21st September, 2005

Ms. Cathryn Fuller
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
Mid City Place
71 High Holborn
London WC1V 6NA

Dear Cathryn,

The Clinical and Cost Effectiveness of oxaliplatin (Eloxatin®) in combination with 5-fluorouracil/leucovorin (5-FU/LV), and capecitabine (Xeloda®) monotherapy, as adjuvant therapies in the treatment of patients with completely resected stage III (Dukes' C) colon cancer.

We would like to thank you for providing us with the Assessment Report for this appraisal Overall, we welcome the conclusions of this report, which we believe to be a balanced and fair reflection of the evidence available. We would also like to make some additional and more specific comments as detailed below.

Clinical Effectiveness

- *Potential for cure.*

It is accepted that all patients with Stage III colon cancer will undergo surgical resection of the colon with a curative intent. Despite this, it is also accepted that as many as 60% of these patients will relapse with a recurrence of their disease. The aim of adjuvant chemotherapy is therefore, to eliminate as far as possible, any residual occult micro-metastases that may still be present after surgery, and to decrease the incidence of recurrence. This ultimately increases the potential for cure and long-term survival in these patients.

It is imperative to highlight this primary objective of any adjuvant treatment which is to use the most effective treatment to gain the maximum possible chance of cure. This objective remains the highest priority for both patients and clinicians who expect and plan for such curative treatment.

Based on the evidence submitted, oxaliplatin (in combination with 5FU/LV) remains the only chemotherapy treatment to have consistently demonstrated a significant reduction in the risk of relapse or death and a significant improvement in disease-free survival at four years when compared to a widely accepted standard treatment of 5FU/LV alone. Therefore, current evidence strongly favours the combination of oxaliplatin plus intravenous 5FU/LV as the optimal adjuvant therapy to deliver the maximum potential for cure[1].

- *Disease-free survival and overall survival.*

The Assessment Report discusses the relevance of the primary end-point of disease-free survival (DFS) and the extrapolated trend for overall survival in relation to the data for capecitabine. It is important to also highlight a similar but stronger trend (demonstrated in the MOSAIC study) for oxaliplatin in delivering a long-term overall survival benefit for patients.

The importance of DFS as an appropriate (and perhaps the best) surrogate marker for long-term survival and /or cure, and the correlation observed between incremental improvements in DFS and overall survival benefits is widely accepted amongst the oncology community.

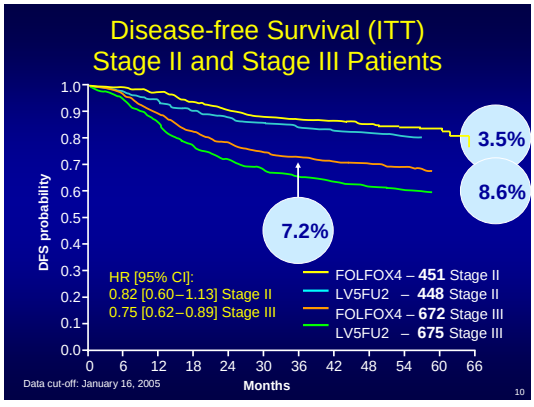
In the MOSAIC study, this link between DFS and survival benefit was clearly demonstrated as summarised in the tables and survival curves shown below.

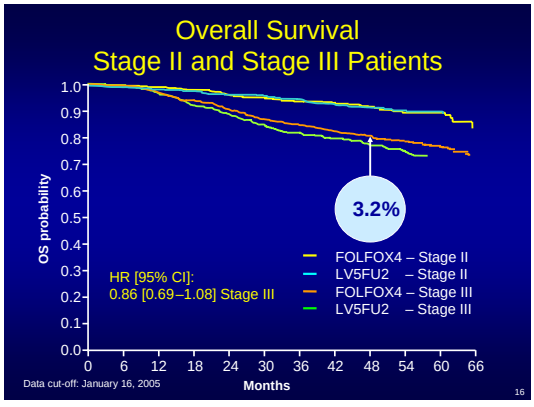
Disease-free survival (ITT)

Update	Median follow-up	FOLFOX4	LV5FU2	Absolute difference
April 2003[2]	37.9months	78.2%	72.9%	**5.3%**
June 2004[3]	48.6 months	75.9%	69.1%	**6.8%**
January 2005[3]	56.2 months	76.4%	69.8%	**6.6%**

Overall survival for Stage III patients (ITT)

Update	Median follow-up	FOLFOX4	LV5FU2	Absolute difference
April 2003[2]	37.9months	84.0%	81.9%	**2.1%**
June 2004[3]	48.6 months	79.2%	76.6%	**2.6%**
January 2005[3]	56.2 months	80.2%	77.0%	**3.2%**





- *Benefits in the elderly*

The Assessment Report states that the median age of diagnosis is over 70 years of age for colon and rectal cancer and that colorectal cancer is a significant cause of premature death,

with almost half of all related deaths occurring in people under 75 years of age. Furthermore, the report states that the mean age of patients used in the clinical studies was considerably lower than that observed in clinical practice. The Report concludes that the benefits may therefore potentially be overestimated in the cost effectiveness analysis for both products (oxaliplatin and capecitabine).

Although the differences in the mean age between the trial population and clinical practice may exist, there is reassuring evidence available from clinical trials in a number of different tumours (not just limited to colon cancers), which indicate that age in itself is not (and should not be) considered a prognostic factor for treatment benefits or survival outcomes[4,5.] Despite the fact that older patients are generally less likely to be referred and/or treated with chemotherapy (for example, due to other co-morbidities), there may be patients for whom adjuvant therapy would be appropriate and for these patients, the relative gain in clinical benefits, in particular the potential for cure, is likely to be similar to the younger patient population. Therefore in general, the benefits of treatment of elderly patients who are eligible for chemotherapy should not be underestimated nor discouraged.

- *Safety - neurotoxicity*.

The report emphasises the main safety concern of oxaliplatin which is neurological impairment. It states the 'all grade' neurotoxicity of >85%, and grade 3 neurotoxicity of >8%, and that although this does appear to improve within a one year time frame for the majority of patients, the report states that approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment.

Although this information is factually correct, we believe that the report needs to further differentiate between the various grades of neuropathy involved in order to provide a more balanced perspective and to avoid misinterpretation of the severity and incidence of these side effects.

As clearly indicated in the table below, the fact that the vast majority of the neurosensory symptoms that developed either during treatment or at follow-up, were either Grade 0 or 1, needs also to be put into context when describing the incidence and severity at various stages of follow-up. For example, at 18 months follow-up, almost 96 % of the incidences were grade 0 or1, and only a very small minority (0.5%) had grade 3 neuropathy at this stage.

Incidence of neurosensory symptoms (%)

Grade	During treatment	6 month follow-up	12 month follow-up	18 month follow-up
0	7.9	59.0	70.5	**76.3**
1	48.2	31.9	23.6	**19.8**
2	31.6	7.8	4.8	**3.4**
3	12.4	1.3	1.1	0.5

Cost-Effectiveness

We interpret the Assessment Report conclusion as both oxaliplatin (in combination with 5FU/LV) and capecitabine monotherapy are likely to be cost effective for routine use within the NHS and we support this conclusion.

We also note that the Assessment Group include estimates of relative cost-effectiveness for oxaliplatin and capecitabine. While we understand that such a comparison is of interest (and indeed NICE directed the Assessment Group to make this comparison), we assert and agree with the conclusions of the Assessment Group that insufficient data are available to make any conclusions derived from this comparison robust. The results generated are, therefore, of experimental interest only and are not sufficient to form the basis of guidance to the NHS.

We therefore suggest that it is inappropriate to refer to these results in the Executive Summary of the report. However, of more importance, we rely on the Assessment Group to ensure that in presentation of their analyses to the Appraisal Committee; the analyses are appropriately downgraded compared to the main health economic conclusions in the report.

We also note that the Assessment Group have not included any assessment of the cost effectiveness of treatment for Duke's stage B patients within the report. While Duke's stage B is outside the scope of this appraisal the Institute at the scoping stage did direct the assessment group to consider Duke's stage B if the data allowed. An assessment of cost effectiveness for this patient group could have added further clarity to the overall consideration of adjuvant treatment for colon cancer in the NHS.

- *The sanofi-aventis economic model.*

The Assessment Report finds the general methodology of the sanofi-aventis economic model to be sound, however the Assessment Group note that the extrapolation technique used may overestimate disease-free survival. While the sanofi-aventis methodology for this aspect of the model differs to the approach adopted by the assessment group, the final results of the cost-effectiveness analysis are similar and we feel that this methodological discussion is more a matter of interest than a matter of concern.

As a point of clarification, the assessment report noted that the paired bootstrap sensitivity analysis conducted by sanofi-aventis was conducted on a random sample of 1000 patients with replacement from the trial. We did use a random sample of 1000 patients however the analysis was also run 1000 times, therefore the sensitivity analysis conducted was much more rigorous than reflected in the assessment report.

- *The independent economic model.*

We are unable to offer specific comment on the independent economic model as we are not able to view the model developed by the Assessment Group. However we are pleased to note that the results of this model are similar to those from our own submission.

Comments to the Appraisal Committee on the interpretation of the Assessment Report.

In the Institute's recommendations that are published following this appraisal, we strongly encourage the Institute to provide clinicians and patients with guidance that reflects the superiority of oxaliplatin-based treatment as demonstrated in two large randomised trials

favouring oxaliplatin plus 5FU/LV (FOLFOX4), over the commonly used and established 5FU regimens, irrespective of its infusion or bolus delivery mode. This demonstration of the significant additional benefit associated with the addition of oxaliplatin to a 5FU regimen in terms of both disease-free survival and the potential for cure, provides a very strong rationale for recommending oxaliplatin (FOLFOX4), as the first-choice treatment option for those eligible to receive chemotherapy. This is the most effective chemotherapy option for maximizing the chances of a complete cure.

We acknowledge that there still remains significant geographical variation in the choice of 5-FU regimens currently in use in the UK. It is accepted that no significant survival difference has yet been proven between the oral drug (capecitabine) and the bolus Mayo regimen. In addition no evidence of a survival difference has yet been proven between the bolus Mayo regimen and the infusional 5FU/LV regimens. However, the infusional 5-FU/LV therapy has shown improved progression-free survival and a significantly better adverse event profile compared to bolus 5-FU/LV, and these points need to be taken into consideration in choosing the most appropriate 5FU regimen.

In conclusion, the choice of which 5FU regimen to use should be viewed as a secondary consideration to the first-choice treatment with oxaliplatin. We believe that patients and clinicians would greatly value the freedom to choose whichever regimen of 5FU to combine with oxaliplatin that best suits the needs and circumstances of the patient. This tailored choice, depending on individual circumstances, would be highly encouraged and supported by oncologists and patient groups alike.

Yours sincerely

Mike Baldwin
Head of Health Technology Appraisals

Tel no
office 01483 554180
mobile 07831 341586

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