Health Technology Appraisal:
Pemetrexed for the Treatment of Malignant Pleural Mesothelioma

Thank you for your letter of 23 March inviting me to comment on the Appraisal Consultation Document.

It is not mentioned that the evidence for efficacy of pemetrexed is considerably strengthened by similar results in the EORTC trial of raltitrexed, a similar drug. In my view it would be appropriate to make it clearer that the evidence for efficacy of pemetrexed is reasonably good and that it is not being recommended for treatment of NHS mesothelioma patients purely on cost grounds.

In considering costs, it is not clear that adequate account has been taken of the likelihood that patients in whom pemetrexed is ineffective, as judged by lack of radiological evidence of tumour response and or lack of clinical benefit, would receive fewer than the hypothesised average of five cycles of therapy, in many cases only two. It is likely that less than half the patients would continue to five or six cycles and these would be the patients who benefited most from it.

At paragraph 7.2 it is suggested that pemetrexed be used only in clinical trials that compare it with other treatments. At paragraph 4.3.8 and 5.2 it is suggested that future studies should compare pemetrexed with MVP and vinorelbine. Neither regime has yet been shown to increase survival compared with supportive care. If the current BTS MSO-1 study were to demonstrate that either or both regimes does so the median survival advantage is likely to be small, of a similar order of magitude or less than that conferred by pemetrexed plus cisplatin. An equivalence study designed to demonstrate lack of meaningful difference between pemetrexed/cisplatin with a median survival advantage of three months and another regime with a similar or shorter median survival advantage would require an unrealistically large number of patients, probably much in excess of 1,000, and it would probably take several years to complete. It is unlikely that many investigators would consider such an exercise worthwhile. Even if they did, it is unlikely that such a study could be funded. If half the patients were randomised to pemetrexed which had not been approved by NICE, other than on the basis of a reference to it being used in clinical trials, it is likely that NHS funding bodies would be reluctant to meet the cost of the drug. The manufacturers of pemetrexed will not do so and it is unlikely that any grant giving body would wish to do so.

While it is reasonable to make an experimental treatment available only within a clinical trial, since it would not otherwise be available to any patients, it is open to question whether it is ethical to determine that standard treatment for a licensed indication shall be available only to NHS patients if they consent to enter a randomised trial. Pemetrexed has been demonstrated in a randomised trial to improve survival and it is licensed for the treatment of mesothelioma. There is no question that it is clinically appropriate treatment for patients who have their own resources. If the position were that

pemetrexed would be made available to NHS patients only if they consented to be randomised in a clinical trial this might be construed by ethics committees as inappropriate coercion to enter a randomised trial.

Future studies likely to be of most interest to investigators and patients are those which will seek to find treatment which will improve survival to a greater extent than does pemetrexed plus platinum. For this purpose trial designs are likely to randomise between what is now regarded in other countries as standard therapy, ie pemetrexed plus platinum, and the same regime plus one or more additional agents, either chemotherapeutic agents or biological agents. If pemetrexed is not approved it is unlikely that any such trials would be possible in the UK because NHS funding bodies are likely to be reluctant to pay for the pemetrexed that would be required in both arms. Hence, far from facilitating future research in treatment of mesothelioma the proposed NICE guidance is likely to hinder it.

Dr R M Rudd