INSTITUTE OF NEUROLOGY

UNIVERSITY COLLEGE LONDON

Department of Neuro-oncology

THE NATIONAL HOSPITAL FOR
NEUROLOGY AND NEUROSURGERY
QUEEN SQUARE
LONDON WC1N 3BG

JR/SA

Ms Alana Miller
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
WC1V 6NA

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Dear Miss Miller

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

Thank you for you sending me the results of the Appraisal Committee's deliberations regarding the above which I am replying to on behalf of the **Association of British Neurologists**. I am surprised and disappointed by the view that the Committee has taken that both carmustine implants and temozolomide should not be recommended for the treatment of newly diagnosed high-grade glioma, except in well-designed clinical studies. This will effectively deny these treatments to the vast majority of patients with high-grade glioma who are not being treated within the context of clinical trials and undermines the substantial body of evidence that has accumulated already from well-designed randomized controlled trials. It will also act as a deterrent for any future clinical trials to be carried out in this country. Furthermore, as carmustine implants have just been accepted for use within NHS Scotland for the treatment of newly-diagnosed high-grade glioma this will inevitably create a true situation of post-code prescribing that NICE was set up to abolish. Of the two technologies, I consider the evidence for the effectiveness of carmustine improving progression-free survival to be weaker than that for temozolomide and would therefore anticipate that The Scottish Medicines Consortium (SMC) will accept the use of temozolomide as well in the future.

This decision needs to be considered in the light of current practice in other developed countries specifically the United States and Europe. In the US, the FDA approved temozolomide almost immediately after the phase II study was published in 2002 (Stupp R *et al.* Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol. 2002 Mar 1;20(5):1375-82) and as a result the concomitant regime has been standard therapy for newly diagnosed high-grade glioma since then. The rest of Europe adopted it immediately after the NEJM article came out in April 2005.

If the NICE guidance is adopted the UK will be the only industrialised country in the world (except Belgium) that has not agreed to fund treatment.

With respect to these specific points raised by the Appraisal Committee:

1) I do not consider that they have considered all the relevant evidence, specifically they failed to take into consideration the subset analysis of median overall survival by prognostic factors from the Stupp (EORTC) Study which was published on-line as an addendum. They showed that the benefit of combined treatment with temozolomide and radiotherapy for patients under the age of 50 was significantly better than those under the age of 50 years who received radiotherapy alone (median survival of 17.4 months vs 13.2 months $p<0.001$). In comparison, the benefit of the combined treatment compared to radiotherapy alone for patients over the age of 50 years was also statistically significant although not as impressive in absolute terms (13.6 months vs 11.9 months). As expected, patients who had had surgical resection fared better than patients who had just been biopsied in both groups (15.8 months vs 9.4 months in the combined arm) and patients with WHO performance status of 0 or 1 also had significantly longer survivals than WHO performance status 2 (17.4 and 14.0 months vs 9.9 months). I therefore believe that there is a sub-group of 'better prognosis' younger patients with high performance status and surgical resection who stand to benefit considerably more from the additional temozolomide than 'poor prognosis' patients and I feel that the appraisal committee have not given due consideration to these factors.

2) As regards cost effectiveness, I am a little perplexed by the conclusion that if the maximum acceptable amount for an additional QALY gained is £50,000 or more and the mean incremental cost per QALY was just under £37,000 for better prognosis patients treated with carmustine and £43,000 treated with temozolomide, why did the committee conclude that they were not cost effective? Clearly the resource impact and implications on the NHS are appropriate if one accepts their conclusions that neither of these technologies should be recommended for use.

3) For the above reasons, I do not consider that the provision recommendations of the appraisal committee are sound and at the end the day, it seems that they have been far too heavily influenced against the technologies by virtue of economic considerations alone.

In every area of cancer treatment, there are new technologies, which offer small but significant survival advantages. Notwithstanding various concerns about the data analysis in the carmustine trial, both these technologies can be considered to offer small survival advantages and certainly in the case of temozolomide, a significant survival benefit at two years which has never yet been demonstrated for any other type of adjuvant chemotherapy. To deny patients the benefit of these technologies on the basis of relatively marginal survival benefits which have been clearly demonstrated and even more marginal cost considerations, which have not been clearly demonstrated, particularly so for good prognosis patients, seems to go against the basic principles of the NHS Cancer Plan which is to ensure that patients with cancer are not disadvantaged with respect to proven treatments in comparison to similar patients elsewhere in the world.

If we are unable to give suitable patients these treatments they are not getting 'best standard' treatment, and this will have a knock-on effect in that patients will be less likely to be referred to MDTs, as they would be perceived to have nothing to offer. In addition, research would stop completely as no treatment would achieve the cost effectiveness bar and we would not be able to enroll patients in future EORTC/International Trials. If there is a possibility of giving Gliadel or Temozolomide, then non-MDT doctors are likely to refer to MDTs early to see if patients would

be suitable or not rather than just resecting or biopsying without discussing at MDT. A negative response from NICE would shoot the NCCC/NICE Commissioning Guidance in the foot and fly directly in the face of the Guideline Development Group.

I look forward to your response.

With best wishes

Yours sincerely

Dr Jeremy Rees PhD FRCP
Senior Lecturer in Neurology & Medical Neuro-oncology
Honorary Consultant Neurologist