), no baseline HQL data (4 patients), or no post-baseline HQL data (26 patients) and, therefore, were ineligible for any HQL analyses. Thus, a comparison of the treatments included 179 patients (89 TMZ, 90 PCB).

#### 8.18.1 Baseline HQL Profile

Baseline HQL profiles, including QLQ-C30(+3) functioning and symptom scale scores as well as BCM20 symptom scores, were generally similar for the 2 treatment groups.

### 8.18.2 HQL of Patients Progression-Free at 6 Months

To assess the relative HQL benefit of being progression-free at 6 months, a change from baseline analysis was carried out for the 20 TMZ patients and 8 PCB patients who were progression-free survivors at 6 months and had HQL data (2 TMZ, 1 PCB were progression-free at 6-months, but did not have HQL data). Results showed that HQL domain scores were improved over baseline in 5 out of 7 HQL domains for TMZ progression-free survivors at 6 months and were lower than baseline in all 7 HQL domains for PCB progression-free survivors at 6 months (Table 51).

**Table 51 C94091 Change from Baseline HQL Score in Progression Free Survivors at 6 Months**

C94-091 Change from Baseline HQL Score in Progression Free Survivors at 6 Months							
Mean (SD) Change in Score							
Functioning Scale a				Symptom scale b			
	Role	Social	Global QOL	Visual disorder	Motor dysfunction	Communication deficit	Drowsiness
TMZ (N=20)	6.1 (21.7)	8.8 (27.4)	-3.4 (30.9)	8.0 (29.0)	-2.3 (28.3)	-4.1 (22.6)	-15.8 (25.7)
PCB (N=8)	-16.7 (33.3)	-25.0 (40.8)	-2.1 (28.1)	6.3 (8.7)	11.1 (17.8)	16.7 (20.6)	8.3 (29.5)

a: Functioning scale score ranges from 0 to 100 with a high score representing a high functioning; a positive change score means improvement in functioning.  
b: Symptom scale score ranges from 0 to 100 with a high score representing a worse symptom; a negative change score means improvement in symptom.

### 8.18.3 Number And Percent Of Patients Improving HQL or Maintaining High Functioning

Treatment effect on patients' HQL was also evaluated by determining the proportion of patients who improved or maintained a high functioning level in an HQL scale at a given time point. An HQL domain score was classified into one of 5 categories: 0-20, 21-40, 41-60, 61-80, and 81-100. HQL improvement or maintenance in good functioning was defined as follows (Table 52):

**Table 52 Definitions for HQL Improvement**

Baseline Score Level	Post-treatment Score level
0-20	41-100
21-40	41-100
41-60	61-100
61-80	61-100
81-100	81-100

The number of patients who achieved HQL improvement or maintained a good

functioning level at 3 months and 6 months in 3 functioning domains (Role, Social, and Global QOL) was assessed. Although the percent of patients who maintained or had improvement in HQL was similar between the groups, a much higher number of TMZ patients than PCB patients remained in the study for HQL assessment (Table 53).

**Table 53 Improvement or Maintenance of a Good Functioning Level**

C94-091- Improvement or Maintenance of a Good Functioning Level				
	Number (%) of Patients a			
	Month 3		Month 6	
	TMZ	PCB	TMZ	PCB
Role	24/47 (51%)	14/28 (50%)	13/23 (57%)	5/7 (71%)
Social	23/47 (49%)	16/28 (57%)	14/23 (61%)	3/7 (43%)
Global QOL	25/47 (53%)	12/27 (44%)	10/23 (43%)	4/7 (57%)

a: Number stable or improved divided by the number who had HQL data at Month 3 and Month 6

#### 8.18.4 HQL Response

HQL response rates were consistently higher across all 7 domains for TMZ patients compared to PCB patients (Table 54). HQL response rates were tabulated based on patients with HQL impairment at baseline (ie, functioning score <90 or symptom score >10).

**Table 54 HQL Response Rates**

	% of Patients with a HQL Response	
	TMZ	PCB
Role	28	18
Social	35	17
Global	18	16
Visual Disorder	35	22
Motor Dysfunction	34	16
Communication Deficit	44	21
Drowsiness	22	15

#### 8.18.5 Quality-Adjusted Survival (Q-TWiST) Analysis

The sponsor also performed a Q-TWiST (Quality-adjusted Time Without Symptom or Toxicity) analysis (not planned in protocol). This analysis indicated that there were no possible utility combinations where PCB was superior to TMZ in quality-adjusted survival time. Overall, the Q-TWiST analysis showed that even when quality of life outcomes such as toxicity and progression are considered together with the overall survival data from the trial, resulting quality-adjusted survival would always favor TMZ.

## 9. Safety in Relapsed Glioma Patients

### 9.1 Temozolomide

Four hundred TMZ treated, relapsed glioma, patients in three clinical trials, received 2202 cycles of Temozolomide. Ninety-five percent (2081/2202) of the cycles were at the specified dose levels (Table 55). The specified doses for TMZ were: 150 mg/m<sup>2</sup> /day over 5 days (750 mg/m<sup>2</sup> total dose) for patients who had received previous chemotherapy and 200 mg/m<sup>2</sup> /day over 5 days (1000 mg/m<sup>2</sup> total dose) for those who had not received prior chemotherapy. Based on their history of prior chemotherapy, most patients were dosed at the correct level.

**Table 55 Distribution of Relapsed Glioma Patients by Cycle and TMZ Dose per Sponsor**

Cycle	Number of Patients			Total
	<150 mg/m <sup>2</sup> /day	150-200 mg/m <sup>2</sup> /day	>200 mg/m <sup>2</sup> /day	
1	3	397	0	400
2	14	346	0	360
3	16	232	2	250
4	16	201	1	218
5	10	159	1	170
6	13	140	1	154
7	9	114	1	124
8	10	101	0	111
9	4	78	0	82
10	4	70	0	74
11	2	54	0	56
12	3	50	0	53
>12	11	139	0	150
Total	115 cycles	2081 cycles	6 cycles	2202 cycles

#### 9.11 Adverse Events

The most common adverse events were nausea, vomiting, headache, fatigue, and constipation, findings that were consistent across all studies (Table 56). Nausea and vomiting were usually mild or moderate and either resolved spontaneously or were readily controlled with standard antiemetics. In addition, the following hematologic adverse events were also reported: thrombocytopenia (9%), neutropenia (4%), leukopenia (4%), and anemia (3%). Recovery from the nadir value to at least grade 2 (or to the baseline value) for each hematologic nadir event usually occurred within 7-10 days (Table 58).

Most adverse events were mild to moderate, and only 11% (45/400) of patients experienced a grade 4 AE (Table 57). The grade 4 hematologic adverse events that

occurred at a frequency of >1% were the following: thrombocytopenia (5%), neutropenia (2%), and leukopenia (2%). Grade 3 adverse events were reported in 41% (163/400) of patients. Many of these adverse events were expected to occur in view of the patient's underlying disease and most were considered related to disease progression. With respect to the types and frequencies of adverse events, there was a high degree of consistency among the various glioma trials. Consequently, in reporting the data, all three glioma trials will be reported together.

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**Table 56 Adverse Events Reported in >2% of Relapsed Glioma Patients Modified From Sponsor**

All Gliomas c		All Gliomas c	
Adverse Event a	TMZ (N=400)	Adverse Event a	TMZ (N=400)
Number of Patients Reporting Any AE	97% (388)		
Nausea	46% (185)	Dyspnea	5% (19)
Headache	41% (162)	Petechiae	5% (18)
Vomiting	38% (151)	Weight increase	5% (18)
Fatigue	31% (122)	Alopecia	4% (17)
Constipation	24% (95)	Purpura	4% (17)
Convulsions	24% (94)	Vision abnormal	4% (17)
Hemiparesis	20% (78)	Candidiasis, oral	4% (16)
Pain	16% (62)	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)	Agitation	4% (14)
Fever	12% (46)	Micturition frequency	4% (14)
Ataxia	11% (45)	Neutropenia d	4% (14)
Asthenia	11% (44)	Pneumonia	4% (14)
Confusion	11% (43)	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)
Urinary incontinence	9% (34)	Dysphagia	3% (11)
Coordination abnormal	8% (33)	Hypertension intracranial	3% (11)
Dizziness	8% (33)	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)
Speech disorder	6% (22)	Embolism pulmonary	2% (9)
Pharyngitis	5% (21)	Erythema	2% (9)
Convulsions local	5% (19)	Facial palsy	2% (9)
Dyspepsia	5% (19)	Hypoesthesia	2% (9)
		Malaise	2% (9)
		Breast pain, female a	3% (4)

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.

**Table 57 Grade 3 and Grade 4 Adverse Events Reported in Relapsed Glioma Patients Modified from Sponsor**

Body System/ Adverse Event <sup>a</sup>	Grade 3	Grade 4		Grade 3	Grade 4
All Gliomas <sup>c</sup> TMZ (N= 400)					
Number of Patients Reporting Any AE	41% (163)	11% (45)			
Nausea	6% (25)	0	Purpura	<1% (2)	0
Headache	7% (28)	0	Vision abnormal	<1% (2)	0
Vomiting	5% (20)	<1% (1)	Myalgia	<1% (1)	0
Fatigue	4% (17)	1% (3)	Leukopenia <sup>d</sup>	2% (7)	2% (6)
Constipation	1% (5)	0	Thrombophlebitis deep	1% (3)	2% (6)
Convulsions	5% (18)	<1% (2)	Neutropenia <sup>d</sup>	2% (6)	2% (7)
Hemiparesis	7% (27)	<1% (2)	Pneumonia	1% (5)	<1% (1)
Somnolence	4% (14)		Thinking abnormal	<1% (2)	0
Amnesia	4% (15)	<1% (1)	Moniliasis	<1% (1)	0
Diarrhea	1% (3)	0	Myopathy	<1% (2)	0
Anorexia	<1% (2)	0	Papilledema	<1% (2)	0
Fever	1% (5)	<1% (1)	Respiratory disorder	0	<1% (1)
Ataxia	3% (10)		Vertigo	<1% (1)	0
Asthenia	04% (15)	1% (4)	Anemia <sup>d</sup>	1% (3)	<1% (2)
Confusion	3% (11)	0	Dysphagia	1% (3)	0
Edema peripheral	<1% (2)	0	Hypertension intracranial	2% (7)	0
Gait abnormal	2% (8)	1% (3)	Concentration impaired	<1% (2)	0
Adrenal hypercorticism	1% (3)	0	Hypokinesia	1% (3)	0
Dysphasia	3% (10)	0	Micturition disorder	<1% (1)	0
Paresis	2% (9)	0	Pulmonary infection	<1% (1)	<1% (1)
Insomnia	<1% (1)	0	Syncope	1% (3)	0
Thrombocytopenia <sup>d</sup>	3% (12)	5% (19)	Apathy	1% (4)	0
Urinary incontinence	3% (10)	0	Embolism pulmonary	1% (5)	1% (3)
Coordination abnormal	1% (4)	0	Malaise	<1% (1)	0
Dizziness	<1% (2)	0			
Paresthesia	<1% (2)	0			
Depression	<1% (1)	0			
Anxiety	<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.

### 9.11.1 Temozolomide Hematologic Toxicity – Study C94-091/I96-058

Hematologic toxicity associated with TMZ treatment, study C94091, is indicated in Table 58. Compared to procarbazine treated patients in the same study, Table 62, TMZ produced more thrombocytopenia with comparable anemia and neutropenia. Most neutropenias and thrombocytopenias were severity grade 3 or 4 with both drugs. Time to recovery from hematologic toxicity is summarized in Table 59.

**Table 58 C94091 Temozolomide Hematologic Toxicity from FDA (112-Pts)**

	Number of Patients	Severity Grade 3/4
Anemia	10	2
Leukopenia	3	2
Neutropenia	11	9
Thrombocytopenia	26	22

**Table 59 Time From Nadir to Recovery for Hematologic Parameters in Relapsed Glioma Patients Modified From Sponsor**

	No. of Nadir Events <sup>a</sup>	Time to Recovery (Days)
		Median
Hemoglobin	12	7.0
Neutrophils	58	9.5
Platelets	86	9.5
White Blood Cells	62	10.5

a: Recovery to:  $\geq 1.5 \times 10^3$  /mm<sup>3</sup> for ANC,  $\geq 100 \times 10^3$  /mm<sup>3</sup> for platelets, 9.5 mg/dL for hemoglobin,  $.3.0 \times 10^3$  /mm<sup>3</sup> for WBC.

#### 9.12 Non-hematologic Laboratory Abnormalities

There were few non-hematologic laboratory abnormalities. Five percent of TMZ-treated patients had increased glucose, 1% had an increased SGOT, 1% had an increased SGPT, and 1% had increased total bilirubin (Table 60). Increased glucose was probably secondary to steroid use in these patients.

**Table 60 Changes in Non-Hematology Laboratory Data from Grade 0-2 to Grade 3-4 During Treatment of Relapsed Glioma Patients From Sponsor**

	TMZ <sup>a</sup>
Alkaline Phosphatase	0/284
Creatinine	<1% (1/289)
Glucose Increased	5% (19/369)
SGOT	1% (3/273)
SGPT	1% (2/243)
Total Bilirubin	1% (4/275)

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

## 9.2 Procarbazine

### 9.21 Non-Hematologic Toxicity Compared to Temozolomide

Non-hematologic toxicity, during the first 56 days of treatment of patients enrolled in C94-091/196-058 is depicted in Table 61. Fifty-six days was chosen because the majority of procarbazine treated patients had therapy discontinued at that time. Toxicity was generally similar between treatment groups [95% (104/110) for TMZ, 90%, (99/110) for PCB]. However, the incidence of grade 3/4 AEs was 26% (29/110) with TMZ compared with 35% (38/110) with PCZ.

**Table 61 Adverse Events TMZ or PCZ - Days 1-56 per Sponsor**

No. (%) Reporting AE	Number (%) of Patients a			
	Temozolomide (N=110)		Procarbazine (N=110)	
	All AEs	Grade 3/4 AEs	All AEs	Grade 3/4 AEs
	104 (95%)	29 (26%)	99 (90%)	38 (35%)
Headache	43 (39%)	9 (8%)	26 (24%)	5 (5%)
Nausea	43 (39%)	4 (4%)	37 (34%)	3 (3%)
Vomiting	33 (30%)	4 (4%)	28 (25%)	5 (5%)
Fatigue	29 (26%)	1 (1%)	22 (20%)	3 (3%)
Ataxia	18 (16%)	2 (2%)	8 (7%)	3 (3%)
Constipation	21 (19%)	1 (1%)	17 (15%)	1 (1%)
Convulsions	12 (11%)	3 (3%)	12 (11%)	6 (5%)
Somnolence	14 (13%)	4 (4%)	6 (5%)	1 (1%)
Edema peripheral	10 (9%)	1 (1%)	7 (6%)	0
Gait abnormal	13 (12%)	4 (4%)	3 (3%)	0
Hemiparesis	12 (11%)	2 (2%)	12 (13%)	5 (5%)
Pain	11 (10%)	1 (1%)	9 (8%)	0
Confusion	7 (6%)	1 (1%)	7 (6%)	1 (1%)
Anorexia	11 (10%)	0	15 (14%)	4 (4%)
Amnesia	6 (5%)	3 (3%)	7 (6%)	0
Coughing	8 (7%)	0	11 (10%)	0
Rash	10 (9%)	0	17 (15%)	1 (1%)
Diarrhea	6 (5%)	0	11 (10%)	2 (2%)
Dysphasia	8 (7%)	2 (2%)	7 (6%)	1 (1%)
Fever	8 (7%)	1 (1%)	3 (3%)	0
Insomnia	9 (8%)	0	8 (7%)	0
Urinary incontinence	8 (7%)	1 (1%)	10 (9%)	0
Aphasia	3 (3%)	1 (1%)	6 (5%)	1 (1%)
Asthenia	5 (5%)	0	6 (5%)	3 (3%)
Candidiasis oral	8 (7%)	0	8 (7%)	0
Paresthesia	5 (5%)	0	4 (4%)	0
Purpura	6 (5%)	1 (1%)	2 (2%)	0
Dizziness	3 (3%)	0	5 (5%)	0
Dyspepsia	2 (2%)	0	8 (7%)	0
Petechiae	5 (5%)	1 (1%)	2 (2%)	0
Pharyngitis	5 (5%)	0	4 (4%)	0
Speech disorder	5 (5%)	1 (1%)	1 (1%)	1 (1%)
Abdominal pain	3 (3%)	0	5 (5%)	1 (1%)
Back pain	3 (3%)	0	6 (5%)	0
Tremor	1 (1%)	0	7 (6%)	0

a: A patient was counted only once if >1 occurrence of a specific AE.

### 9.22 Procarbazine Hematologic Toxicity

Twenty-seven of 110 procarbazine treated patients manifested hematologic toxicity (Table 62). Toxicity was grade 3/4 in 18 of these individuals. One death occurred during drug induced neutropenia. The percent of patients with the various hematologic toxicities was similar for PCZ and TMZ (see section 9.11).

**Table 62 Trial C94091 Procarbazine Hematologic Toxicity from FDA (110 Pts)**

	Number of Patients	Severity Grade 3/4
Anemia	9	4
Neutropenia	5	3
Thrombocytopenia	11	10
Pancytopenia	2	1

### 9.3 Therapy Discontinuation Due To An Adverse Event

As summarized by the sponsor, in clinical trial (C94-091), 3 TMZ patients and 11 PCB patients discontinued treatment due to AEs (Table 63). The 3 discontinuations in the TMZ group were due to: pneumonia (1 patient), thrombocytopenia (1 patient), and a combination of nausea, rash, and vomiting (1 patient); the pneumonia was considered unrelated to treatment. The 11 discontinuations in the PCB group were due to a variety of reasons; 8 were considered treatment-related. In the supportive study (I94-122), 3 patients discontinued because of adverse events. One patient had hematologic toxicity judged as related to treatment by the investigator, one patient discontinued due to a rash judged as probably treatment-related by the investigator, and one patient discontinued due to hematologic toxicity and petechiae judged as related by the investigator. In study C/I94-123, 9 patients discontinued from the study due to adverse events. Five out of the nine discontinuations involved hematologic toxicities (thrombocytopenia with or without neutropenia or leukopenia). Six of the nine discontinuations were considered related to the study drug, 2 were unrelated and the relationship of one was unknown.

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**Table 63 Patients Discontinuing Treatment Due to Adverse Events per Sponsor**

Patient No.	Dose Level a Onset (Cycle/Day)	Relationship to Drug b	Adverse Event	Outcome
<b>Study C94-091</b>				
243	TMZ 150 mg/m <sup>2</sup> (2/43)	Unrelated	Pneumonia (grade 2)	Hospitalized, study medication discontinued
617	TMZ 200 mg/m <sup>2</sup> (9/249)	Unrelated Related	Diarrhea (grade 2) Nausea, vomiting (grade 2)	Study medication discontinued
621	TMZ 200 mg/m <sup>2</sup> (2/86)	Related	Thrombocytopenia (grade 4)	Study medication discontinued
022	PCB 125 mg/m <sup>2</sup> (1/25)	Probable	Pruritus (Grade 3)	Study medication discontinued
102	PCB 125 mg/m <sup>2</sup> (1/28)	Possible Possible	Anorexia (Grade 3) Fatigue (Grade 2)	Study medication discontinued
227	PCB 125 mg/m <sup>2</sup> (1/50)	Unrelated	Intracranial hemorrhage (Grade 1)	Hospitalized, study medication discontinued
237	PCB 125 mg/m <sup>2</sup> (1/6)	Probable	Pulmonary infiltration (Grade 2)	Hospitalized, study medication discontinued
247	PCB 125 mg/m <sup>2</sup> (1/2)	Unrelated	Pneumonia (Grade 2)	Hospitalized, study medication discontinued
281	PCB 125 mg/m <sup>2</sup> (1/18)	Possible	Cachexia (Grade 3)	Study medication discontinued
302	PCB 125 mg/m <sup>2</sup> (1/2)	Probable Probable Possible	Nausea (Grade 3) Vomiting (Grade 3) Headache (Grade 2)	Hospitalized, study medication discontinued
313	PCB 150 mg/m <sup>2</sup> (1/83)	Probable	Rash (Grade 2)	Study medication discontinued
614	PCB 150 mg/m <sup>2</sup> (2/12)	Unrelated	Asthenia (Grade 2)	Hospitalized, study medication discontinued
636	PCB 150 mg/m <sup>2</sup> (1/25)	Related	Drug-induced hepatitis (Grade 4)	Study medication discontinued
642	PCB 150 mg/m <sup>2</sup> (1/20)	Possible	Headache, vomiting (Grade 3)	Study medication Discontinued
<b>Study I94-122</b>				
021	TMZ 200 mg/m <sup>2</sup> /day (1/3)	Probable	Rash, urticaria (both Grade 2)	Received clemastine 1 mg as needed
044	TMZ 150 mg/m <sup>2</sup> /day (1/15)	Related	Thrombocytopenia (Grade 4)	Received platelet transfusions
115	TMZ 150 mg/m <sup>2</sup> /day (2/79)	Related	Pancytopenia (Grade 4) Petechiae (Grade 2)	Received filgrastim, hospitalized
<b>Study C/94-123</b>				
004	TMZ 150 mg/m <sup>2</sup> /day Cycle 19	Unrelated Unrelated	Epilepsy (grade 3) Cerebral edema (grade 3)	Hospitalization, study medic- ation discontinued
037	TMZ 200 mg/m <sup>2</sup> /day Cycle 17	Unknown	Thrombocytopenia (grade 1)	Study medication discontinued
070	TMZ 200 mg/m <sup>2</sup> /day Cycle 2 and Cycle 5	Probably Possibly Unrelated	Thrombocytopenia (grade 4) Fatigue (grade 3) Pulmonary embolism (grade 3)	Hospitalization
076	TMZ 200 mg/m <sup>2</sup> /day Cycle 9	Related Related	Neutropenia (grade 3) Thrombocytopenia (grade 1)	Study medication discontinued

Patient No.	Dose Level a Onset (Cycle/Day)	Relationship to Drug b	Adverse Event	Outcome
081	TMZ 150 mg/m <sup>2</sup> /day Cycle 1	Unrelated Unrelated Unrelated	Asthenia (grade 3) Obtundation (grade 3) Moniliasis (grade 4)	Study medication discontinued, hospitalization
089	TMZ 200 mg/m <sup>2</sup> /day Cycle 14	Possibly	Fatigue (grade 1)	Study medication Discontinued
091	TMZ 200 mg/m <sup>2</sup> /day Cycles 1-4	Related	Thrombocytopenia, leukopenia, anemia (grade 4) Neutropenia (grade 3)	Hospitalization, Study medication discontinued
094	TMZ 200 mg/m <sup>2</sup> /day Cycle 10	Probably Probably	Neuralgia due to shingles (grade 3) Herpes Zoster (grade 3)	Study medication Discontinued
114	TMZ 200 mg/m <sup>2</sup> /day Cycle 2	Related Probably	Fever and leukopenia (grade 3) Thrombocytopenia and hemorrhage (grade 4)	Study medication discontinued

a: Represents the total daily cycle dose administered at the time of patient discontinuation or the last cycle dose administered just prior to patient discontinuation.

b: Relationship determined by the investigator.

#### 9.4 Other Safety Data

Review of physical examinations, neurologic examinations, vital signs, and electrocardiograms did not identify any other toxicities associated with TMZ treatment.

#### 9.5 Deaths

In C94-091, a total of 14 patients (5 TMZ and 9 PCB) died within 30 days of their last dose of study medication. Eleven of these 14 deaths were due to disease progression or disease-related complications (4 TMZ and 7 PCB). The cause of death for 1 TMZ patient was listed as unknown. Two PCB patients died of AEs, with both considered related to treatment, hepatic failure in one, neutropenia in the other.

In I94-122, 16 patients died within 30 days of the last dose of study medication. Eight of these deaths were judged not to be related to TMZ treatment and included 2 with venous thrombosis and/or thromboembolism, 3 with disease progression and 3 miscellaneous. The deaths related to TMZ treatment included 3 with thrombocytopenia, 2 with bleeding in the absence of thrombocytopenia, one with leukopenia, and one each with an ischemic event, brain edema and worsening asthenia.

In C/I94-123, there were 9 reports of deaths within 30 days of the last dose of study medication. Eight of these deaths were related to disease progression or disease-related complications, and the remaining patient (patient 022) died due to an adverse event. Patient 022 developed grade 4 cerebral ischemia, after being hospitalized for grade 2 cerebral edema, grade 3 headache and somnolence, and grade 2 nausea and vomiting, and expired within 20 days of the last dose of study medication. The investigator assessed this event as possibly related to study treatment.

### **9.6 Specific Serious Adverse Events**

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

## **10. Literature Summary**

The relevant literature was reviewed for two purposes 1) To place the results of the three relapsed glioma studies in perspective and 2) to determine the accuracy of current MRI imaging for accurately defining tumor margins.

### **10.1 Relapsed Glioma Trials**

To place the results of the SPRI relapsed glioma trials in perspective the literature was reviewed by the FDA. The following tables (Tables 64 and 65) summarize those trials. Accepted prognostic factors for this group of patients includes age, performance status and prior chemotherapy. Generally, younger patients have better survival outcome compared to older patients although the exact age cut-off for the survival difference varies from one report to another. As expected, patients with good performance status survive longer than patients with poor performance status. Prior chemotherapy has less impact on survival than the former factors but is usually included in multivariate analysis as significantly contributing to outcome. Endpoints in these tables are standard and include response rate and the two survival categories.

As indicated in these tables characteristics of study patients are generally similar from study to study. Outcomes are also relatively comparable with median survival, of systemic therapy relapsed glioblastoma multiforme trials, in the range of 20 to 40 weeks.

As is evident from these trials patients with relapsed anaplastic astrocytoma have better outcomes than patients with glioblastoma multiforme with median survivals often exceeding one year.