Royal College of Physicians

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From [redacted]

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Dear Ms Moore

Re: Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489] – Second Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 28,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to the above ACD. We are grateful for the opportunity to comment and note that this is the second ACD consultation for the appraisal. Although our experts have no new comments we would like to draw the Committee's attention to the comments made by Dr Yvonne Summers (which were supported by the NCRI/RCP/RCR/ACP/JCCO) with regard to the first ACD consultation. We believe that these points are still pertinent and are therefore outlined below.

I was very disappointed to read the contents of the ACD regarding Pemetrexed maintenance in NSCLC and would ask that the following points be drawn to the attention of the committee when it reconvenes on Wednesday 27th March 2013:

1. There has been much discussion about the various models used by the manufacturer and the ERG and extensive debate over the survival benefit gained in the pemetrexed arm in the post progression period. In section 4.16, page 23, line 1, the document states, "The Committee heard from the clinical specialists that a continued benefit of pemetrexed over best supportive care after disease progression would not be expected". Whilst we could not explain why there was an improvement in outcome for patients on the pemetrexed arm of the trial in the post progression period, the patient derived data from the PARAMOUNT study shows a greater improvement in overall survival compared to progression free survival (2.9 versus 1.3 months respectively). Whether or not this finding is expected these are the results that were observed and cannot be discounted.

2. With regard to end of life supplementary advice and in particular reference to the small patient population calculations (section 4.20) we would make the following comments:

a) Maintenance. There was a lengthy discussion at the committee meeting about why there has been virtually no uptake of pemetrexed maintenance following non-pemetrexed doublet 1st line chemotherapy since NICE approved its use in June 2010 (TA190). It was discussed that patients with non-squamous NSCLC who were PS 0-1 and fit for pemetrexed and cisplatin 1st line are receiving this treatment preferentially, thus making them ineligible for pemetrexed maintenance under current guidelines. The fact that so few patients have received pemetrexed maintenance since June 2010 gives us almost 3 years of data which confirms that patients who are not fit for cisplatin and pemetrexed 1st line therapy, but receive another 1st line treatment, are extremely unlikely to be fit for maintenance therapy for the same reasons that excluded them from pemetrexed treatment in the first place (i.e. poor PS, co-morbidities, etc.). There is no evidence in the literature that any significant proportion of PS 2 NSCLC patients become PS 0-1 after chemotherapy. It is therefore unreasonable to assume as is stated (section 4.23, page 27) "As there was a similar number of such patients receiving first-line chemotherapy which did not contain pemetrexed, there was likely to be a similar number of patients eligible for 'switch maintenance' therapy". I would strongly dispute this point and would suggest that the original estimate of 535 patients is closer to a correct estimate of potential patient numbers.

b) 2nd Line treatment. Making calculations from the LUCADA database is welcomed, as this is the most accurate reflection of UK practice, however in making an estimate of numbers of patients potentially suitable for second line pemetrexed treatment, there is no reference to this valuable resource having been used by the committee (section 4.24, page 28). Instead there is a rough calculation which suggests that if a third of PS 2 patients get 1st line treatment, then this number is approximately 1500 and then ALL of these 1500 patients are then suitable for 2nd line pemetrexed. This conflicts directly with the LUCADA database for 2011 which shows that there are 1762 PS 2 patients with stage IIIB/IV non-squamous NSCLC and, of these, 462 had 1st line chemotherapy. In UK practice 25% of PS 0-1 patients receive 2nd line chemotherapy (and in PS 2 patients this is probably closer to 5%). Even if 25% were taken as the proportion receiving 2nd line therapy, the number would be 115. At the committee meeting there was discussion that NICE has not approved the use of 2nd line pemetrexed for patients with NSCLC and so the actual numbers of patients receiving 2nd line treatment in the UK is close to zero.

In summary, it would appear that the total number of patients potentially eligible for any pemetrexed treatment that the committee came to was 8761, but my adjustments would reduce this to 6811. I would hope that in view of the above information, the question of whether pemetrexed is considered to fulfill the end of life criteria would be revisited.

Furthermore, I would like to take this opportunity to emphasise that pemetrexed maintenance treatment is of substantial benefit (3 months improvement in survival with maintained quality of life) to a selected small number of lung cancer patients for whom the outcome is so poor (median survival 9 months).

I hope that these comments are helpful in reaching a final decision.'

Yours sincerely