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Dear Alana,

RE: CARMUSTINE IMPLANTS AND TEMOZOLOMIDE FOR THE TREATMENT OF NEWLY DIAGNOSED HIGH-GRADE GLIOMA. (APPRAISAL CONSULTATION DOCUMENT)

Schering-Plough welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for temozolomide (TMZ) in newly diagnosed glioblastoma. It is a matter of great concern that NICE has drafted an ACD with a preliminary recommendation that TMZ should not be used within the NHS for the treatment of newly diagnosed glioblastoma. This constitutes an alarming denial of patient access to a treatment that represents a major breakthrough in malignant glioma. Schering-Plough's principal comments in relation to the ACD are as follows:

1. The EORTC study unequivocally demonstrates the superior efficacy, acceptable toxicity, and preservation of quality of life by TMZ in the treatment of newly-diagnosed glioblastoma.[1] Recommendations for further research, as set out in section 5 of the ACD are therefore perverse.

2. The suggestion to conduct a head-to-head trial of TMZ versus PCV in this patient population is wholly inconsistent with published clinical trial evidence.

3. The Assessment Group (AG) economic model contains critical errors. Recommendations based on the results of the AG model are unreliable.

4. Contrary to the final scope for this appraisal, the AG failed to consider the cost-effectiveness of TMZ in subgroups that are easily defined according to the scientific literature. Consistent with current UK clinical practice, patients with known poor prognostic factors (WHO performance status >2) are unlikely to receive aggressive therapy.

Schering-Plough believes that the AG model contains a number of critical errors and that the estimates of cost-effectiveness generated are therefore unreliable. However, with respect to the overall recommendations set out in the ACD, Schering-Plough requests that NICE reconsider these in the context of important and relevant precedents for recommending end-stage cancer treatments with ICERs exceeding £30,000/QALY. NICE has previously accepted an ICER of £49,000/QALY for the treatment of the blast crisis phase of chronic myeloid leukaemia with imatinib (Rawlins and Culyer, 2004).

In addition NICE has previously issued positive guidance for other oncology treatments, where the cost/QALY has exceeded an incremental £30,000/QALY, and additionally in the *absence* of an incremental cost per QALY. In these cases, the economic outcome was incremental cost per life year gained (as was used in the Schering-Plough submission for this appraisal) or incremental cost per year of disease free progression.

The AG concludes that treatment with TMZ yields an ICER of £46,000/QALY and suggests that TMZ may not be cost-effective. Given the precedent of NICE accepting ICERs exceeding £30,000/QALY for other treatments of end-stage cancers, the preliminary ACD recommendation should be re-considered.

Schering-Plough requests an explanation as to why the AG failed to respond to our final comments regarding the HTA report, as set out in our letter of November 11th. This was previously agreed with the Institute. In our letter of November 11th, we requested that the AG respond to specific issues in relation to the HTA report including the failure to evaluate cost-effectiveness in established patient subgroups, and a number of errors in relation to the estimation of treatment costs by the AG. We request feedback on this matter as soon as possible.

SCHERING-PLOUGH RESPONSE TO ACD

Section 1.3

The ACD states that 'Clinical studies on …temozolomide for the treatment of newly-diagnosed high-grade glioma in adults and children should include research into: impact on quality of life, long-term effectiveness, subgroups for which the treatments may be particularly effective, and comparison with other chemotherapy regimens.'

Schering-Plough Response:

While further research is always useful, we would encourage the Appraisal Committee to consider the following:

Re: Quality of life

A quality of life analysis of EORTC 26981 was published in November, 2005 in *Lancet Oncology* by Taphoorn et al.[2] These data were submitted as "Academic in Confidence" as part of our original dossier. In this study, quality of life was not impaired with the addition of TMZ to radiation.

More important, as progression-free survival was also significantly improved by the combined treatment, it indicates that the survival benefit conferred on patients was in time without progression. That is, the treatment does not merely lengthen disease progression, it provides meaningful, quality of survival.

Re: Long-term effectiveness

In a patient population where the average survival was historically less than 12 months, the EORTC study median follow-up of 28 months, with 26% of TMZ patients alive at 2 years, represents long-term effectiveness.

Re: Subgroups that derive substantial benefit

We would like to make the Appraisal Committee aware of the Appendix 1 to this letter, which contains Supplemental Table 1 and Supplemental Figure 1, originally published in the on-line version of the NEJM article. In the study, virtually all subgroups derived significant benefit from TMZ/RT versus radiotherapy alone, attesting to the robustness of the study data. Patients with poor prognostic factors (i.e., poor performance status; WHO PS = 2) did not derive substantial benefit from combined modality treatment.

Re: Comparison with other chemotherapeutic regimens

We would like to make the Appraisal Committee aware of the study published in 2001 in the *Journal of Clinical Oncology* by the MRC Brain Tumour Working Group.[3]

The UK MRC trial categorically demonstrated no survival benefit with PCV plus radiotherapy compared to radiotherapy alone in patients with high-grade astrocytoma, Grade III and Grade IV (*see Appendix 2, Figures 2 and 4*). Therefore, there is absolutely no basis for subjecting patients with grade IV glioblastoma to the toxicities of PCV, an ineffective regimen, as proven by the UK

MRC trial. In fact, this trial provides complete and total support for the study design used in the EORTC trial, i.e. a control arm with radiotherapy only.

Section 2.6

The ACD states: 'Adjuvant chemotherapy is not considered part of standard therapy in the UK, but is used more routinely in the USA.'

Schering-Plough Response:

We agree that, in light of the MRC trial, adjuvant chemotherapy with PCV is not considered part of standard therapy in the UK. However, this statement contradicts the Appraisal Committee's recommendation that TMZ be studied in conjunction with other chemotherapies (see Response to Section 1.3) in this patient population of newly-diagnosed glioblastoma. We are unclear as to why the Appraisal Committee would recommend a head-to-head trial versus a regimen that has been demonstrated to show no survival benefit and is admittedly not standard of care in the UK.

Section 4.1.10

The ACD states: 'Median survival was 14.6 months (95% CI: 13.2 to 16.8 months) in the radiotherapy plus temozolomide group and 12.1 months (95% CI: 11.2 to 13 months) in the radiotherapy only group.'

Schering-Plough Response

The AG and the ACD fail to address the results of the subgroup analysis as reported in the NEJM publication by Stupp et al.[1] We would like to draw the Appraisal Committee's attention to Appendix 1 in this letter, which contains Supplemental Table 1 and Supplemental Figure 1, originally published in the on-line version of the NEJM article. In this study, virtually all subgroups derived significant benefit from temozolomide/RT versus radiotherapy alone, attesting to the robustness of the study data. Patients with generally accepted poor prognostic factors, i.e. poor performance status (WHO PS = 2), did not derive substantial benefit from combined modality treatment.

Section 4.1.11

The ACD states: 'Patients with reduced MGMT activity…In the group with normal MGMT activity.'

Schering-Plough Response:

We would like to correct the inaccurate terminology contained in the Appraisal Committees assessment. The analysis conducted by Hegi et al. studied MGMT promoter methylation.[4] They did not measure activity of the MGMT enzyme. Furthermore, there is no established definition of "normal" MGMT activity. As this was a post-hoc, retrospective analysis, the only appropriate conclusion that can be drawn is with respect to the methylation or non-methylation of the MGMT promoter. Inferences with respect to treatment response or relative activity of the MGMT enzyme are not reliable.

Section 4.2.9:

The ACD states: '…the mean incremental cost of temozolomide plus radiotherapy compared to radiotherapy alone was £8,560…A speculative analysis of patients with better prognosis found that the mean incremental cost per QALY was just under £43,000.'

Schering-Plough Response:

Estimates of cost-effectiveness derived by the AG model, both in the base case and the 'speculative analysis' are unreliable for a number of important reasons and these are summarized below.

Drug-acquisition costs for TMZ as concurrent chemotherapy are incorrect. The recommended length of concurrent chemotherapy is 42 days as stated in the product SPC and not 49 days as assumed in the AG model. Section 3.7 of the ACD acknowledges this to be the correct dosage regimen. The EORTC trial data supports 42 days as the median treatment duration.

The AG model underestimates costs associated with treatment at first relapse. Schering-Plough market research, conducted among clinical experts in the UK, indicates that in clinical practice approximately one third of patients receive TMZ at first relapse. Notwithstanding the uncertainty surrounding the exact proportion of patients in question, excluding this cost entirely from an economic evaluation is plainly inappropriate and results in an unreliable estimate of the cost-effectiveness of TMZ.

The AG failed to conduct relevant sub-group analyses, as set out in the Final Scope for this appraisal. Clinical benefit in well-defined patient sub-groups exceeds that observed in the overall patient population. Cost-effectiveness estimates in patient sub-groups would be substantially lower than that reported in the AG reference case. A recommendation regarding TMZ that does not consider available sub-group data is perverse (see Appendix 1: Additional subgroup survival analyses from Stupp et al, NEJM).

The AG has overestimated the cost of TMZ as adjuvant chemotherapy. Whilst the AG model is difficult to validate and lacks transparency, it would appear that patients receiving TMZ as adjuvant chemotherapy are allocated 6 cycles of treatment. In contrast, the Stupp study reported that patients received a median of 3 cycles of adjuvant chemotherapy.

These four points detailed above, when considered in combination, invalidate the reference-case and the 'speculative analysis' conducted by the AG. An ACD recommendation that relies upon these cost-effectiveness estimates is therefore not an appropriate basis for a recommendation. It is clear that in a subgroup of patients, where clinical benefit is markedly greater, the cost-effectiveness ratio for TMZ would be considerably lower than the reported AG reference-case, particularly in view of the incorrect modelling of treatment costs for both concurrent chemotherapy and second-line chemotherapy.

Section 4.3.3

The ACD states: '…that there was some evidence suggesting that chemotherapy with the PCV regimen may also be an effective treatment option. It acknowledged that there were no trials comparing temozolomide to other regimens such as PCV.'

Schering-Plough Response:

We are unaware of any data to suggest that PCV is an effective treatment option in newly-diagnosed glioblastoma. Substantial evidence exists to the contrary. A large (N = 674) randomized trial conducted in 15 centres throughout the UK showed no benefit to PCV chemotherapy used in conjunction with radiation in patients with glioblastoma.[3] For patients receiving RT alone, median survival was 9.5 months. For those receiving RT-PCV, median survival was 10.0 months. The authors concluded that the trial "failed to demonstrate a place for adjuvant chemotherapy with PCV in the treatment of high-grade astrocytoma" and that "no-chemotherapy control arms remain ethical in randomized trials of high-grade astrocytoma." Consequently, there is no rational basis for recommending that TMZ be compared to PCV or other such chemotherapy.

Section 4.3.4

The ACD states: '…that the length of survival of patients in the control arm of the largest RCT for temozolomide was better than is currently the norm in UK clinical practice.'

Schering-Plough Response:

The MRC trial has shown that, in routine clinical practice throughout the UK, the median overall survival for patients with high-grade astrocytoma (grade III or IV) receiving RT alone is 9.5 months. In the EORTC trial, the control arm achieved 12 month overall survival. It is not surprising that the treatment results for RT are different in the MRC and the EORTC trial, as important prognostic factors are not consistent between the trials: e.g. Performance status 0 reported in 25% of the MRC trial and 38% of the EORTC trial; conversely Performance status 2/3 in 25% and 12% respectively; tumour biopsy or less 42% and 16% respectively.

If, in the context of the trial, patients undergoing RT therapy performed better than expected (either in the UK or elsewhere) in the control arm, this would only mean that in regular clinical practice, the difference between patients receiving radiation alone versus TMZ as part of first-line treatment would be even greater.

Of note, a recent study by Beresford et al from the Mount Vernon Cancer Centre and Charing Cross Hospital examined whether the results of the EORTC trial could be replicated in clinical practice in the UK.[5] The records of 102 high grade glioma patients who received radiotherapy plus TMZ from 1998-2003 were reviewed. A regimen similar to the one in the EORTC trial was employed to these patients (radiotherapy at 60-65 Gy in 30-37 fractions over 6 weeks, TMZ administered at 75 mg/m^2 daily for 6 weeks during radiotherapy, followed by adjuvant TMZ for 6 cycles on days 1-5 of a 28 day cycle (150-200 mg/m^2/day). Patients treated with concurrent TMZ and radiotherapy demonstrated an improved median survival by log-rank comparison of 12.5 months, compared to 9 months for patients treated solely with radiotherapy (p=0.029). These results show that this combined modality regimen can be replicated in clinical practice, with significant clinical impact. We acknowledge that this data was not available at the time of the initial HTA; nonetheless it has an important bearing on the interpretation of clinical trial evidence for TMZ as set out in the ACD, section 4.3.4.

Section 4.3.7

The ACD: '…it [*the Appraisal Committee*] considered evidence from experts that glioma can have a considerable impact upon the quality of life of patients, which may deteriorate rapidly after the onset of disease progression.'

Schering-Plough Response:

We would like to draw the attention of the Appraisal Committee to the quality of life analysis of EORTC 26981 published in November, 2005 in *Lancet Oncology* by Taphoorn et al.[2] These data were submitted as "Academic in Confidence" as part of our original dossier.

We would also like to point out that there was an overall improvement in progression-free survival of approximately 2 months associated with TMZ treatment. It can then be inferred that patients lived longer, with improved quality of life, as the addition of TMZ did not negatively impact their quality of life.

Section 4.3.11

The ACD states: '…The Committee concluded on the balance of the economic evidence, including the consideration of second and subsequent line' treatments (as far as was possible), that the use of carmustine implants and temozolomide…would not be a cost-effective use of NHS resources.'

Schering-Plough Response:

As detailed elsewhere in Schering-Plough's response to the ACD, basic errors in the calculation of drug acquisition costs for TMZ and the failure to appropriately incorporate costs associated with TMZ treatment at first relapse render the cost-effectiveness estimates unreliable. Further, the AG failed to consider the cost-effectiveness of TMZ in clearly defined patient subgroups. An ACD recommendation, based upon the economic evidence set out by the AG, is therefore perverse.

Section 4.3.13

The ACD states: 'The Committee considered whether there might be subgroups of patients for who the use of treatments may be more effective and cost-effective. It acknowledged the results of a retrospective analysis of patients with reduced MGMT activity… The Committee concluded that this early research [MGMT as a biological marker for better response] was promising and that further research into biological markers of chemosensitivity and the use of such markers to identify subgroups of patients in whom the treatments may be more effective should be pursued.'

Schering-Plough Response:

In respect of 'subgroups of patients for whom the use of treatments may be more effective and cost-effective' the ACD makes no reference to subgroups, such as the groups outlined in the appendix of the Stupp et al NEJM paper.[1] It is unclear as to why the AG has failed to consider these classical subgroups, particularly since the cost-effectiveness case in these populations can be substantially stronger than in the overall patient population (see Appendix 1 for subgroup survival analyses).

Regarding further validation of the MGMT data, we believe the Appraisal Committee is aware of the large, randomized, phase III trial that Schering-Plough is supporting in order to validate this finding prospectively.

However, until this hypothesis is proven and, until physicians are able reliably and consistently to identify those subgroups of patients who are clearly deriving substantial clinical benefit from the use of TMZ in combination with radiation, we strongly question whether it is ethical to deny such patients access to life-prolonging treatment, because a subset of patients may not derive as much benefit.

Section 5.2

The ACD states: '…the Committee considered that further research into the effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed glioblastoma is required. Such studies should include:

- **A robust design, adequate sample size, and appropriate statistical analysis**
- **Analysis of the effect of treatment upon health-related quality of life**
- **A comparison of treatment regimens with other active chemotherapy treatments, such as the PCV regimen**
- **A consideration of the effectiveness of treatments in children as well as adults**
- **A consideration of the subgroups in whom the treatments may be particularly effective, such as those defined by biological markers.'**

Schering-Plough Response:

The EORTC study, an independent RCT of TMZ in newly diagnosed, glioblastoma achieved international acclaim as unequivocal evidence of the first major clinical advance in this patient population for 30 years or more. The data resulted in the first plenary session presentation ever on the topic of brain tumours at ASCO, the most significant cancer meeting in the world. This presentation was followed by 2 major publications in the most prestigious New England Journal of Medicine, and subsequently confirmed by other positive clinical trials.

A robust design, adequate sample size, and appropriate statistical analysis

EORTC 26981 was designed by the EORTC Brain Tumour Group, an independent, academic research organization. The EORTC received an unrestricted educational grant and study drug from Schering-Plough. The results of the trial, when submitted for market authorizations, were granted priority review by the US FDA, the Canadian Ministry of Health and the Japanese Ministry of Health.

There should be no remaining questions with respect to the trial design. This is the largest study of its kind in glioblastoma. The sample size and statistical analysis were deemed appropriate by both the EMEA and the US FDA, as market authorization was granted.

Analysis of the effect of treatment upon health-related quality of life

Health-related quality of life was analyzed in EORTC 26981, and published in November 2005 in *Lancet Oncology*. The addition of TMZ to radiotherapy did significantly prolong relapse-free and overall survival and did not have a negative impact on patients' quality of life.

A comparison of treatment regimens with other active chemotherapy treatments, such as the PCV regimen

We do not believe that PCV is an appropriate comparator given data from the phase III trial by the Medical Research Council. Furthermore, PCV, in combination, or as single agents, is not licensed for use in the treatment of newly-diagnosed glioblastoma. Current standard of care in the majority of industrialized nations has largely abandoned PCV due to its enormous toxicity. It is effectively not a therapeutic choice of any significance.

As the Medical Research Council concluded, their own trial failed to demonstrate a role for PCV in the treatment of glioblastoma patients. We believe that any trial design that would randomize patients to receive RT-PCV would be unethical and further reduce the standard of care for glioma treatment in the UK, which currently lags substantially behind the other industrialized nations.

A consideration of the effectiveness of treatments in children as well as adults

We agree that it is important to continue to investigate treatment options in children with brain tumours. However, any speculation with respect to the activity of TMZ in paediatric patients is outside the scope of the trial and outside the scope of the dossier prepared by Schering-Plough. We request therefore, that the review should only examine the appropriateness of use in those patients that meet the enrolment criteria of EORTC 26981.

A consideration of the subgroups in whom the treatments may be particularly effective, such as those defined by biological markers

We agree that the retrospective analysis by Hegi et al.[4] is important in its hypothesis generation and are thus supporting the first, truly global, cooperative group trial in this patient population to prospectively investigate the finding with a reproducible, validated assay.

However, until the results of the trial are available, as we note above, we strongly question whether it is ethical to deny all patients access to life-prolonging treatment because a subset of patients may not derive as much benefit as others.

Once again, we are grateful for the opportunity to comment on the ACD and look forward to continued dialogue with NICE regarding the issues raised in this letter.

Sincerely,

James Morris
HTA Manager

Appendix 1. Subgroup Analyses from Stupp et al, NEJM 2005.

Supplemental Table 1. Subset Analysis of Median Overall Survival by Prognostic Factors

		Median survival, months	
Characteristic	**Number patients**	**RT**	**TMZ/RT**
Age			
< 50	172	13.2	17.4*
≥ 50	401	11.9	13.6*
Gender			
Male	360	11.4	14.1*
Female	213	12.8	16.3*
Prior Surgery			
Resection	480	12.9	15.8*
Biopsy Only	93	7.9	9.4
WHO performance status			
0	223	13.3	17.4*
1	277	11.9	14.0*
2	73	10.5	9.9
Baseline Steroids			
Yes	408	11.0	13.5*
No	164	16.2	19.7†

*$P < .001$
†$P = .005$
WHO = World Health Organization

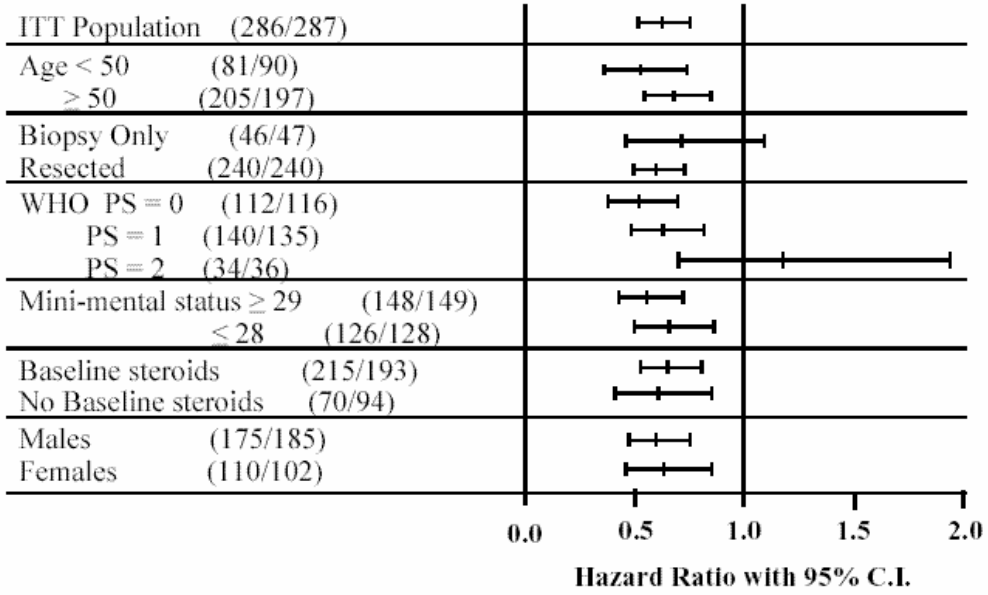
Supplemental Table 2. Nonhematologic Toxicity ≥ Grade 2 by Treatment Group

Adverse event	RT (N = 286)		TMZ/RT (N = 287)	
	Grade 2	Grade 3/4	Grade 2	Grade 3
RT ± concomitant TMZ, n (%)				
Fatigue	61 (21)	14 (5)	74 (26)	19 (7)
Other constitutional symptoms	14 (5)	2 (<1)	20 (7)	5 (2)
Rash and other dermatologic	15 (5)	2 (<1)	26 (9)	4 (1)
Infection	4 (1)	6 (2)	3 (1)	9 (3)
Vision	35 (12)	4 (1)	39 (14)	3 (1)
Nausea/vomiting	9 (3)	2 (<1)	38 (13)	2 (<1)
Adjuvant TMZ, n (%)				
Fatigue	—	—	73 (25)	18 (6)
Other constitutional symptoms	—	—	12 (4)	6 (2)
Rash and other dermatologic	—	—	13 (5)	5 (2)
Infection	—	—	6 (2)	12 (5)
Vision	—	—	28 (10)	2 (<1)
Nausea/vomiting	—	—	52 (18)	4 (1)
During the entire study period,* n (%)				
Fatigue	65 (23)	20 (7)	108 (38)	38 (13)
Other constitutional symptoms	18 (6)	2 (<1)	27 (9)	12 (4)
Rash and other dermatologic	17 (6)	3 (1)	35 (12)	9 (3)
Infection	5 (2)	8 (3)	7 (2)	20 (7)
Vision	44 (15)	6 (2)	59 (21)	5 (2)
Nausea/vomiting	9 (3)	3 (1)	79 (28)	6 (2)

RT = Radiotherapy; TMZ = Temozolomide.

*Entire study period was defined as from study entry to 7 days after disease progression.

Supplemental Figure 1: Hazard ratio of subgroup analyses



Forest plot showing the hazard ratio and 95% confidence intervals of prognostic subgroups.

Appendix 2. Survival Curves from MRC, J Clin Oncol 2001.

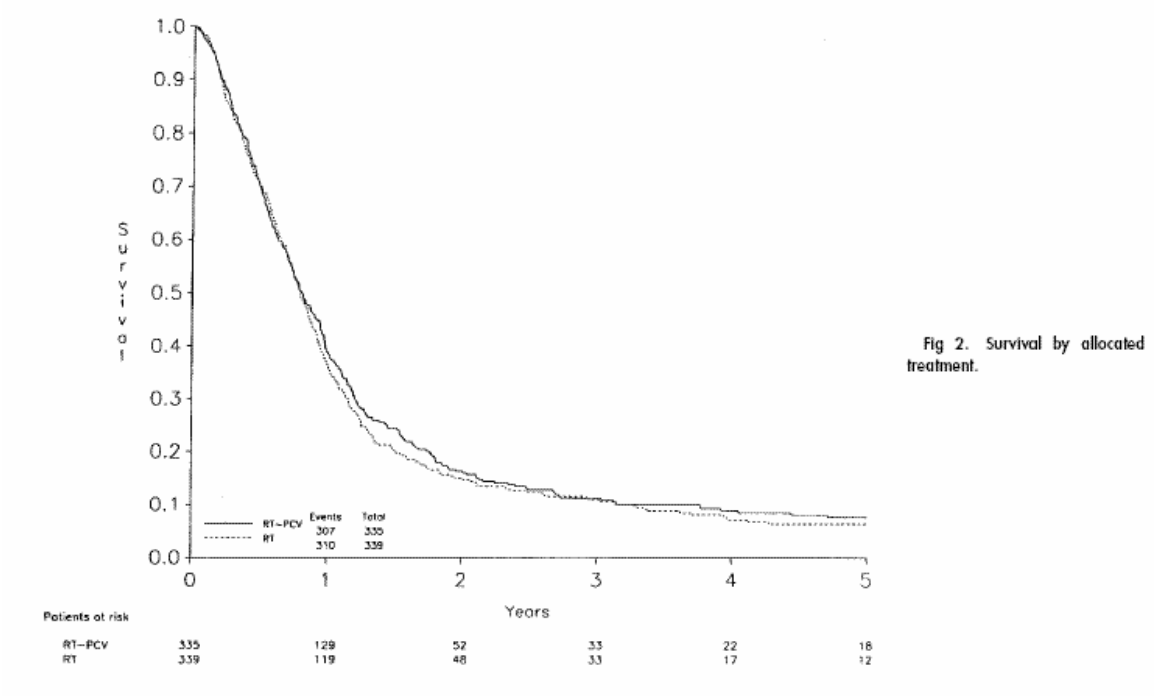


Fig 2. Survival by allocated treatment.

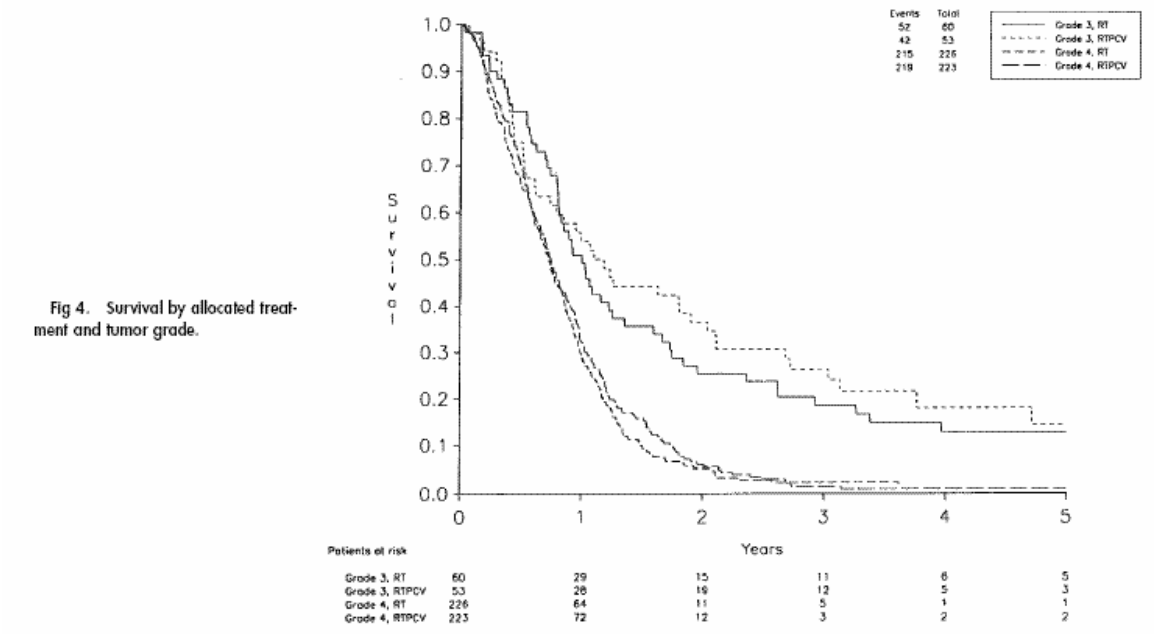


Fig 4. Survival by allocated treatment and tumor grade.

References

[1] Stupp R, Mason WP, van den Bent MJ, et al. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.

[2] Taphoorn, MJB, et al. Health-related quality of life in patients with glioblastoma: a randomized controlled trial. Lancet Oncology. 2005; 6: 937-44.

[3] Medical Research Council Brain Tumour Working Party. Randomized Trial of Procarbazine, Lomustine, and Vincristine in the Adjuvant Treatment of High-Grade Astrocytoma: A Medical Research Council Trial. J Clin Oncol. 2001. 19:509-518.

[4] Hegi, M.E., et al. MGMT Gene Silencing and Benefit from Temozolomide In Glioblastoma. New Eng. J. Med. 2005. 352:997-1003.

[5] Beresford M, Thompson J, Power D. Treatment of newly diagnosed high-grade glioma with concomitant and adjuvant temozolomide and radiotherapy - UK experience. European Journal of Cancer Supplements Volume 3, No. 2, October 2005, Page 141