RESPONSE TO NICE TECHNOLOGY APPRAISAL OF CARMUSTINE WAFERS AND TEMOZOLAMIDE IN PATIENTS WITH HIGH GRADE GLIAL TUMOURS

Prof Garth Cruickshank on Behalf of the Society of British Neurological Surgeons

1. The NICE Technology Appraisal of Carmustine wafers and Temozolomide in patients with high grade glial tumours had recognised significant survival benefit from patients involved in a randomised control trial (N=240) receiving Gliadel (Carmustine) wafers at first surgery (2.3 months). Similarly, it has been accepted that from a randomised control trial where 287 patients receiving Temozolomide after surgery, there was a significant increase in survival of 2.5 months and a more than doubling of long-term survival at two years from 10% to 26%. Hence, the grounds for NICE Technology Appraisal refusal to support funding of Carmustine and Temozolomide are purely on a cost basis.

2. NICE have misunderstood that progression does not lead ultimately to "rapid deterioration and death" and that survival with a useful quality of life occurs regularly after determination of tumour progression. This is especially true where determination of progression is a function of the assessment periods or based on imaging. Indeed, the concept of progression-free survival in patients with glioblastoma is not universally accepted and that patients can have prolonged periods of useful clinical performance above a well accepted performance threshold.

3. The differences in survival from these trials is small but significant and represents truly pragmatic results obtained from multi-centre trials of data published in peer review journals and applauded and accepted internationally (see New England Journal of Medicine, May 2005)

4. The differences in survival shown by these randomised control trials for these drugs is reviewed in terms of £/QALY. It is clear that there are errors in the abstract nature of the model used by the AG by comparison with clinical experience which was not represented on the committee despite expert input. As a result interpretations of disease state and their progression as well as costs for treatment and survival have been incorrectly applied. As a result the £/QALY estimates used by the committee are an over-statement of the true costs.

5. By their own admission (see NICE Summary Report 4.3.10) an improvement in these QALY estimates could only be achieved by improvement in survival of 6 ÷ 2.5 or around about 2.2 x improvement in median survival to around six months (using AG figures). Such a relative increase is not possible with any current cytotoxic agents for any solid tumour and is an unreasonable expectation.

6. The use of these two agents to treat tumours has been accepted in Scotland, the London Drugs Group, several PCTs throughout the UK. It has been accepted in the US (despite NICE's comments about the FDA 4.1.3) and it is also accepted for treatment in Germany, Belgium, France, Italy, Spain and Australia. Such a universal acceptance places patients in the UK in a uniquely underprivileged situation.

7. The above decision to decline use of these drugs in the UK, places the medical profession and stake holder organisations in an impossible position. In addition and most importantly it would cause enormous anguish, anxiety and suffering to many patients and their carers if a total embargo on the use of Temozolomide and Carmustine was instigated. It is also an illogical decision compared with that of 2001 now that later, better, data for Temozolomide are available.

8. It is accepted that benefits from survival for Carmustine and Temozolomide are small but significant. It is accepted that new/better treatments must be sought through well designed trials and that any trial can be better designed in retrospect. However, we maintain that the two trials mentioned above form the core of current data representing well designed trials carried out as pragmatically as possible and which are recognised by oncological experts as the best work in the this field for many years and across many tumours. This is especially true for such a group of solid tumours which could be described as "rarer cancers", i.e. less than 10/100,000 of the population.

9. It is recognised that there will be a considerable outcry from patients and medical carers if the current draft NICE position is not revised. In addition, it should be recognised that there are currently no NICE recommendations with respect to the use of Carmustine whatsoever. It would be truly unacceptable for the NICE Technology Appraisal to leave the situation for use of these two drugs as status quo for the next two years. There has been significant under spending on

this group of patients and failure of responsible authorities to recognise the particular needs of these patients. As a result, an all party parliamentary group will pursue these issues through political channels and will use these concerns as a platform for placing pressure on the Government during Brain Tumour Awareness Week in March 2006.

10. As a result of all of the above, the SBNS represented by its 206 neurosurgical consultants in the UK who deal directly with these patients propose that the clinical benefit of Carmustine and Temozolomide is recognised by allowing limited gatekeeper access to the use of these drugs and that financial control is exerted by recognition that clinical selection of patients will not reduce unit costs but will substantially reduce the total bill for this group of patients, by limiting access to around 25% of patients most likely to benefit from these treatments, i.e. 25% of 1700 patients at a total cost of between £6,000 and £11,500 per patient per treatment, i.e. around 125 patients per year.

11. The application of the included criteria (see appendix) will allow sensible managed access to these expensive drugs to allow the UK to remain in the forefront of brain tumour research and enable us to continue to take part in international clinical trials. It will allow time for the MGMT test to become clearly established. It will protect medical personnel from being compromised in their description of best clinical practice to patients, provide a rational basis to control the use of these drugs that will be acceptable to both patients and practitioners alike, reduce the risks of complaint, criticism and possible medicolegal attack from patients as a result of a blanket ban. It would not place the UK at a disadvantage from the European situation which would leave them open to litigation as has been discussed in the press. Finally, by limiting availability this way, doctors will be legitimately able to discuss with patients what treatment is best for them individually.

12. The SBNS accepts the body of work that NICE has done but does not accept their interpretation of a number of important clinical, experimental, and practical implications of the technical data available. In addition, the SBNS recognises that the current NICE position will leave them in an extremely difficult position which will lead to many patients being disadvantaged with respect to treatment. It recognises that a total ban on access to these drugs is unacceptable and

recommends a sensible rational plan for limited controlled availability of these medications in a sensible workable mechanism. The SBNS strongly counsels the NICE appraisal group to reconsider their current recommendations and to elevate section 5.2, final sentence, "subgroups in whom treatments may be particularly effective" be the level of the recommendation based on the associated criteria and the developing use of biological markers.

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GLIADEL IN NEWLY DIAGNOSED HIGH GRADE GLIOMAS

Agreed clinical criteria for prescribing.

1) Imaging appearances indicate high grade glioma and high likelihood of achieving ≥80% excision with <10% risk of deficit and complete dural closure.

2) Intra-operative biopsy must be performed and confirms high grade glial tumour e.g.

- Anaplastic Astrocytoma
- Anaplastic Oligodendroglioma
- Anaplastic Oligoastrocytoma
- Gliosarcoma
- Glioblastoma

3) Performance level ≥60 Karnofsky, WHO 0,1,2.

4) Up to 70 years of age.

5) No prior chemotherapy or radiotherapy.

6) That subsequent radiation can be commenced within 4-6 weeks from surgery.

7) Support for patients through

- Clinical Nurse Specialist
- Easy out-patients department access to oncologist and neurosurgeon.

8) That ongoing audit is maintained of patients, indicating complications and outcome.

9) Cost model would respect that any patient receiving treatment at the initial surgery would not be expected to be eligible for treatment with Gliadel at recurrence.

10) Encourage assessment of MGMT studies.

TEMOZOLOMIDE: CHEMORADIATION AND ADJUVANT THERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA

Agreed clinical criteria for prescribing.

1) Patients who have ≥80% excision of tumour.

2) Patients with histological confirmation of glioblastoma.

3) Performance level ≥60 Karnofsky, WHO 0,1,2, after surgery.

4) Up to 70 years of age.

5) No prior chemotherapy or radiotherapy.

6) Radiotherapy commencing within 6 weeks post surgery, ideally by 4 weeks, using radiotherapy regimen as EORTC study with weekly assessment of full blood count and CD4. Site must commit to whole drug programme as described in study i.e. chemoradiation and adjuvant therapy must be used.

7) Support for patients through

- Clinical Nurse Specialist
- easy out-patients department access to oncologist and neurosurgeon.

8) That ongoing audit is maintained of patients, indicating complications and outcome.

9) Cost model would respect that any patient receiving treatment at the initial surgery would not be expected to be eligible for treatment with Temozolomide at recurrence.

10) Encourage assessment of MGMT studies.

NICE Technology Appraisal Document: Source responses to Appraisal Document item numbers

Collated and edited responses from SBNS members by Prof Garth Cruickshank

1.1 NICE review of Temozolomide in 2001 related to patients with recurrent high grade tumours in which after consideration of limited evidence agreed its use after PCV treatment at a cost of around £9000 per patient for around 1.5 to 2 months median additional survival benefit from 6 months to eight months. It is unclear what the status of this recommendation is in the light of the current appraisal document. Especially where the evidence for early treatment with this agent has shown improvement in overall survival, and is currently being compared against PCV treatment at recurrence in a randomized clinical trial (NCRI/BR12).

2.6 Incorrect information. Sentence three implies that inoperable ie non-debulkable patients will only receive palliative treatment. This shows a lack of understanding of the issues. There is as yet no clear RCT evidence to confirm that debulking is superior to biopsy where subsequent treatment involves a full course of radiotherapy. Thus patients who do not have debulking will usually have a biopsy performed and both will be considered for radiotherapy equally dependent on their performance level.

The related issue from the two RCT studies (Stupp et al [Temozolomide] and Westphal et al [Carmustine]) is that subgroup analysis (see appraisal document 4.1.12) showed that radical resection appears to improve the response to both these treatments in this trial design.

3.2 Carmustine implants are not just indicated they are indeed licensed for use in newly diagnosed high grade gliomas. (cv comments made about Tmozolomide 3.6 inconsistent)

4.1.3 Despite these comments, the FDA did indeed give license for Carmustine wafers to be used in newly diagnosed high grade gliomas with extensive resection.

4.2.3 The time to onset of symptoms is discussed. It is unclear whether the concerns about estimation of period based on mean or median times relate to Temozolomide as well. It is fair to say that although the FDA felt it necessary to reanalyse the data for Carmustine wafers they still felt they had a reasonable situation to grant a licence.

The assumption about difference in cost being primarily due and more or less entirely due to the implants themselves is justified by the data. (see section 4.2.4)

A utility value of 0.8 for patients without symptoms implies that the diagnosis alone is sufficient for a drop in utility data. It was unclear where the evidence for this is within the AG document. It seems more likely that the utility value is an estimate based on the shape of the performance curve, and many patients even with a diagnosis of brain tumour will still have a high performance level and a utility value nearer to 1. The use and estimation of the utility value is clearly open to discussion where mean estimates clearly represent an average utility over a regular fall in performance. The situation is far from clear that this pattern is universally is so, and a threshold estimate may be more useful. (see later comments on 4.3.9)

4.2.4 The statement that the £ per QALY for Carmustine was understated because of *(a)* "assumptions" used to estimate survivals and *(b)* omission of treatment costs. In response to *(a)* the weighting of this approach is unclear and the impact on the QALY estimate implied by this statement is implicitly damning without qualification. As regards the omission of treatment costs, other than those with implants themselves, these were excluded because <u>there are none</u> and it is incorrect to imply otherwise.

4.2.7 It would be wrong to create a cost benefit model which stepped outside of the patient groups included in the two major trials where the additional synthesised data included could have a mutual impact on the subset of RCT data eg incorrect stratification. We have concerns about how this model has been

developed and extrapolated beyond the data available from the RCT process. It is fair to say that the Markov model used by the AG is unvalidated in this patient group.

The discussion of the local cost data model in the original technical report has not included a balanced assessment of the relative GNP and spending on cancer treatment in Europe or in this context, e.g. the relative spending on brain tumour of patients in the UK versus Europe. Hence, local analyses of cost (£ per QALY) and threshold limits should be compared with similar levels and thresholds for the European sector. The importance of this is that it would form an important prima facie basis for individual patients to mount a legitimate claim against restrictions on prescribing Carmustine and Temozolomide as a result of this draft appraisal. (See Barbara Clark case on Herceptin: Human Rights Act and European Court) This is particularly true where clinicians caring for these patients would naturally support patients to have these treatments, as the best available, comparably with the rest of Europe.

Patients do not have a constant "deteriorating quality of life" as many oncologists looking after these patients will agree. It was clear at the discussions meeting held at NICE HQ that this concept was <u>not</u> grasped by the committee. It is probably relevant that no oncologist or oncologist practicing in this area resides on the committee or was involved in the writing of the technical report. In our experience it is unusual for there to be such total agreement between oncologists overall and oncologists working in this area to approve these two new treatments. This discrepancy from practising clinical activity needs resolving.

4.3.1 On reviewing the data we accept that the committee has a wide range of expertise and that it took advice from experts. However, we are concerned that the acceptance of these two treatments by oncologists in the UK and throughout the world but not by this committee reflects the fact that the views of patients and carers in this area has not been fairly represented in the deliberations of this committee. This is clearly true in the technical report which <u>lacks any oncological input</u> in the writing.

4.3.2 This statement is incorrect and shows lack of understanding of patients with this tumour. Patients <u>do not</u> universally decline once progression has occurred.

Progression is hard to define as is remission in this case. Patients may develop focal signs of may notice nothing of what is grossly apparent on imaging. Most patients have fluctuation in performance with their disease and are managed accordingly. These fluctuations probably reflect ongoing disease and may be classified as progression or may not. Decline is not immediate and is not by any means "usual". Most patients with these cancers link their quality of life with their survival and a few months increase in survival contributes significantly to quality of life. In addition, the hope that they might live for two years, i.e. from 10% to 26%, is of huge importance to both carers and to patients.

4.3.3 The assessment of the committee concerning long-term survival was ill founded. There is available data that confirms that the QOL in the long-term survivors was maintained (R Rampling personal communication). Secondly, despite their bias, the differences in long-term survival from 10-26% - a considerable increase was statistically significant and, therefore, not "too small". It was unreasonable of the committee to take this attitude if the effect of selection of patients would be to increase the likelihood that up to 25% of these patients might live two years.

4.3.4 We were grateful for the committee's acceptance that the whole pathway for these patients must be supported. It is important as it has relevance to the implementation of these treatments and has been underwritten by the new draft NICE IOG for patients with brain tumours. It would be illogical for the technology appraisal group to ignore the fact that the IOG group has been impressed by these RCT's and will utilise the IOG implementation to ensure that new treatments, and particularly these treatments, can be implemented effectively.

4.3.5 It is not helpful to invoke implications about other treatments and omit unavailable data here. It implies that our lack of certainty about existing and future data would always negatively impact on the decisions to use Carmustine or Temozolomide in the future. Is there a confusion/mistake with Temozolomide and Carmustine here.

4.3.6 Despite the implied concerns here the FDA carefully considered the data and licensed Carmustine based on their positive assessment of the submission. It is clear that although the overall gain in survival was indeed small, but significant,

and in terms of patients who live for twelve months or so, two to two and a half months improvement in survival is not small, it is considerable. It is unreasonable for the committee to downplay the impact that 2.3 months on survival can be for patients and their carers. It is particularly true when there is evidence of maintained quality of life.

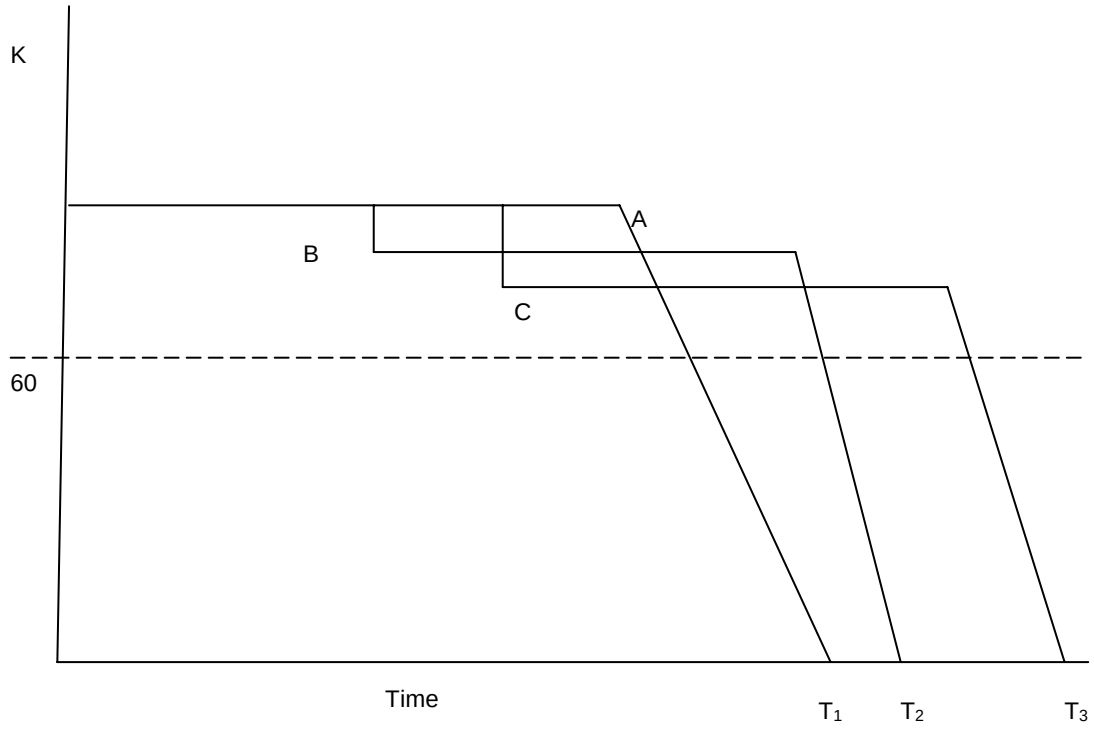
4.3.7 The experts explained that performance free survival was difficult to assess and that following disease progression, as said above, is not routinely followed by "rapid deterioration".

The committee would be wrong to place much store by disease assessment based on imaging. However, this should be taken to imply that it is *the method of assessment for tumour response* that is inadequate, and that the status of performance free survival may be just as equally positive or negative and not just always negative by inference. In other words imaging 'deterioration' often has little relation to clinical deterioration.

4.3.8 We are pleased that the committee recognised the difficulties in absolute pathological definition of high grade glioma. It is unclear, however, how they have taken this into account numerically in their interpretation of the information from the AG in reaching their conclusions.

4.3.9 We agree that both the <u>disease</u> and its <u>treatment</u> may have measurably difference effects on the quality of life and survival. However, it is clear that the understanding of quality of life (QOL) in this group of patients by both the AG and the committee was influenced by the abstract AG model which misleads on the performance after "progression". More sensitivity to the views of those experienced in defining the disease and its care would have helped correct this and would have clarified the position. For example, quality of life is very difficult to assess in the latter stages of disease and many professionals working in this area

use a different paradigm to approach this.



In the figure above, the Y-axis represents performance level measured in Karnofsky units. The X-axis represents time. The three graphs A, B and C represent progression of disease in three different patients with glioblastoma multiforme. Patient A shows the pattern roughly assumed to be the normal pattern described by the AG model dying at time T1. Patient B shows early deterioration by drops in performance which is treated and measurably stable until deterioration at T2. Patient C shows an intermediate deterioration but outlives A and B to T3. However, both B and C have a prolonged but useful performance level above a Karnofsky of 60. Thus, A deteriorates later but dies earlier and B and C deteriorate earlier but have a useful existence above a recognised threshold for independence. On this basis we would question whether the AG model is valid and that the committee have been too influenced by its seeming precision without adequate regard to its weaknesses.

4.3.10 Again, there is an over-emphasis on the time of when PFS ends and deterioration begins and its rate.

The comment about the Weibull statistical approach is not about whether something is an over or under estimate of survival and seems to imply that in someway the data is unreliable. We refute this but agree with the committee that

its axiomatic agreement that there were improvements in survival in the two RCTs for these two compounds is substantiated.

Of considerable concern, however, is the final statement in this section. If we follow the logic of this argument we would have to see an increase in survival to nearly six months between the treatment in control groups to bring the £ per QALY much lower. We doubt whether there are any recent treatments in any of the solid tumours that have been able to demonstrate a six month improvement in survival let alone a three month improvement. This is an unfair and unreasonable target for research in this area to achieve and does by implication make it impossible for these patients ever to receive a £ per QALY target that would satisfy the NICE criteria. In other words, the patients are debarred from available cancer treatment by virtue of their diagnosis – this is by NHS terms unreasonable.

4.3.11 The committee has apparently misunderstood the AG analysis and are now intending to contradict themselves. Secondary treatments have apparently been shown to be ineffective whatever time they are given so that the treatment we give to patients after failing the treatments presented in these RCTs is immaterial. Furthermore, these RCT studies compared subsequent treatments in each arm and dismissed them as ineffective at influencing the outcome. Hence, there is no question about "uncertainty here". The message from the RCTs is that early treatment with these treatments produces an effect which is substantially greater than when they are used at a later date, which makes NICE's current position illogical with respect to the ruling in 2001 on Temozolomide used at recurrence. The committee should ignore discussion of subsequent or other treatments as they are by their own admission and through the acceptance of the AG report ineffective. To disbar patients from these upfront treatments by virtue of the fact that patients survive and then cost money is unreasonable.

Cost effectiveness of treatment has both an economic basis as well as a societal/political basis. The latter is responsible for the setting of thresholds which assume all decisions are made on a comparably fair process to all applicants. We feel that there are significant questions about the committee's analysis of the RCT data which is at odds with international bodies, reputed journals, and the National Oncological Conference and impact on the assessment of 'willingness to

pay'. There are concerns that NICE's application of cost benefit thresholds as applied fails to take account of:

(i) Discrepancies between oncologists' interpretation of patient performance and the distinctions made by the committee.

(ii) Misunderstandings around possible achievable improvements in survival for a particular cost.

(iii) Failure to appreciate that spending on brain tumours is low and that even additional costs for these drugs remains low per capita by comparison with patients with lung and breast cancer. The impact of this is to make research in this area more expensive as the Sponsor must pick up the cost which they have to recoup in the licensing period.

(iv) Even though the £ per QALY cost may be high to numbers of patients who could be selected for this treatment, the number of patients is low and will result in a reasonable and transparently determined cost to the NHS which would allow this rarer cancer to achieve equity of funding with other cancers.

(v) It is reasonable to argue that factors other than health status are important in quality of life assessments since some people are unable to convert healthy life into good quality of life. However it is normal to consider quality of life in the context of what health status of a reasonably fit person of that age might hope for, and to ignore all aspects of quality of life that are not caused by illness and /or modified by treatment and care. We maintain that the knowledge that a person is in the 'best 'available treatment contributes directly to their 'health status' and that to have this denied will seriously and adversely affect there QOL to the extent that it will alter the conditions under which the AG assessment was performed. In other words the extent of the 'additional suffering' that is likely to ensue from the current NICE position must be considered.

Prof G Cruickshank 23 January 2006