Carmustine implants and temozolomide for the treatment of newly-diagnosed high-grade glioma

Comments on Appraisal Consultation Document

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Contents

Executive Summary

Link Pharmaceuticals does not agree with the preliminary recommendations of the ACD with respect to carmustine implants. The evidence presented in this response document supports a cost/QALY in the Westphal ITT population of £27,900. In addition, a subgroup analysis of patients who have undergone maximal surgical resection is presented which demonstrates an even more favourable cost/QALY. The rationale supporting this is summarised in this Executive Summary and covered thoroughly in the main body of this response document, which has been structured to address the three questions posed.

The comments presented are limited to carmustine implants and Link is not in a position to comment on the ACD recommendations for temozolomide.

1. Whether you consider that all of the relevant evidence has been taken into account.

The ACD has considered the two pivotal phase III clinical trials for carmustine implants, Valtonen and Westphal.

However a major weakness in the ACD is that the long term follow up data which was statistically significant in an unstratified analysis has been largely disregarded. These data have been accepted for publication in Acta Neurochirurgica and demonstrates the real clinical benefit of carmustine implants for patients.

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.

2.1 Clinical effectiveness

The ACD states that the evidence for carmustine implants is questionable and small particularly with respect to:

- clinical significance
- quality of the clinical data
- determination of the time to onset of symptoms

Consequently the ACD presents an unfavourable and in part simply incorrect interpretation of the clinical evidence for carmustine implants and fails to recognise the clinical significance of the benefits of the product for patients with this devastating disease. (A condition where patient outcomes are poor, long term survival is rare and, until now, where no clinically significant advances have been made in the past 20 years.)

2.1.1 Clinical significance of the patient benefits for carmustine implants

In this disease setting where the current gold standard therapy in the UK is surgery and radiotherapy, the median survival is only 12 months. The ACD does not give sufficient recognition to the clinically meaningful median survival gain of 2.2 months, (a 20% increase compared to placebo), for patients receiving carmustine implants. Similarly the ACD does not give sufficient emphasis to the five fold increase in 3 year survival giving real hope to patients treated with carmustine implants.

2.1.2 Quality of the clinical data for carmustine implants

The Assessment Group (AG) has placed undue emphasis on the initial deliberations of the FDA review of carmustine implants giving an impression that the data set is weak. However subsequent deliberations by the FDA, which are not in the public domain and which include consideration of the long term survival data, resulted in the licensing approval of carmustine implants for newly-diagnosed high-grade glioma in the USA in February 2003. Consequently the clinical evidence for the use of carmustine implants is considered robust and clinically meaningful for clinicians, patients and their carers.

2.1.3 Determination of the time to onset of symptoms

Estimation of the symptom free survival benefit is critical in determining the true cost per QALY for carmustine implants.

The AG uses progression free survival (PFS) determined by radiological imaging, (an outcome related to tumour burden rather than patient symptoms), as a measure for the onset of symptoms and consequently the AG states there is no PFS benefit from carmustine implants. PFS based on radiological imaging in the presence of carmustine implants is beset with uncertainty because it is confounded by post operative oedema, enhancement produced by the implants themselves and the subsequent effects of radiotherapy. These effects result in a diagnosis of progression/recurrence (but not necessarily the onset of symptoms) when in fact it may not have occurred and the use of this method of determining the time to onset of symptoms in these patients should be questioned.

The pivotal Westphal study of 240 patients evaluated the time to decline of 11 neuroperformance measures, a prespecified and valid alternative to radiological imaging in determining the onset of symptoms. These neuroperformance results show a mean time to onset of symptoms of 7.4 weeks. Link therefore used these neuroperformance measures (which are more closely related to symptom development than radiological imaging) as the best available indicator of the onset of symptoms.

The AG rejected this approach based on the FDA reanalysis of neuroperformance data which censored patients prior to death as opposed to Westphal who included death as a timepoint. However, the FDA acknowledged that their approach lost 75% of this important data. The AG presented the FDA approach as embodying fact and the company approach as not. In practice, neither the company nor the FDA approach to censoring is intrinsically correct.

Furthermore carmustine implants are administered locally at the time of surgery and release active drug over approximately 3 weeks. It is, therefore, implausible that carmustine implants do not slow progression for six months relative to placebo but then produce a survival benefit in the post progression period, several months after the drug has been eliminated from the body.

The AG themselves state (p87 of Assessment Report): "*there is no good evidence that … any chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours offers any benefit in slowing the rate of disease progression* ***after*** *recurrence"*. This is an obvious contradiction within the Assessment Report and serves to highlight and support the implausibility that the majority of any survival gain for carmustine implants will be after the onset of symptoms.

2.2 Cost effectiveness

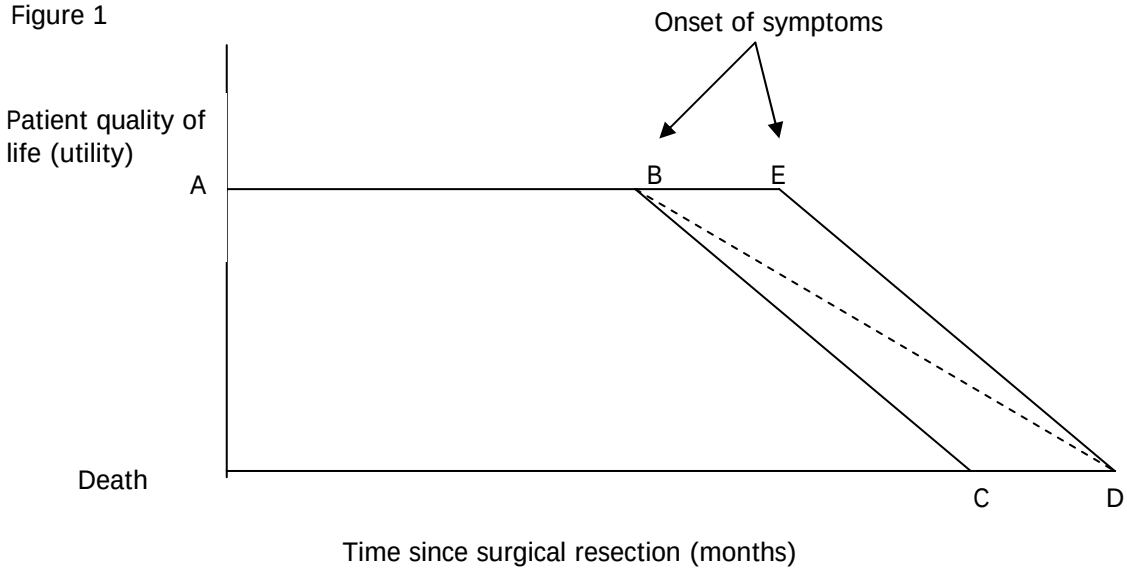
The cost effectiveness presented in the ACD is based on flawed assumptions which result in the worst case scenario for carmustine implants. In particular this approach has underestimated the symptom free survival and the mean survival resulting in an overestimation of the ICER for carmustine implants. It is therefore an unreasonable interpretation of cost effectiveness.

Different modelling structures were adopted by Link and the AG. However these are not the cause of the differences in the derived ICER estimates which are the result of markedly different assumptions about the effects of using carmustine implants (in particular the time to the onset of symptoms) and the costs of so doing (incremental costs).

2.2.1 Quality Adjusted Life Years (QALYs)

The key issue is the measure of time to onset of symptoms and the profound effect this has on the cost estimates is best demonstrated diagrammatically and is illustrated in Figure 1 below:

Figure 1



For those patients able to undergo surgical resection of their tumour, the patient experience can be characterised as an initial post operative period which is relatively free of symptoms and of relatively high utility represented by A to B or E. Once symptoms reoccur, at point B or E, there is a period of decline to death with progressively reducing quality of life. For simplicity, and in the absence of evidence this has been approximated linearly.

Treatment with carmustine implants extends life. In the estimation of the QALY gain it is very important to determine if this extension to life comes before or after the onset of symptoms. If it is all after the onset of symptoms, then the QALY gain is given by the area BCD. If it is all before the onset of symptoms then the QALY gain is given by the area BEDC, which is twice the area.

Use of neuroperformance data from Westphal gives an estimate represented by BEDC based on a longer symptom free survival period. The AG estimate is best represented by BCD with only a 1.3 week period of symptom free survival, i.e. most of the survival gain is implausibly after the onset of symptoms.

2.2.2 Costs

The cost estimates used in the ACD are based upon a value judgement which has been explicitly rejected in NICE methodology. The AG treated the incremental costs in the carmustine implant arm of the model as <u>not</u> being driven by any different (from placebo) symptoms caused by carmustine implants. The source of the extra costs in that arm arise from the fact that people live longer and

receive standard care while doing so. The same logic could reject a free drug which extended survival of dialysis patients by twenty years because dialysis has a cost/QALY of c.£80k. Similarly, the same logic would find a drug to be cost-effective if it shortened the life of dialysis patients. Appraisal Committees can easily see the absurdity of the latter but seem to have missed it in its former manifestation. The principle is that if patients are kept alive who go on to receive standard care that is a good thing. The AG should not incorporate what is effectively a cost effectiveness analysis of those subsequent treatments. They are regarded as separable.

2.2.3 Cost/QALY estimate for Westphal ITT population

Considering the above points (time to onset of symptoms of 7.4 weeks, no incremental costs and mean survival calculated from individual patient survival data of 2.45 months) Link presents a cost/QALY for the total Westphal patient population of £27,900. The data supporting this ICER are presented in Appendix 1.

2.2.4 Cost/QALY estimate for subgroup of Westphal ITT population (maximal resection)

The ACD indicates that subgroups in whom the treatment may be particularly effective should be considered. Link is therefore taking this opportunity to present data on such a subgroup, patients undergoing a maximal resection. This is considered a valid subgroup as it comprises 111 patients balanced between the two study arms. The difference in median survival between the carmustine implants and placebo arms was 2.15 months (p=0.006, unstratified log rank analysis) and the calculated mean survival gain was 4.2 months. Unlike the ITT patient population, if only GBM patients (n=101) in the maximal resection subgroup are considered the median survival at 2.10 months remains statistically significant (p=0.0191 unstratified log rank analysis). These impressive survival benefits give further hope to those patients receiving a maximal resection.

Link has modelled these maximal resection results using the AG's incremental costs (which are incorrect in Link's opinion), to calculate cost/QALY. Link demonstrates below how these costs change with differing lengths of time to the onset of symptoms:

- ICER of £36,700 for a 0.3 month gain in symptom free survival using radiological imaging to determine progression free survival.
- If a 1.31 month gain in symptom free survival is assumed the ICER is £30,000.
- ICER of £22,900 for a 3.0 month gain in symptom free survival using the mean of the 11 neuroperformance measures for the subgroup.

The Appraisal Committee will see that only at implausibly short periods of less than 1.31 months, given a mean survival gain of 4.2 months, would carmustine implants be found not to be cost-effective. If the incremental costs are removed the ICER would be substantially lower.

2.3 Resource impact and implications for the NHS

The preliminary ACD recommendations have no resource impact for the NHS. However a recommendation allowing the use of carmustine implants on the NHS has only a small resource impact. There are 1,860 new patients with high-grade glioma each year in England and Wales accounting for less than 2% of all primary cancers. However for individual patients a high-grade glioma on average results in 20 years of lost life. The direct costs to the NHS of funding carmustine implants for all eligible patients would be less than £2 million per annum.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

Link does not agree with the preliminary recommendations of the Appraisal Committee. As discussed in this response document the interpretation of the clinical and cost effectiveness evidence for carmustine implants are flawed resulting in an unsound and unsuitable basis for guidance to the NHS because:

- The body of clinical evidence confirms that carmustine implants provide physicians and their patients suffering from high-grade glioma an opportunity to significantly extend survival and, importantly, improve symptom free survival.
- Implementation of the preliminary recommendations would deny patients the opportunity for a five fold increase in 3 year survival with carmustine implants.
- The NHS cancer plans aims to improve survival rates in line with other European countries. Denying UK patients access to carmustine implants which are in common clinical practice and fully reimbursed in the US, Australia (PBAC, April 2006) and many parts of Europe will be in conflict with this objective.
- The benefits of NHS treatment with carmustine implants can be offered on a cost effective basis to the relatively small number of eligible patients suffering from this devastating condition.

Carmustine implants provide a real and tangible benefit for patients with this devastating disease. The final recommendations of the Committee should therefore support the use of carmustine implants in newly-diagnosed high-grade glioma patients which have been shown to improve median and long term survival and to be cost effective to the NHS.

Response Document

Carmustine implants for the treatment of newly-diagnosed high-grade glioma

1. Whether you consider that all of the relevant evidence has taken into account

1.1 Efficacy data

The efficacy of carmustine implants has been studied in two phase III clinical trials, Valtonen[1] and Westphal,[2] both of which have been considered in the preparation of the ACD.

However the long term follow up data from the Westphal study which has been accepted for publication in Acta Neurochirurgica, a peer reviewed journal, has not been given sufficient consideration in determining the efficacy of the product. These data demonstrate a statistically significant (p=0.017) non-stratified median survival benefit for carmustine implants of 2.2 months. In addition the opportunity for a five fold increase in long-term survival for a small number of patients with this devastating disease has not been recognised or put into a clinical context in the ACD.

The AG has relied heavily on deliberations recorded in the minutes from an FDA meeting in 2001 on the subject of carmustine implants. This has introduced bias against carmustine implants in the Assessment Report. The main points arising from the FDA minutes are shown in the response to ACD Section 4.1.3 of this document. Subsequent deliberations by the FDA, which are not in the public domain and which include consideration of the long term survival data, led to the approval of carmustine implants for newly-diagnosed high-grade glioma.

1.2 Subgroup analysis (cost effectiveness of carmustine implants in patients undergoing maximal resection)

The ACD in Sections 4.3.13 and 5.2 ask that subgroups in whom the treatment with carmustine implants may be particularly effective should be considered. Link is taking this opportunity to present data on such a subgroup, patients undergoing maximal surgical resection. This subgroup analysis was not part of the original statistical analysis plan and has only been investigated now in response to the ACD request. Please see Appendix 2 for the full analysis.

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate

Link does not consider the summaries of either the clinical or cost effectiveness for carmustine implants to be reasonable interpretations of the evidence and therefore does not agree with the ACD preliminary recommendations. If these were to become final, clinicians, patients and carers would be

deprived of carmustine implants, a product that has a demonstrated statistically significant improvement in median and 3 year survival. Both these outcomes are clinically meaningful in an area of medicine that has lacked any advances over the past 2 or 3 decades. In addition the cost impact to the NHS if all eligible patients were to receive carmustine implants is relatively small at less than £2 million annually.

2.1 Clinical effectiveness

The clinical effectiveness of carmustine implants has been subject to intensive review by regulatory agencies leading to approval of the product in major international markets including USA, Canada, Europe (via the Mutual Recognition Procedure) and Australia.

ACD Section 4.1.3 - *The AG reported that the Food and Drugs Agency (FDA) in the USA expressed several concerns when it evaluated the trial.*

The concerns raised by the FDA appear to have been unconditionally accepted by the AG as being the definitive situation without recourse to any counter arguments or consideration of the points raised by Link in the response to the Assessment Report.

Despite the initial FDA comments they, and many other regulatory agencies worldwide, have subsequently approved carmustine implants for the treatment of newly-diagnosed high-grade glioma patients indicating their satisfaction with the evidence for the efficacy of the product.

Furthermore carmustine implants have received favourable reimbursement recommendations in a number of countries including the USA, via their Medicare/Medicaid health schemes, France, Spain and Greece. Most recently the PBAC in Australia has recommended that carmustine implants be made available in that country from April 2006.

In particular, it [the FDA] was concerned about:

a) An imbalance between the types of tumours in study arms, which could have favoured carmustine implants.

The original histopathological diagnosis did not demonstrate an imbalance between study arms and the imbalance referred to in the ACD is solely based on the FDA analysis of the histopathology which is discussed below.

The inclusion of grade 3 and 4 gliomas in the RCT reflects the reality of the clinical situation whereby it is not possible to make a definitive intra-operative diagnosis beyond classification of a glioma as

Three patients were lost to follow up during the original phase of the Westphal study. However when the long-term follow up data was collected the outcome of two of these patients was known and only one patient, in the placebo arm, remained lost to follow up. This had the effect of changing the median survival gain from 2.3 to 2.2 months.

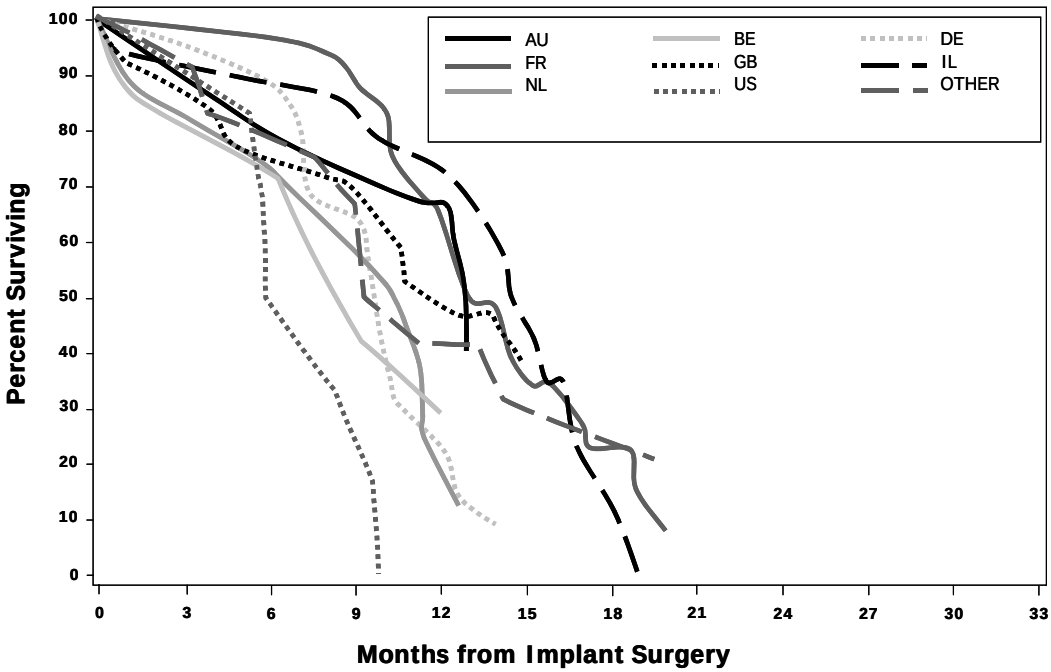
e) In addition, the manufacturer analysed the data which included stratification by country, and the FDA reanalysed this data without stratification.

The statement by the AG that stratification was not a pre-specified analysis is simply incorrect.

Stratification by country as a potential covariant was pre-specified in the statistical analysis plan for the Westphal study at the request of the FDA following their review of the protocol in 1997 and is therefore a valid analysis of the data. A copy of the original statistical analysis plan can be made available to the Appraisal Committee if this provides the necessary reassurance on this point.

In the Westphal study stratification by country is a logical analysis given the study design. A review of the survival data for the placebo arm at a country level, presented in Figure 2 below, demonstrates a degree of scatter with a median survival range between approximately 6 and 15 months. This variability is potentially greater than the anticipated treatment affect. Country as a variable must therefore be accounted for in the final analysis.

Figure 2: Survival data for placebo patients by country



It is important to note that the estimated hazard ratio of 0.71 for survival by the Kaplan Meier method is the same regardless of stratification or non-stratification and represents a 29% mortality risk reduction. The estimate of absolute clinical benefit of carmustine implants is therefore not affected by stratification only its variance thereby affecting its estimated statistical significance.

In addition the long term survival analysis, conducted at least 36 months after the recruitment of the last patient, showed a statistically significant survival benefit for carmustine implant compared to placebo (p=0.017 unstratified log-rank analysis) thus validating the results from the original phase of this study.[4] A statistically significant (p=0.01 unstratified log rank analysis) 5-fold increase in 3 year survival (9.2% vs. 1.7%) was also shown in favour of carmustine implants. This potential for long term survival, albeit in a small number of patients is extremely important for patients, carers and their doctors alike.

ACD Section 4.1.4 *[The data reported below relate to the unstratified analysis unless otherwise stated.] The median survival was 13.8 months (95% CI: 12.1 to 15.1) in the carmustine implant group, and 11.6 months (95% CI: 10.2 to 12.7) in the placebo group. The Kaplan–Meier hazard ratio was 0.77 (log rank statistic: p = 0.08). Based on data from longer-term follow-up, the Kaplan–Meier hazard ratio was 0.73 (log rank statistic: p = 0.02). At 12 months 59.2% of the carmustine implant group and 49.6% of the placebo group were alive, at 24 months survival was 15.8% and 8.3%, and at 36 months survival was 9.2% and 1.7% in each group respectively (all estimates calculated on the basis of survival data censored at the relevant time period).*

Using the pre-specified stratification by country as a valid statistical tool yields the following data for the original phase of the study:

- Gain in median survival 2.2 months (p=0.03 stratified log rank analysis)
- Hazard ratio of 0.71 (p=0.03 stratified log rank analysis). Please note that Link believes the 0.77 value given in Section 4.1.4 to be a typographical error.

The long term follow up data is unstratified and therefore these data do not change from that given in the ACD.

Survival at 3 years is statistically significant between the two treatment arms, p=0.01 log rank analysis.

ACD Section 4.1.5 – *There was no difference in progression-free survival [PFS] between treatment groups. The median time to progression was 5.9 months (95% CI: 4.4 to 8.3) in the carmustine implant group and 5.9 months (95% CI: 4.7 to 7.4) in the placebo group.*

This comment touches on some very important issues of principle, which in turn have profound implications for the estimation of the cost effectiveness of carmustine implants.

Progression free survival (PFS) is taken as having two meanings:

1. the absence of symptoms
2. no evidence of tumour regrowth

The AG use of PFS in their cost effectiveness analysis relates to the absence of symptoms as stated on page 91 of the Assessment Report *"the model takes progression to relate to symptomatic, rather than pathological, disease progression".* Link is in agreement that this is the correct way to estimate patient utility. However the AG has used radiological imaging which relates to pathological disease progression rather than being a measurement of symptom onset. This is in direct contradiction to their statement above. For the reasons previously provided in Link's response to the Assessment Report and laid out again below, PFS measured by radiological imaging cannot and does not provide an accurate measure of **symptom free** survival.

Indication of tumour recurrence on radiological imaging does not necessarily predict the onset of new symptoms. A high-grade glioma will be symptomatic when there are about 10^{10} tumour cells.[5] A maximal resection removing at least 90% of the tumour mass will reduce this cell number to 10^{9}. Progression as defined by an increase in the mass by 25% will not in many cases reflect the growth of a tumour to a size likely to cause reappearance of symptoms. This is not likely to occur until the residual cells have doubled at least 4 times.

Radiological imaging is not the most meaningful measure of progression from the clinicians' or patients' perceptive. Therefore using measures that correlate with the onset of symptoms is more appropriate than a simple increase in tumour size. Neurologic status and functional impairment are deemed to be equally appropriate measurements of tumour activity and therefore onset of symptoms,[6] especially in the palliative care setting where the aim of new therapy is prolongation of functionally independent survival.

Generally tumour activity or progression is assessed by radiological imaging and indeed in the Westphal study, PFS was determined by radiological means in 70% of patients. However there are a number of factors related both to patients with high-grade glioma generally and the use of carmustine implants specifically that make measurement of PFS by radiological methods problematic and subject to a high degree of inaccuracy. This was acknowledged by the FDA who stated that PFS is difficult to assess in this patient population previously treated with surgery, radiotherapy or steroids.[7,8]

PFS measured by imaging techniques is assessed as the change in size of a tumour (or the development of a new lesion) on CT or MRI. The definition of tumour progression is an increase of more than 25% in the size of an enhancing abnormality in relation to previous scans. Different PFS results between studies may reflect the varying interpretations of progression on imaging. However accurate measurement may be confounded by several factors making it difficult to reliably assess these scans, even in the absence of implants. The size of an enhancing glioma following surgery and radiotherapy might represent a loss of tumour cells or an alteration in the properties of the blood-tumour barrier or blood brain barrier. Even if there has been some tumour cell kill a number of factors make the interpretation of imaging response in glioma difficult. A high-grade glioma has complex shapes with apparent projections and margins may be indistinct. Different scanning techniques have a major influence on interpretation of images. The timing of the scan following injection of an imaging medium alters the apparent size of an enhancing lesion. In addition, surgery, corticosteroids and excessive doses of radiation all affect the region of enhancement, making an objective assessment of progression difficult.

This is particularly true for carmustine implants where radiological progression in the presence of the implants may be further confounded by the immediate post-operative oedema and enhancement that the implants themselves may produce.[9] Furthermore, Kleinberg et al have demonstrated that treatment effects such as necrosis can radiographically mimic the findings of recurrent tumour in a proportion of patients[10] and De Wit et al[11] have demonstrated the problems with interpretation of radiological imaging.

In conclusion radiological imaging is not the most appropriate measure for onset of symptoms for patients with high-grade glioma and especially where carmustine implants have been inserted. Consideration of alternative measurements for the onset of symptoms must therefore be used.

ACD Section 4.1.5 – *The manufacturer's analysis suggested that the time to decline of KPS and time to progression on neurological indices were statistically significantly improved in the carmustine implant group. However, a reanalysis of these data was conducted, which treated deaths as censored. This reanalysis found that the differences were a result of survival times between the treatment arms, which suggests that there was no independent effect by treatment on the time to decline of neurological indices and KPS.*

See Link's response to ACD Section 4.1.3. part c.

2.2 Cost effectiveness

ACD Section 4.2.3 - *The AG expressed concern about the estimation of time to symptoms using this approach because it was based on median values rather than mean values.*

Following criticism in the Assessment Report on the use of a mean of medians (8.2 weeks) for the 11 neuroperformance measures this was recalculated based on the mean of mean data (7.4 weeks) in Link's response to the report. The cost effectiveness model was only moderately sensitive, in this instance, to the choice of means or medians.

ACD Section 4.2.3 - *No statistically significant differences were found between treatment arms in the time to decline of functional status and time to deterioration of neurological performance scores in 10 of 11 indices when the data were reanalysed by the FDA.*

Neither the approach taken by the FDA nor that taken in the Westphal study is intrinsically correct. The reality lies somewhere between these two extremes as discussed in the response under ACD Section 4.1.3. part c.

ACD Section 4.2.3 - *It was assumed that the only difference in costs between the two treatment groups was the cost of the implants themselves (mean: 6.54 wafers per patient).*

The Assessment Report criticises the approach taken to costing treatments on grounds of principle. The approach recommended by the AG was considered by the NICE Methodology Committee at its most recent review of methodology and explicitly rejected (Personal Communication, Prof Mark Sculpher, Chair of Committee). The committee argued that the decision to treat someone, and thus keep them alive, should not be contingent on subsequent, separable decisions. It is quite possible

that use of carmustine implants will enable a few patients to live very much longer than they otherwise would and therefore to incur a variety of health care costs, some related to management of glioma and some not. These incurred expenditures are a consequence of success in keeping the patient alive and should not be used to penalise the drug. The extension of the AG logic could lead to new technologies that keep people alive into old age not being found to be cost-effective because of the high costs of care in old age

ACD Section 4.2.4 - *The estimated mean incremental cost of carmustine implants was £4250 and estimated mean QALYs gained were 0.16. The base-case incremental cost-effectiveness ratio (ICER) was £28,000 per QALY gained. A probabilistic sensitivity analysis suggested that if the maximum acceptable amount to pay for an additional QALY is £20,000, then the probability of carmustine implants being cost effective is 0.28. This probability rises to 0.57 if the maximum acceptable amount was £30,000 per additional QALY. …… The AG considered the model structure to be sound, but concluded that the main ICER of £28,000 per QALY gained was underestimated because of the assumptions used to estimate survival and the omission of treatment costs other than those of the implants.*

By contrast Link contend that the assumptions embodied in the AG model, particularly in respect of the time to the onset of symptoms, the estimation of mean and median survival and the inclusion of incremental costs, are extreme, unreasonable and in part methodologically unsound.

When constructing a cost effectiveness model a number of assumptions must be made in building the base case. The assumptions made by Link are based on the clinical evidence and are no less robust or valid than those made by the AG. The same data set is used for both base cases and the differences reflect the uncertainties surrounding the data. Link would criticise the AG for using the worst case values and Link may have been open for criticism for using values at the other extreme. The reality lies between these two sets of assumptions and this level of uncertainly in the models should be recognised by the Appraisal Committee.

Whilst Link's ICER may be an underestimation the ICER estimated by the AG is certainly an overestimation.

ACD Section 4.3.1 - …… *It [the Committee] considered evidence on the nature of the condition and the value placed on the benefits of carmustine implants and temozolomide by carers of people with glioma, those who represent people with glioma, and clinical experts.*

The comments on the Assessment Report received from clinician consultees do not appear to Link to have been given sufficient weight in the preliminary ACD recommendations.

ACD Section 4.3.6 - …… *However, it [the Committee] concluded that the gain in overall survival shown in the trial was small, irrespective of the concerns expressed by the FDA.*

In a disease with such a poor prognosis where little survival benefit has been demonstrated in the past 20 years a 2.2 month increase in median survival is a clinically meaningful outcome. This is comparable to the 2.5 month increase seen with temozolomide and in both cases this represents approximately a 20% increase in survival compared to the respective control arm. The 1 year survival rates for the carmustine implants and temozolomide study arms are also comparable at 59.2% and 61.1% respectively. Furthermore the long term survival data for carmustine implants are even more impressive, representing a 5-fold increase in survival at 3 years, (p=0.01 unstratified log-rank analysis). In this context the overall survival gain in not small.

ACD Section 4.3.7 - …… *The Committee concluded that the evidence to illustrate a beneficial impact on progression-free survival of carmustine implants was weak.*

Carmustine implants have been shown to increase median survival by 2.2 months compared to placebo. The AG and the ACD suggest that the majority of this survival is post progression. However this implicit conclusion that symptom free survival was approximately one week out of the 2.2 months median survival gain is clinically implausible. How can carmustine implants which are administered at the time of the surgical resection and which are active for about 3 weeks have no impact on slowing disease progression or development of symptoms over the next six months yet provide a survival benefit in the progressive state, a time when no drug can possibly be present?

The Assessment Report stated:
"We also considered post-progression survival (estimated by subtracting median PFS from median overall survival). From the data reported by Westphal and colleagues 2003, we calculated a median life expectancy following recurrence of 8 months for patients treated with BCNU-W compared to 5.7 months for those who received placebo wafers. In the trial reported by Valtonen and colleagues 1997, post-progression survival was doubled in the BCNU-W group at 5.6 v. 2.5 months.
We are unable to undertake significance testing on these second-order measures without access to more extensive data. As neither RCT demonstrated a benefit in terms of PFS, any claimed treatment effect must be due to differences in survival after disease progression." [page 47]

With regard to progression free survival AG state *"there is no good evidence that …. any (other) chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours offers any benefit in slowing the rate of disease progression after recurrence*." *[page 87]*

These two statements on pages 47 and 87 of the Assessment Report appear to directly contradict each other. Link agrees with the statement on page 87 and considering the pharmacology and clinical use of carmustine implants **it is intuitive that the greatest clinical benefit will occur while carmustine is actually present i.e. in the period immediately following implantation and the benefit must therefore be prior to disease progression.** The biological basis for this is discussed below.

The infiltrative nature of gliomas means that despite maximal surgical resection there are inevitably residual tumour cells either at the margins of the resection cavity or within 2 or 3cms of the margin. Tumour regrowth over time therefore occurs in virtually all patients. The aim of chemotherapy and radiotherapy is to slow the rate of tumour regrowth and prolong symptom free survival.

Carmustine is an alkylating agent that acts by disturbing the fundamental mechanisms concerned with cell proliferation, in particular DNA synthesis and cell division. Carmustine can act on cells at any stage of the cell cycle however cytotoxicity usually occurs when cells enter the S phase and hence progression through the cycle is blocked.

The effects of applying carmustine locally will therefore result in apoptosis of tumour cells only while carmustine is present to produce its cytotoxic effects i.e. during the period of carmustine release from the implant. Given that 70% of carmustine is released within 3 weeks of implantation and that once released it has a short half-life of 22 minutes, the duration of chemotherapeutic action is likely to be in the region of 5 to 6 weeks. Full pharmacokinetic information was provided in Link's original submission.

This immediate cytotoxic action at the time of surgery retards tumour regrowth and permits the patient to present for radiotherapy with a lower residual tumour burden than would otherwise be the case. This should enhance the efficacy of subsequent radiotherapy as the tumour burden has been minimised.

Therefore the 2.2 month increase in median survival produced by carmustine implants must be prior to tumour progression as by this point there cannot possibly be any remaining chemotherapeutic activity due to carmustine. Intuitively, and as intimated by the AG, carmustine implants cannot affect the course of tumour progression several months after implantation.

The ACD takes an extreme position in assuming that virtually all survival benefit is post progression, an assumption that is pharmacologically counterintuitive. This is the worst case scenario for carmustine implants. The best case scenario would be if all the survival gain were symptom free.

The reality must fall somewhere between the two extremes and a sensitivity analysis of this variable is presented in the modelling discussion presented in the subgroup analysis in Appendix 2.

ACD Section 4.3.9 - *.....* *The Committee concluded that the economic analysis submitted by the AG was the most appropriate. This was because estimates of survival were based on measures of overall survival from the two largest RCTs. Additionally, this economic analysis incorporated an estimate of the effect of the disease on health-related quality of life.*

Link agree that the Markov model submitted by the AG is valid and accept that the mean survival advantage, the proportion of that survival which is progression (i.e. symptom) free and the relevant extra costs of treatment are all important determinants of the estimated cost effectiveness. However:

- The AG's estimation of the mean survival gain provided by carmustine implants is wrong, and an underestimate. It is based on a modelled Weibull curve that, despite the claims of the AG, is a poor fit in crucial part to the real life data. A fuller commentary on this point was presented in Appendix 3 of Link's response to the Assessment Report but in summary the AG model underestimates median survival by 27% and also results in an estimated mean survival gain smaller than the median survival gain actually observed in the Westphal study for carmustine implants. The fit of the Weibull curve is particularly poor at the tail which is most important for estimating mean survival.

- The way in which symptom free survival has been estimated by the AG presents the most disadvantageous case for carmustine implants. Link has argued in the response to the Assessment Report and in this ACD response that PFS estimated on radiological changes is misleading, and even more so when implants are present to further confound the images. Link has also argued that a better PFS estimate would use time to neuroperformance decline. The AG note that the statistical significance of the eleven neuroperformance measures depends on the way in which the measures are censored at death and this has been discussed under ACD Section 4.1.3.c above. In summary censorship at the last observation before death underestimates any advantages achieved in this final period before death while censorship at death probably assumes too generous a benefit during that period.

  As a consequence of their deliberations the AG assume in their modelling that there is only 1.3 weeks advantage to carmustine implants over placebo in progression free survival. Given the accepted (albeit underestimated) advantage in overall survival, this is implausible. As argued above, the nature of the treatment with carmustine implants is such that its effects must come soon after surgery, i.e. well before progression, and it is likely that most of the survival advantage will therefore be symptom free.

- The Assessment Report criticises the use of the mean of medians in the measurement of neuroperformance decline. Link accepts that in principle, means are more appropriate and therefore included a calculation based on the mean of means (7.4 weeks) of neuroperformance outcomes rather than mean of medians (8.2 weeks) in the response. The results are only moderately sensitive, in this instance, to the choice of means or medians.

- Importantly, the AG criticises the approach taken to costing treatments on grounds of principle. The approach recommended was considered by the NICE Methodology Committee at its most recent review of methodology and explicitly, see discussion under ACD Section 4.2.3 above.

Link therefore feels that the AG's criticism of the costings used are unfounded and restate the results obtained using Link's cost effectiveness model.

ACD Section 4.3.10 -…… *The Committee considered that fitting a Weibull curve to the RCT survival data resulted in a slight underestimate of the median survival gain from carmustine implants, and slight overestimate of the survival gain from temozolomide.*

The median survival gain attributable to carmustine implants from the Westphal study is 9.97 weeks whereas the predicted median survival gain from the Weibull model is only 7.31 weeks, page 218 of Assessment Report. This represents a 27% error in favour of the placebo arm and Link contends this **is not a slight underestimation** of the median survival gain from carmustine implants.

Furthermore the mean survival gain estimated by the AG from carmustine implants is given as 9.7 weeks (page 141 of Assessment Report) compared to a mean survival gain derived from the Westphal data of 10.6 weeks (2.45 months). This represents an 8% error again in favour of the placebo arm. As the mean gain is driven by a small number of long-term survivors this value must be larger than the median gain.

Taking this into consideration Link contends that the assumptions used in the AG's economic model are inaccurate and add to the general detriment to the estimation of ICERs for carmustine implants.

ACD Section 4.3.10 - …… *It [the Committee] also concluded that the results of the sensitivity analyses showed the survival gain from treatment would have to increase considerably for the incremental cost-effectiveness ratios to decrease substantially.*

The AG only conducted a series of one way sensitivity analyses varying a single factor whilst fixing all the others. In reality the uncertainties of the data (as noted in the Assessment Report on page 135 to

136) suggests that this is not a robust method of testing. A multi-variant analysis would be more appropriate given the uncertainties surrounding many of the base case assumptions. Link did perform such an analysis in the original submission. Relatively modest changes in cost estimates and symptom free survival together affect the estimate of cost per QALY.

ACD Section 4.3.11 - ……*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 for the treatment of newly diagnosed glioma would not be a cost-effective use of NHS resources.*

This conclusion is based on inappropriate assumptions which Link does not agree with.

ACD Section 4.3.13 - *The Committee considered whether there might be subgroups of patients for who the use of treatments may be more effective and cost-effective. ……*

In response to the suggestion in the ACD a subgroup analysis of patients who have undergone a maximal surgical resection has been undertaken and is presented in Appendix 2. This subgroup contains 111 patients (approximately half of the ITT population in the original trial) and is therefore of sufficient size to allow meaningful conclusions to be drawn, although this analysis was not pre-specified in the original protocol.

2.3 Resource impact and implications for the NHS

The ACD states that there are 1860 new cases of high-grade glioma annually in England and Wales. According to Whittle[12] only 25% of patients will meet the criteria of the Westphal study which represents the evidence base for carmustine implants. Using this value only 465 patients annually will be eligible to receive carmustine implants at a total cost to the NHS based on 6.5 implants per operation of £1,966,000. Furthermore if only patients who undergo maximal surgical resection are treated with carmustine implants (see Appendix 2) then the cost to the NHS would be halved to less than £1 million per annum.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

The preliminary recommendations do not constitute a suitable basis for guidance to the NHS because:

- The body of clinical evidence confirms that carmustine implants provide physicians and their patients suffering from high-grade glioma an opportunity to significantly extend survival and, importantly, improve symptom free survival.
- Implementation of the preliminary recommendations would deny patients the opportunity for a five fold increase in 3 year survival with carmustine implants.
- The NHS cancer plans aims to improve survival rates in line with other European countries. Denying UK patients access to carmustine implants which are in common clinical practice and fully reimbursed in the US, Australia (PBAC, April 2006) and many parts of Europe will be in conflict with this objective.
- The benefits of NHS treatment with carmustine implants can be offered on a cost effective basis to the relatively small number of eligible patients suffering from this condition.

In this devastating disease the recommendations of the committee should be to support the use of carmustine implants which have been shown to improve median and long term survival and to represent cost effective use of NHS resource.

Appendix 1

Cost effectiveness analysis for the ITT patient population from the Westphal study

Validation of Link model against the Assessment Group model

An executable copy of the AG model is not available to Link. In order to demonstrate the convergent validity of Link's model with that of the AG the former was run for the full Westphal population (n=240) using the assumptions built into the AG model. These assumptions were:

- Carmustine implant cost of £687.50 (which was incorrect and subsequently amended by the AG).
- Incremental cost assumptions as per Table 57 of the Assessment Report at £1,853.
- Mean survival (9.7 weeks) and PFS (1.3 weeks) as in Table 58 of the Assessment Report.
- Utility pre-PFS of 0.888 (mean utility for stable disease state from Table 58 of the Assessment Report) that was assumed to decline linearly from the onset of symptoms until death.

Based on these assumptions Link's model gives a cost per QALY for the full ITT group comparable to that quoted in the ACD, £63,839 and £57,000 respectively. This suggests that when the assumptions are harmonised the two models have similar but not identical predictions.

Link's model can therefore give an informative demonstration of the importance of each of the assumptions and alternative scenarios based on these assumptions are presented below.

Scenario 1	Correction of the carmustine implant price error brings the cost/QALY down to £63,447.
Scenario 2	Keeping the correct price for carmustine implants and using a mean survival figure of 2.45 months as derived from individual patient survival data from the Westphal study, rather than from AG Weibull curve, reduces the cost/QALY by ~£4,000 to £59,500.
Scenario 3	Keeping the correct price for carmustine implants, using the mean survival figure as in scenario 2 above and using a 7.4 week symptom free survival assumption based on neuroperformance measures lowers the cost/QALY by a further £17,500 to £37,564.
Scenario 4	Taking scenario 3, but removing any incremental costs as argued previously reduces the cost/QALY by nearly £10,000 to £27,900.

Scenario 5 The case for making the changes in scenarios 1, 2 and 4 are strong. Given the difficulties in determining the time to onset of symptoms discussed previously this scenario uses an assumption of an increase in time to onset of symptoms due to carmustine implants of 4.35 weeks. This is halfway between that estimated by the AG (1.3 weeks) and that estimated by neuroperformance measures (7.4 weeks) giving a cost/QALY of £33,500.

Appendix 2

Cost effectiveness analysis for the subgroup of patients who have undergone maximal surgical resection and been given carmustine implants

The ACD under Sections 4.3.13 and 5.2 indicates that subgroups in whom the treatment with carmustine implants may be particularly effective should be considered. Link is taking this opportunity to present data on such a subgroup, those patients who underwent a maximal surgical resection. This subgroup analysis was not part of the original statistical analysis plan and has only been investigated now in response to the ACD request.

Clinical evidence

The maximal resection group in the Westphal study is defined as those patients in whom at least 90% resection of the glioma was possible. In the majority of included patients the resection was in excess of 95%.

The median survival gain for patients receiving carmustine implants was 2.15 months, p=0.006 unstratified log rank analysis.

The carmustine implant and placebo arms were well matched on demographics, number of implants used and the percentage resection. There was some imbalance in the number of grade III tumours, 13.8% and 3.8% for the carmustine implant and placebo arms respectively. Consequently survival data is also presented for patients with GBM within the maximal resection subgroup, see Table 5, and demonstrates a statistically significant difference in the gain in median survival (2.1 months p=0.0191 unstratified log rank analysis).

Table 1 – Baseline demographic characteristics of maximally resected patients (n=111)

Demographic characteristic		Carmustine implant (n=58)	Placebo (n=53)
Sex	Male n (%)	39 (67.2)	34 (64.2)
	Female n (%)	19 (32.8)	19 (35.8)
Age (years)	Mean	52.3	54.5
	Range	28 - 65	33 - 67
Karnofsky performance score			
	60	4	8
	70	9	3
	80	15	13
	90	14	18
	95*	0	1
	100	16	10

* The baseline KPS was recorded as 95 in 1 patient representing an intermediate level of function in the judgement of the responsible clinician

Table 2 – Final histological diagnosis

Tumour type	Treatment group	
	Carmustine implant (n=58)	Placebo (n=53)
Glioblastoma multiforme	50 (86.2)	51 (96.2)
Grade III glioma	8 (13.8)	2 (3.8)

Table 3 - % resection of high-grade glioma

% resection	Carmustine implant		Placebo	
	Patient number	%	Patient number	%
100	45	77.6	38	71.7
99	2	3.4	2	3.8
98	1	1.7	0	0.0
95	4	6.9	4	7.5
90	3	5.2	5	9.4
Missing data	3	5.2	4	7.5
Total number of patients	58	100.0	53	100.0

Table 4 – Number of implants used

Study arm	Patient number	Mean implants used	Minimum implants used	Maximum implants used
Carmustine	58	6.41	2	8
Placebo	53	6.74	3.5	8

Table 5 – Survival data

Patient group	Survival (months)			
	Carmustine implants	Placebo	Difference	P value *
All patients (n=111)				
Median	14.75	12.60	2.15	0.0061
Mean	18.00	13.80	4.20	
GBM patients (n=101)				
Median	14.60	12.50	2.10	0.0191
Mean	16.98	13.68	3.30	

* This is an unstratified log rank analysis.

Table 6 – PFS as determined by different methodologies

Measure	PFS (months)		
	Carmustine implants (n=58)	Placebo (n=53)	Symptom free gain (months)
Radiological imaging	8.8	8.5	0.30
Mean time to KPS decline	15.0	12.4	2.60
Mean (of means) time to neuroperformance decline	65.8	52.5	3.06

Cost effectiveness of carmustine implants in maximal resection subgroup

Link's model has subsequently been used to estimate the cost effectiveness of carmustine implants in the maximal resection subgroup of patients discussed above. The number of implants used remains at the slightly higher mean level of 6.54 for the Westphal ITT group.

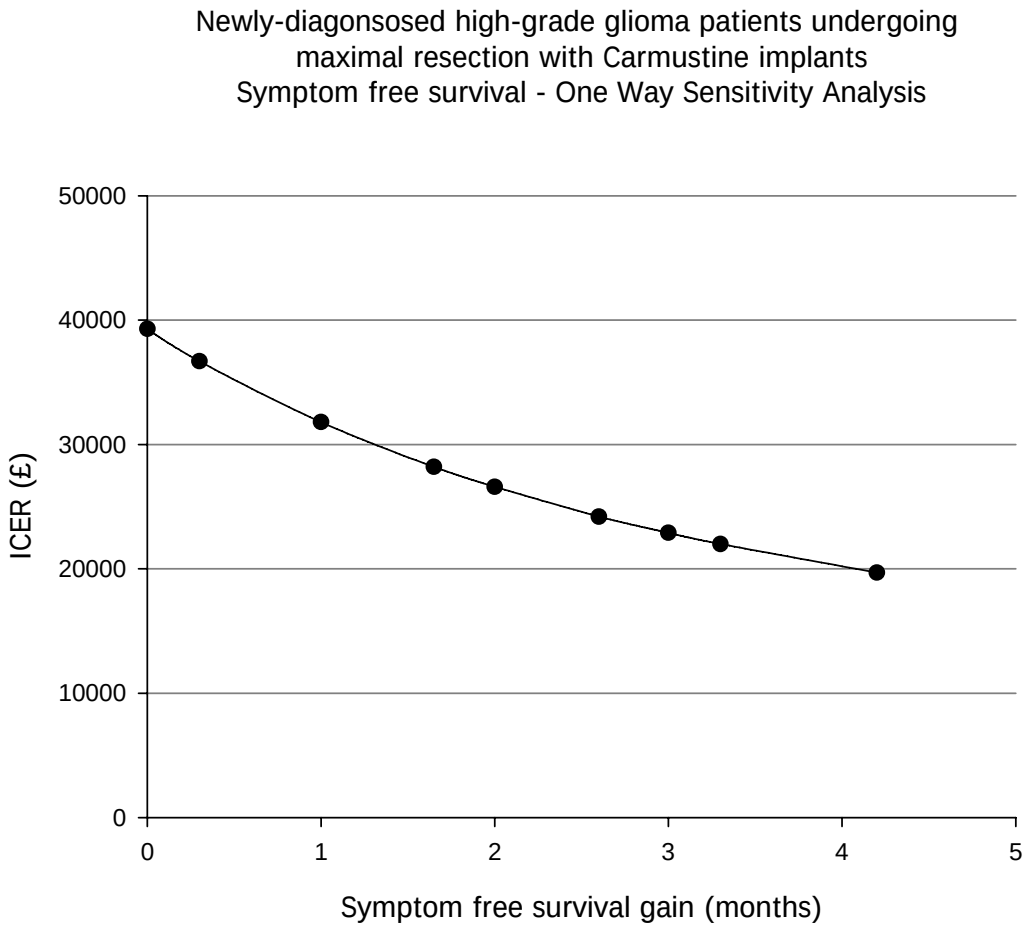
The results under varying assumptions relating to symptom free survival are given below. It will be seen that for most of the range of symptom free survival the ICER achieves conventionally accepted levels of willingness to pay. Only under the extreme assumptions of very low symptom free survival relative to the total gain in survival does the cost per QALY exceed £30,000.

Table 7 – effect of symptom free survival assumption on ICER per QALY for maximal resection subgroup

Gain in symptom free survival (months)	Comments	ICER per QALY
0.3	Difference derived from PFS as measured radiological imaging (AG assumption)	36,700
1.31	Survival gain providing a cost per QALY at the willingness to pay level of £30,000	30,000
1.65	50% of mean survival gain for GBM patients within maximal resection group	28,200
2.6	Difference in PFS as measured by decline in KPS	24,200
3.0	Difference in PFS as measured by mean of mean neuroperformance measures (Link assumption)	22,900
3.3	100% of mean survival gain for GBM patients within maximal resection group	22,000
4.2	Difference in mean survival for ITT patients in maximal resection group	19,700

Presenting these data graphically, as shown in Figure 3 below, demonstrates that a progression free survival gain of 1.31 months gives an ICER per QALY at a willingness to pay level of £30,000.

Figure 3


Newly-diagonsosed high-grade glioma patients undergoing
maximal resection with Carmustine implants
Symptom free survival - One Way Sensitivity Analysis
ICER (£)
50000
40000
30000
20000
10000
0
0
1
2
3
4
5
Symptom free survival gain (months)

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