To: Sarah Cumbers **Date: 23 February 2005-02-23**

Herewith our expert's comments on the "Technology assessment report commissioned by the HTA programme on behalf of NICE"

The use of irinotecan, oxaliplatin and Raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (review of Guidance No. 33).

In submitting these comments, I wish to draw attention to certain potential conflicts of interest, outlined in a seperate document, provided to NHS Quality Improvement Scotland.

This document reviews the use of irinotecan and oxaliplatin as first line therapy in combination with 5-FU based therapy and the use of raltitrexed, where 5-FU is not tolerated or inappropriate.

It does not consider the use of oral fluoropyrimidine therapies and it will be important for the NICE Appraisals Committee to consider whether any guidance given allows the combination of irinotecan and oxaliplatin with **any** established fluoropyrimidine agents/regimens.

It does not consider the impact of the increasing use of combination chemotherapy as adjuvant therapy. For many of the studies quoted, this would have been an exclusion criterion.

In relation to raltitrexed, it only considers comparisons with 5-FU and there are no direct comparisons with best supportive care in patients where 5-FU is not tolerated or inappropriate (the most relevant comparison). Indeed, the previous guidance and this review make no comment as to the use of raltitrexed in patients with ischaemic heart disease or those developing cardiac type chest pain whilst receiving 5-FU. This is possibly one of the more common uses of raltitrexed in the U.K.

The document presents estimates of cost-effectiveness and comments on the unreliability of many of these estimates. This clearly makes it difficult to truly gauge the appropriateness of the introduction of these treatments, in comparison to other interventions. This issue should be discussed further … one point I noted is that the cost of irinotecan in one study was approx. £8600 and £3452 in another … do the reviewers have a view as to the most appropriate, as clearly it has a significant impact on the apparent cost-effectiveness? However, the data presented suggest that both oxaliplatin and irinotecan provide cost effective therapy for this disease.

The review I was provided with omits detailed data from the FOCUS trial, but the comment is made that the combination arms provide a significant advantage over the current NICE recommended, sequential fluoropyrimidine and single agent irinotecan. If true, this provides compelling evidence for the use of combination regimens. The review also states that use of combination regimens leads to median overall survival durations of 20 months, compared to a maximum of 16.2 months for sequential monotherapy. I am not sure that this was confirmed in the FOCUS trial.

However, the literature does seem to support prolongation of survival in patients receiving all 3 agents at some point in their disease "journey" and internationally this is becoming the standard of care. However, the issue of sequencing treatments is still unresolved. The data seem to suggest that combination of either oxaliplatin or irinotecan with a fluoropyrimidine as first line therapy results in similar efficacy, although toxicity profiles differ. Febrile neutropenia, the major life threatening toxicity, appears more common with irinotecan combinations, but oxaliplatin is associated with neuropathy.

In the UK, the NICE recommended 2nd line therapy is irinotecan monotherapy. I am unaware of data relating to its use following oxaliplatin containing combination therapy, although data are available for its use in combination with irinotecan in this setting, which show a low response rate. Although there are pre-clinical data suggesting synergy when irinotecan is combined with 5-FU, the question of combination versus single agent as second line therapy has not been addressed, to my knowledge. The use of the combination in 2nd line does reduce the dose-intensity of the administered irinotecan by about 30% and also adds considerably to the cost and complexity of the regimen, if it is combined with bolus/infusional 5-FU. Therefore, I feel that the current recommendation for 2nd line treatment is still "tenable", unless data can be provided to show an advantage for combination treatment

There has been at least one study that has assessed the value of adding oxaliplatin to a fluoropyrimidine with single agent irinotecan as "programmed" second line therapy. This is the LIFE (Longevity Improvement with Front Line Eloxatin) study, sponsored by Sanofi. Preliminary data were presented at ASCO in 2003, but I am unsure whether efficacy data have been published.

In summary, on the basis of the review provided to me (although lacking some of the more confidential data) and my personal opinions:

- Oxaliplatin, irinotecan and appropriate fluoropyrimidine therapies should all be available to patients treated within the NHS. The sequencing of these agents will depend on individual patient preference and fitness (combination therapy and/or second line therapy will not be appropriate for all patients) and also previous therapy, particularly in patients relapsing shortly after adjuvant treatment.

- Raltitrexed should be available for use in patients with advanced disease where the use of 5-FU is not tolerated or inappropriate.

I would also urge NICE to consider reviewing:

- The use of oxaliplatin and irinotecan as adjuvant therapy.

- The role of antibody therapies such as bevacizumab and cetuximab, both of which are now licenced in this disease, and are associated with major cost implications.

Duncan Jodrell