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sanofi aventis
Because health matters

NICE
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Re: Addendum to sponsor submission to NICE - Eloxatin® for the treatment of colorectal cancer (adjuvant), submitted 29th April 2005

Dear Ms Marschke,

The sanofi-aventis submission for the Health Technology Appraisal, *Oxaliplatin and capecitabine for the treatment of colorectal cancer (adjuvant)* was sent to the Institute on 29th April 2005.

We would like to communicate the availability of newly published data which has a bearing on our submission and will help the Appraisal Committee in their decision making process.

At the *2005 ASCO Annual Meeting,* in Orlando, USA (13th - 17th May 2005), investigators, led by Professor Norman Wolmark, presented the results of a large and very recently concluded study, NSABP-C07. The results of this trial further substantiate the clinical effectiveness of the addition of oxaliplatin to weekly 5-FU/FA in the adjuvant treatment of colorectal cancer already demonstrated in the MOSAIC trial. The importance of this new study is that the randomised patients received their adjuvant treatment via bolus, a regime that is also commonly used throughout England and Wales, rather than through infusion as in the MOSAIC study.

Please find enclosed an addendum to our submission with an executive summary and details of these new data.

Yours sincerely,

Mike Baldwin
Head of Health Technology Appraisals

Eloxatin® (oxaliplatin) for the adjuvant treatment of colon cancer.

Addendum to submission to NICE

sanofi-aventis

June 2005

Executive summary

- A recently reported, large American study, NSABP Protocol C-07, presented at the 2005 May ASCO Meeting, further substantiates the results from the MOSAIC trial. The study shows a significant disease free survival benefit from the combination of oxaliplatin/5-FU/FA over 5-FU/FA alone, both administered by intravenous bolus.
- The new evidence from NSABP C-07 supports our cost effectiveness analysis summarised in this addendum that the ICER for oxaliplatin plus either a bolus or an infusional 5-FU/FA regimen is similar (at £6,244 and £4,805 respectively).

Introduction

The sanofi-aventis submission to NICE detailing the clinical effectiveness of Eloxatin (oxaliplatin) in combination with 5-FU/FA for the adjuvant treatment of patients who have undergone complete surgical resection for stage II and III colon cancer was submitted on 29th April 2005. The submission was largely based on the MOSAIC study; and the results clearly showed the statistically significant disease free survival (DFS) benefit for oxaliplatin/5-FU/FA over the standard 5-FU/FA therapy.

The recent study, NSABP Protocol C-07, presented at 41st annual meeting of the American Society of Clinical Oncology (ASCO) 2005, adds new significant evidence to this submission. This new study substantiates the findings of the MOSAIC trial as both studies show an increase in DFS results from the addition of oxaliplatin, irrespective of the route of administration of 5FU. In this newly reported study, 5-FU is delivered as an intravenous bolus, which is one of the standard administration regimens in the UK.

Copy of the ASCO 2005 Abstract[1]

Study: a phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07

N. Wolmark, H. S. Wieand, J. P. Kuebler, L. Colangelo, R. E. Smith

Background: The primary aim of this two-arm randomized prospective study was to determine whether FULV + oxaliplatin (FLOX) would prolong 3-year disease-free survival (DFS) compared to FULV.

Methods: Between February 2000 and November 2002, 2,407 patients with follow-up (1207 and 1200 in the respective arms) with stage II (28.6%) or III carcinoma of the colon were randomized to receive either FULV (5-FU, 500 mg/m2 iv bolus weekly x 6; LV, 500 mg/m2 iv weekly x 6, each 8 week cycle x 3) or FLOX (same FULV regimen with oxaliplatin 85 mg/m2 iv administered on weeks 1, 3, and 5 of each 8 week cycle x 3). The primary end point was DFS. Events were defined as first recurrence, second primary cancer, or death.

Results: The median follow-up for patients who were still alive was 34 months. The hazard rate (FLOX vs. FULV) was 0.79 with 95% CI (0.67, 0.93), a 21% risk reduction in favor of FLOX. (See table below.) Grade 3 NCI-Sanofi neurosensory toxicity was noted in 8% of patients on FLOX and 1% of those receiving FULV. Hospitalization for diarrhea or dehydration associated with bowel wall thickening occurred in 56 patients on FLOX and 34 patients on FULV. There were 14 and 15 deaths while patients were on treatment for FULV and FLOX, respectively.

Conclusion: The addition of oxaliplatin to weekly FULV significantly improved 3-year DFS in patients with Stage II and III colon cancer.

	N	Events	3yr % DFS
FULV	1207	332	71.6
FLOX	1200	272	76.5

Note: The study is supported by Public Health Service grants U10-CA-12027 and U10-CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. N. Wolmark and J. P. Kuebler have served on advisory boards and have received honoraria from Sanofi-Synthelabo, Inc.

[1] www.asco.org

Cost Effectiveness Analysis

The submitted economic evaluation considered the cost-effectiveness of oxaliplatin in combination with an infusional 5-FU/FA regimen based on the MOSAIC trial. As part of the sensitivity analysis in this evaluation, we estimated the cost-effectiveness of oxaliplatin given in combination with a bolus 5-FU/FA regimen. The new supporting evidence from NSABP Protocol C-07 suggests that the clinical effectiveness of Eloxatin (oxaliplatin) in combination with 5-FU/FA in bolus or infusional form is equivalent. This new evidence adds weight to our conclusion that the ICER for bolus or infusional combinations is similar, as summarised below.

The cost of a bolus 5-FU/FA regimen was based on the Mayo regimen and was estimated from NHS reference costs as 5 day-cases of 'chemotherapy with a digestive system diagnosis' (HRG F98). Probabilities of starting cycles of bolus 5-FU/FA were obtained from the X-ACT trial[2] and the unit costs for drug acquisition are those shown in Table 1.

Table 1. Unit costs for study drug acquisition and administration

Item	Unit cost	Source
Oxaliplatin	£330 / 100 mg	BNF, 2004 (powder for reconstitution, 100 mg vial)
Fluorouracil	£64 / 5000 mg	BNF, 2004 (50 mg/ml, 100 ml vial)
Folinic acid	£90.98 / 350 mg	BNF, 2004 (10 mg/ml, 32 ml vial)
Day case for chemotherapy	£246.51	National Reference Costs 2003 (code F98)

The administration cost for the combination 'Mayo+oxaliplatin' was based on a cost of £1,479.06 per cycle and probabilities of starting each cycle estimated from the oxaliplatin arm of the MOSAIC trial. The total cost of treatment for combination therapy was estimated at £12,338 as shown in the Table 2:

Table 2. Estimation of the cost of adjuvant chemotherapy with the Mayo regimen in combination with oxaliplatin

Cycle	Probability starting cycle	cost admin	cost drug acquisition	cost oxaliplatin
1	100.00%	£1,479.06	94.15	
2	96.98%	£1,434.44	91.31	
3	92.01%	£1,360.82	86.63	
4	87.18%	£1,289.44	82.08	
5	82.05%	£1,213.59	77.25	
6	76.62%	£1,133.28	72.14	
Total		£7,910.63	£503.57	3923.4
Grand total				**£12,338**

[2] Scheithauer W, McKendrick J, Begbie S, Borner M, Burns WI, Burris HA *et al*. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. *Ann.Oncol* 2003;**14**:1735-43.

This compared to a treatment cost of £7,436 for the Mayo regimen (see Table 3).

Table 3. Estimation of the cost of adjuvant chemotherapy with the Mayo regimen

Cycle	Probability starting cycle	cost admin	cost drug acquisition
1	100.00%	£1,232.55	94.15
2	96.10%	£1,184.46	90.48
3	93.74%	£1,155.36	88.26
4	91.79%	£1,131.31	86.42
5	90.35%	£1,113.60	85.07
6	88.50%	£1,090.82	83.33
Total		£6,908.10	£527.71
Grand total			**£7,436**

Based on total treatment costs (including chemotherapy costs, follow-up, etc) as shown in Table 4 below, the predicted ICER for the Mayo plus oxaliplatin regimen compared with the Mayo regimen is £6,244 per QALY gained.

Table 4. Results of sensitivity analyses on cost of study chemotherapy

	FOLFOX4	LV5FU2	Difference
Mayo+oxaliplatin vs. oxaliplatin			
Costs	£19,072	£14,826	£4,246
QALYs	9.257	8.577	0.680
ICER	£6,244		
Base Case ICER	£4,805		

In our submission, it was assumed that the benefit of oxaliplatin would be equivalent whether in combination with the Mayo regimen or the de Gramont regimen. This assumption of equal benefit has been substantiated by the similar results achieved by the NSABP C-07 and MOSAIC trials.

The base case ICER from our economic evaluation (infusion comparison) was £4,805. Based on our assumptions of chemotherapy costs combined with the disease free survival benefit demonstrated with a bolus regimen in the NSABP C-07 study, the ICER for oxaliplatin and bolus 5-FU/FA regimen appears to be similar to the ICER for oxaliplatin and the infusional 5-FU/FA regimen.