COMMENT BY NHS QIS NOMINATED EXPERT ON ASSESSMENT REPORT FOR APPRAISAL: Oxaliplatin and Capecitabine for the adjuvant treatment of colorectal cancer.

This is a very substantial piece of work but, in essence, is based upon extrapolation from only three clinical trials. There is no study available (and we could ask why?) addressing the key issue. The trial we need to answer this question would randomise as follows: Capecitabine alone vs Capecitabine+Oxaliplatin vs Degramont alone (LV5FU2) vs deGramont+Oxaliplatin (FOLFOX4). It would include prospectively obtained data on QOL both in the short term and in the long term.

I now list the problems I have with the data:

We no longer base decisions about adjuvant treatment on Dukes B vs C (Stage II vs Stage III) we take T stage and other pathological factors into account. There are identifiable patients with Dukes B tumours whose survival is lower that definable subgroups within Dukes C (see O'Connell et al JNCI 96; 1420 2004)

The Mosaic study was published on the basis of the data provided to the authors by the pharmaceutical company – it appears that the authors may not have had full access to the raw data.

The benefit of FOLFOX4 over LV5FU2 is confined to patients under the age of 65 (I attach the relevant graphic from the NEJM paper on Mosaic), a minority of patients in Scotland. Only 28% of patients with resected Stage III colorectal cancer in our region are under the age of 65, 37% are over 75.

The X-ACT study uses a control arm that we would regard as ineffective and toxic.

The hazards of adjuvant chemotherapy using Oxaliplatin and/or Capecitabine have not been adequately explored in a population with the degree of co-morbidity that exists in Scotland. The lower temperatures here might also be relevant with respect to the cold-induced neuropathy associated with Oxaliplatin.

I have problems with the economic analysis. The majority of patients with colorectal cancer are over 70 years old. They do not enjoy the prospect of a "50 year time horizon". I share the authors concerns that they may be over-estimating the economic benefits of more intensive treatment. If costs, both in terms of money and toxicity, are immediate, and if benefits are deferred by 5 to 10 years then this may, in an elderly population, be no bargain.

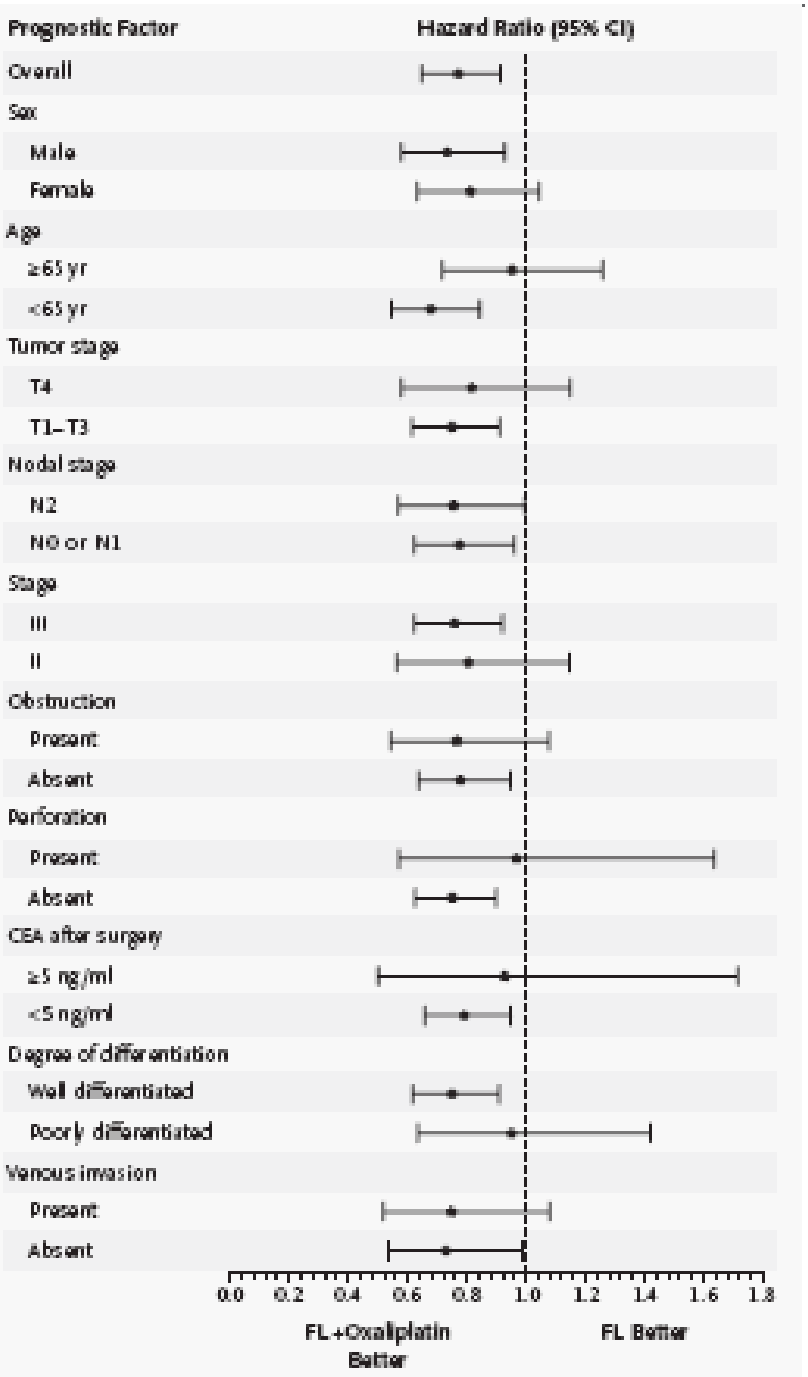

Figure 3. Hazard Ratios and 95 Percent Confidence Intervals for Recurrence in the Group Given Fluorouracil and Leucovorin (FL) plus Oxaliplatin, as Compared with the FL Group, According to Baseline Prognostic Factors and the Intention to Treat.

CEA denotes carcinoembryonic antigen.