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Date 10th April 2006
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Your letter
Your ref. Cetuximab Assessment Report

Dear Ms Marschke,

Health Technology Appraisal
Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

I am writing on behalf of Merck KGaA with comments regarding the technical content of the Assessment Report (AR) - commissioned by NICE and produced by the School of Health and Related Research (ScHARR) – towards the assessment of cetuximab (Erbitux®) in metastatic colorectal cancer.

Broadly, we find the Assessment Report (AR) to be a detailed and balanced appraisal of cetuximab. In this letter, we concentrate on aspects of the AR which require further discussion and analysis by the Appraisal Committee, in particular:

1. The specific decision problem under consideration (AR: Section 4)
2. The survival modelling approach adopted by ScHARR, with particular reference to the control arm (best supportive care) and the potential for bias and structural error within this model (AR: Section 6.2.2)
3. The health economic decision problem in salvage mCRC (AR Section 4)
4. External validity of the cetuximab/irinotecan clinical results (AR: Section 5.3.3.2)

1. The specific decision problem under consideration

The AR addresses the question of the clinical and cost effectiveness of cetuximab/irinotecan in comparison to oxaliplatin/5FU&FA or active/best supportive care; the literature search conducted by the AR authors makes the point that no randomised or non-randomised studies of cetuximab/irinotecan have yet addressed the decision problem head-to-head.

The limitation of conducting systematic technology assessments of products at an early stage of clinical development has been widely discussed in the literature, and was also the subject of discussion at the NICE scoping meeting for this appraisal, chaired by Prof.

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Barnett on June 17th 2005.[1] In common with a number of previous NICE technology appraisals, the AR for cetuximab was required to utilise the evidence base available given that i) head-to-head data for the decision problem is not available ii) the pivotal trial (BOND) was not designed or powered to assess overall survival as a primary endpoint iii) patients in the cetuximab monotherapy arm of BOND were permitted to cross-over into the cetuximab/irinotecan combination arm upon disease progression - therefore confounding survival estimates, and iv) that establishing clinical trials for 'end-stage' cancer with a 'gold standard' best supportive care arm (i.e. patients do *not* receive an active treatment) is ethically problematic and, practically, very difficult to achieve, as patients are unwilling to take the chance of entering a clinical trial in which they may be randomised to a trial arm without active treatment.

Interventions for oncology are often licensed upon compelling evidence of activity in an indication which addresses an unmet clinical need; however this can present a particular challenge for standard health technology assessment analysis. At the scoping stage of this appraisal we sought to highlight that, in the context of UK treatment pathways for the management of metastatic colorectal cancer (mCRC), cetuximab/irinotecan offers a new (third-line) treatment option to patients.

The recent re-review of NICE technology appraisal 31for oxaliplatin and irinotecan endorses the use of these agents as first-line and second-line treatments - sequentially where possible. Given this updated NICE guidance, it is unlikely that oxaliplatin will be a realistic third-line treatment option for clinicians, as patients would effectively be re-challenged with oxaliplatin having already progressed on this agent. The comparison of cetuximab/irinotecan vs. oxaliplatin/5FUFA is therefore of limited value.

Generally, the AR is not sensitive to the specific clinical context of mCRC in a salvage setting. For the small patient group eligible for treatment with cetuximab/irinotecan, it is problematic to mechanically compare the magnitude of clinical benefit (in terms of survival, tumour response, progression free survival or any health-related outcome) to health-related outcomes in earlier lines of treatment; positive health outcomes are clearly more difficult to obtain as treatment progresses. In the case of cetuximab/irinotecan, the majority of patients included in the pivotal BOND trial were heavily pre-treated with previous lines of chemotherapy, and were selected for EGFR-expression, an established indicator of poor prognosis.[2,3,4] The survival modelling approach adopted by ScHARR has not captured this, principally by confounding the model results through the use of an inappropriate comparator best supportive care arm (discussed below in more detail).

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[1] Schulpher M et al. Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty - When is their sufficient evidence? *Value in Health* 2005,8;4:433-446

[2] Giacomelli et al. Persistence of Epidermal Growth Factor Receptor and Interleukin 10 in Blood of Colorectal Cancer Patients after Surgery Identifies Patients with High Risk to Relapse. *Clinical Cancer Research*. Vol. 9, 2678-2682, July 2003.

[3] Hemming et al. Prognostic Markers of Colorectal Cancer: An Evaluation of DNA Content, Epidermal Growth Factor Receptor, and Ki-67. *Journal of Surgical Oncology* 51:147-152, 1992.

[4] Mayer et al. The Prognostic Significant of Proliferating Cell Nuclear Antigen, Epidermal Growth Factor Receptor, and mdr Gene Expression in Colorectal Cancer. *Cancer*, 71; 8:2454-2460

2. Review of the ScHARR survival model

2.1 Modelling active/best supportive care: The ScHARR survival model is founded upon three studies with an active/best supportive care arm (Cunningham et al, Barni et al, Rao et al). However, no adjustment has been made within the model to control the differences in prognostic factors found in the baseline characteristics of the patient groups between the active/best supportive care arm and the cetuximab/irinotecan arm of the model.

We have highlighted differences between the treatment groups **(Table 1)** which invalidate the survival estimates obtained for the active/best supportive care arm in the ScHARR model. This table demonstrates clearly that the baseline characteristics of the BSC population used are not directly comparable to the patients included in the BOND study.

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Table 1 Health outcomes in the active/best supportive care trials used by ScHARR

	BOND (mono)[5]	Barni et al.[6]	Rao[7]	Cunningham[8]
Patient numbers	111	50	133	90ǂ
Age, years	58	59	62	62
Line of previous chemotherapy	1 24% 2 37% ≥3 39%	1 100%	1 4.5% 2 52% 3 31% 4≥ 13%	1 58% 2 26%
Performance Status	KPS>60	Median 80	ECOG 0-2	WHO 0-2 0: 31% 1: 46% 2: 23%
EGFR expressing	Yes	No	No	No
Cross-over permissible	Yes (n=56)	No	No	No
1 line of chemotherapy	24%	100%	4,5%	58%*
2≥ lines of chemotherapy	37%	0%	52%	26%
3≥ lines of chemotherapy	39%	0%	44%	NR
Oxaliplatin	64%	0%	35%	NR
Irinotecan	100%	0%	73%	NR
Oxaliplatin + irinotecan	64%	0%	31%	NR
Median Overall Survival (months)	6.9m Chemotherapy + cross-over	9.0m (estimate) No chemotherapy	6.1m No chemotherapy	6.5m 31% received chemotherapy
One year survival (%)	35% (estimate)	12%	28.1%	14%
Partial Response (%)	11%	0%	0%	NR
Stable Disease (%)	22%	0%	13%	NR
Progressive Disease (%)	53%	100%	81%	NR
Not reported/evaluable	14%	NR	7%	NR

NR: Not reported
**Patients (Cunningham 1998) had received no more than 2-lines of prior 5FU.*
ǂ 63% of patients had documented progression on 5FU

Of the three options for the modelling of expected survival in the A/BSC arm of the economic evaluation, we believe each option is inferior to the modelling of A/BSC arm in the economic evaluation provided by Merck, due to lack of controlled evidence used and the inherent biases introduced. The methods employed by ScHARR compare the results of one arm of one trial (cetuximab/irinotecan) with another arm of other trials. By using this approach, the results for the A/BSC arm of the ScHARR model are probably more representative of the patient group these trials are evaluating (i.e. non EGFR-expressing 2nd-line patients) than they are of the A/BSC group. The differences (or lack of) observed between the treatment groups in the ScHARR model can not be attributed *only* to differences in the treatments received.

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[5] Cunningham *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New England Journal of Medicine 2004,* 351(4):337–45.

[6] Barni et al. A randomised study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. *Oncology,* 1995; 52 243-245

[7] Rao et al. Phase III Double-Blind Placebo-Controlled Study of Farnesyl Transferase Inhibitor R115777 in Patients With Refractory Advanced Colorectal Cancer. Journal of Clinical Oncology 2004; 22:3950-3957

[8] Cunningham et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet,* 1998; 352:1413-18 (the authors of the Assessment Report have referenced the Cunningham et al 1998 study from *Seminars in Oncology,* Vol. 26, No. 1, Suppl. 5 (February), 1999: 6-12. This secondary reference contains less data than the original publication. We have therefore reverted to the original reference, as above)

Evidence that the methods employed in the ScHARR model are flawed lies in results which are inconsistent with randomised controlled data. Within the ScHARR model, overall survival was estimated for the cetuximab/irinotecan, cetuximab monotherapy and ASC/BSC treatment groups **(Table 2).**

Table 2 Life years gained results from ScHARR cetuximab model

Treatment group	Life years gained	Reference
cetuximab/irinotecan - no stopping rule (ScHARR AUC method)	0.79	ScHARR cetuximab model (sheet: 2.1 BONDCetuxIrRegression; cell: T3)
cetuximab monotherapy (ScHARR AUC method)	0.73	ScHARR cetuximab model (sheet: 2.2 BONDBSCRegression; cell: T3)
ASC/BSC (Barni et al.)	0.77	ScHARR cetuximab model (sheet: 1.7 PublishedEmpiricalBSC; cell: L6)

The estimates from the model (above) suggest that BSC survival would be *superior* to cetuximab monotherapy (0.767 vs. 0.727 LYs). This implies that cetuximab monotherapy is, objectively, harmful to patients - a result which is clearly contradictory to all available evidence (see the AR literature search). The survival model submitted by Merck provides a more reliable estimate of the effectiveness of A/BSC because it attempts to control for the underlying characteristics of the patient population. This is achieved by applying relative statistics (the hazard ratio) to controlled data rather than comparing absolute results from different trials with different characteristics.

2.2 Modelling of cetuximab/irinotecan: The analysis of the survival data from the BOND trial was complicated by the lack of knowledge about survival rates beyond the largest complete follow up time. In the presence of right censored observations, the area under the curve estimate of mean survival time will underestimate the true mean, as the Kaplan-Meier curve does not reflect the event of interest for all subjects. As a consequence, an approach suggested by Gelber et al (1993) was used to impute survival times for the censored observations.

The methodology consists of fitting parametric survival models to the tails of the Kaplan-Meier survival curves and using the estimated models to impute survival times for the censored observations. In this analysis, the tail-end of the survival curves were approximated by a parametric curve as far back as the last point in time where the survival curves for the two treatments were observed to diverge.

The expected survival time for each censored observation is then estimated by adding the known follow up time for that observation to the predicted survival time from the parametric survival curve conditioning the individual's survival up to the censored time. The predicted value for each censored observation is calculated by generating a survival probability from a uniform distribution and calculating where this probability cuts the time axis of the tail distribution conditional on the censored time. In keeping with standard imputation methodology this process is repeated a number of times (here 10).

It is then possible to use the imputed times along with the known (uncensored times) to calculate the area under the curve estimate of mean survival time. Plotting a Kaplan Meier curve for all times (imputed and known) will lead to a curve that does not necessarily mimic the parametric curve used to predict the survival values as the parametric curve will, as with the original Kaplan-Meier curve, underestimate the mean survival time.

More generally, a critical error in the ScHARR model can be traced to the AR, where it notes:

'Owing to the lack of direct evidence concerning the potential survival benefit conferred by cetuximab therapy over active/best supportive care, some form of indirect comparison is necessary. Given that such comparisons are required, fewer assumptions would have been required by comparing health outcome for the cetuximab plus irinotecan treatment group against the observed survival benefits associated with active/best supportive care as reported by Cunningham et al (1998)'[9]

This statement leads to a one-dimensional design of the subsequent model. The AR notes that the Merck method of adjusting survival is 'dubious', but then fails to critically examine the ScHARR model that is proposed as a replacement. Not only is the validity of the A/BSC arm in the ScHARR survival model highly questionable methodologically, it significantly overestimates survival of patients receiving A/BSC in the third-line treatment setting. Whilst the AR states that fewer assumptions are required through the approach adopted by ScHARR, we would request that the Appraisal Committee pay particular attention to the validity of the approach adopted.

By design, median overall survival data does not reflect the exceptional survival benefit observed in certain patient groups. Given the difficulties of comparing different treatment options assimilated from different studies that included dissimilar patient populations, there is merit in examining the absolute benefit of cetuximab/irinotecan therapy demonstrated in the BOND study. The 8.6 months survival demonstrated in this group is impressive when applied to the salvage setting of mCRC; as does the 9.8m surivival recorded in a recent study of cetuximab/irinotecan in patients that had failed both oxaliplatin and irinotecan previoulsy.[10] Indeed, NICE have endorsed irinotecan (mOS 2.3m; HR 0.70) and oxaliplatin (mOS 1.1m; HR 0.84) as second-line treatment options despite a relatively modest improvement in survival recorded with these agents.[11]

Moreover, a recently published study of cetuximab/irinotecan following at least two lines of previous therapy (including oxaliplatin and irinotecan) confirmed the expected survival times demonstrated in BOND. study This study also confirmed, once more, the correlation between survival and skin rash

3. The health economic decision problem in salvage mCRC patients

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[9] NICE Assessment Report. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. February 2006. p.80

[10] Vicenzi et al. Cetuximab and irinotecan in a third-line setting in advanced colorectal cancer patients. A single course phase II trial. *BJC* 2006 94, 792-797.

[11] NICE TA93 Colorectal cancer (advanced) - irinotecan, oxaliplatin and raltitrexed (review) - Guidance. August 2005. p

The incremental cost per life-year gained for cetuximab/irinotecan is relatively high compared to other healthcare interventions - the payer perspective should also consider cetuximab/irinotecan in the context of a number of factors specific to the therapy, and patient population under consideration.

The Merck survival model has shown that cetuximab/irinotecan significantly improves patient life-expectancy (0.91 vs. 0.47 LYs). It has been proposed that the *proportion* of life-saved should be a consideration in decision making - over and above the absolute level of life-saved.[12]

Many disease types shorten life to a greater or lesser extent; if a expensive new treatment allows a terminal cancer patient to live three months longer, then it seems intuitively unfair that this should be ascribed the same low value-for-money rating (i.e. cost per-QALY threshold) as a treatment that gives three additional months of life to those with a non-life threatening disease. For patients with a poor prognosis, the absolute level of life-saved will likely be relatively low. The concept of ascribing higher cost-effectiveness thresholds to patients with lower life-expectancy is consistent with the 'rule of rescue', which applies greater value to therapies for patients with poor prognosis and few available alternatives and which are life-saving. Given that in the UK, cancer survival is an established national health priority (NHS Cancer Plan) it is reasonable to accept a higher threshold of cost-effectiveness for this patient group.

4. Applicability of results

The AR states that the BOND cohort included a population whose mean age was 5-10 years younger that the UK mCRC population. Whilst the average age of all patients with CRC may be around 70 years, the population who actually receive chemotherapy for their disease tends to be younger on average. Accompanying this letter we include the results of research conducted on behalf of Merck Pharmaceuticals. Audited records (n=2337) of patients receiving chemotherapy for mCRC from May 2004 to November 2005 shows that the median age of patients receiving any line of chemotherapy for metastatic colorectal cancer is 63. 1 - 64yrs (range <36yrs to >76yrs). The median age of patients receiving chemotherapy in the 3rd line setting is 58.7- 62.8yrs (range <36yrs to >76 yrs).

Yours sincerely,

Jeremy White
Health Technology Assessment Manager
Merck KGaA

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[12] Camidge et al. Prognosis without treatment as a modifier in health economic assessments *BMJ* 2005;330;1382-1384

Metastatic Colorectal Cancer
ERBITUX tracking study
UK report

Abridged report for NICE April 2006

MERCK KGaA

Contents

- Objectives
  - To monitor the demographics of patients with metastatic colorectal cancer treated with chemotherapy in UK.
  - To monitor the lines of chemotherapy received by these patients.
- Method
  - Data is collected from actual patient records in the UK (under absolute confidentiality according to market research guidelines)
- Metastatic Colorectal Cancer patients:
  - Total population
  - 1st line
  - 2nd line
  - 3rd line and more

Method

- Each physician provided his approx. 10 latest patient cases for metastatic colorectal cancer treated with chemotherapy.
- Three waves of research have been conducted
  - Wave 1 (May-June 2004): 77 oncologists, n=791 cases
  - Wave 2 (Dec 04-Jan 05): 77 oncologists , n=796 cases
  - Wave 3 (Oct-Nov 2005): 76 oncologists, n= 780 cases
- Wave 2: 42/77 (55%) physicians had participated in Wave 1
- Wave 3: 49/76 (65%) physicians had participated in Wave 2

Sample Description (cont'd)

- Regional breakdown (wave 3- typical of all waves)

Scotland & N.Ireland	7	9%
Northern & Yorkshire	10	13%
North West	5	7%
Trent & Anglia	8	11%
Eastern Region	12	16%
Southern Region	1	1%
Central Region	7	9%
W. Midlands	8	11%
S. West & Wales	7	9%
London	11	14%

- Hospital type:

Cancer centre	80	66%
Cancer unit	26	34%

Sample Description (cont'd)

- Doctor Grade: (wave 3 – typical of all waves)

• SPR	50	66%
• Consultant	20	26%
• Associate Specialist	3	4%
• Staff grade	3	4%

- Clinical Specialty :

• Medical oncologist	23	30%
• Clinical Oncologist / Radiotherapist	53	70%

Method

- These physicians work in 60 different hospitals that can be split in:
  - "small hospitals" : less than 280 MCRC patients treated per year
    = 45% of hospitals corresponding to 20% of patients
  - "medium hospitals" : more than 280 and up to 480 MCRC patients treated per year
    = 32% of hospitals corresponding to 31% of patients
  - "large hospitals" : more than 480 MCRC patients treated per year
    = 23% of hospitals corresponding to 49% of patients
- Since each physician gives the same number of patient cases, patient cases have been weighted according to the type of hospital in which the cases were collected, so that the sample of patient cases is similar to the general population of patients :
  - Small (weighting = 0.44),
  - Medium (weighting = 0.91)
  - Large (weighting = 2.41)

Metastatic Colorectal Cancer

Total population of patients treated with chemotherapy

Patient profile (1-8)

		Wave 1 (791 patients)	Wave 2 (796 patients)	Wave 3 (750 patients)
AGE	- 36	1%	-	1%
	36 to 45	4%	4%	4%
	46 to 55	15%	16%	12%
	56 to 65	34%	36%	35%
	66 to 75	34%	32%	34%
	76 and older	10%	10%	11%
	NA	2%	2%	1%
	MEAN	63,1	63,1	64
GENDER	MALE	61%	60%	59%
	FEMALE	39%	40%	41%
PATIENT TYPE	IN PATIENT	11%	10%	16%
	OUT PATIENT	89%	90%	84%
	NHS PATIENT	95%	96%	91%
	PRIVATE PATIENT	1%	1%	1%
	NA	4%	2%	8%

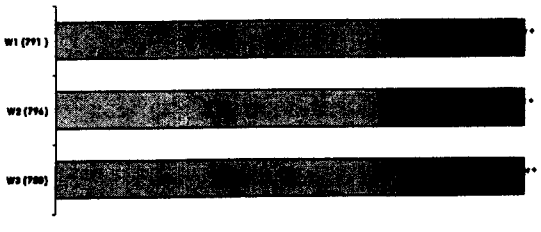
Patient profile (9-11)

		Wave 1 (791 patients)	Wave 2 (796 patients)	Wave 3 (750 patients)
DUKES STAGE AT TIME OF DIAGNOSIS OF CRC	A	7%	7%	6,4%
	B1	4%	4%	3,3%
	B2	14%	15%	15%
	C1	19%	20%	21%
	C2	17%	17%	14%
	D	40%	37%	39%
SITE OF CRC	COLON	60%	62%	74%
	RECTUM	36%	33%	25%
	NA	3%	5%	1%
PATIENT PERFORMANCE STATUS (ECOG)	0	37%	32%	38%
	1	53%	55%	57%
	2 or 3	9%	12%	5%
	NA	2%	-	-
PATIENT METASTATIC SITES	LIVER	64%	59%	68%
	LUNGS	21%	20%	20%
	LIVER&LUNGS	12%	12%	10%
	OTHER	14%	14%	10%
	BRAIN	1%	1%	1%
	BONE	4%	5%	4%
	OTHER (Spleen ; Ovary ; Kidney)	1%	4%	2%
HAS TUMOUR RESECTABLE AT DIAGNOSIS OF METASTASIS?	YES	15%	16%	21%
	NO	77%	67%	74%
	NA	4%	7%	5%

Metastatic Colorectal Cancer

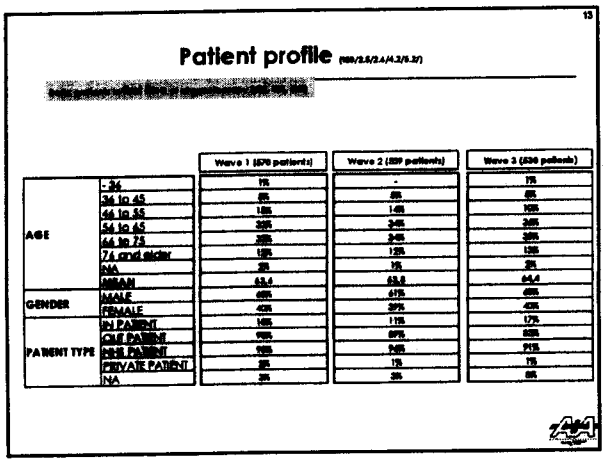
Lines of therapy

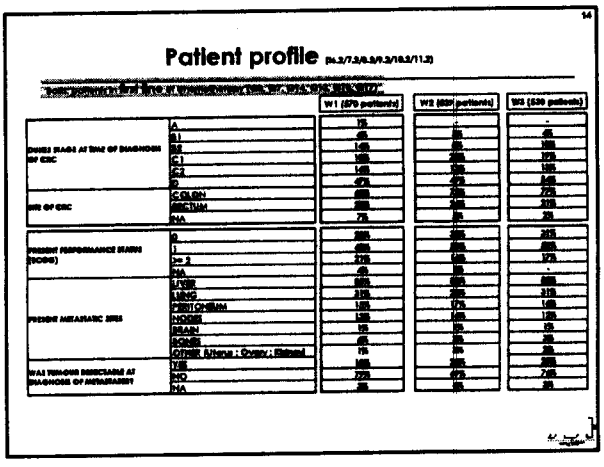
Current Line of therapy (10)



Metastatic Colorectal Cancer

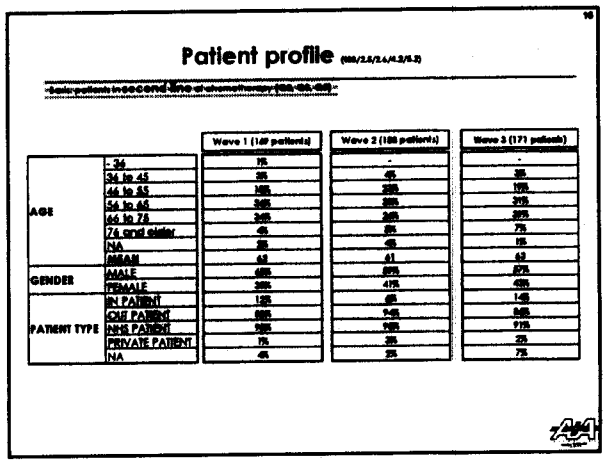
1st line

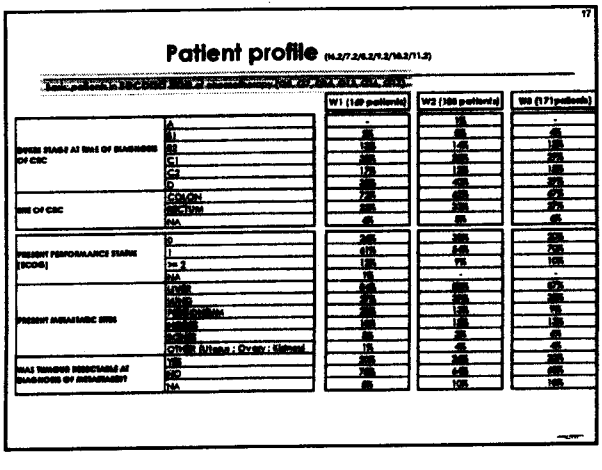




Metastatic Colorectal Cancer

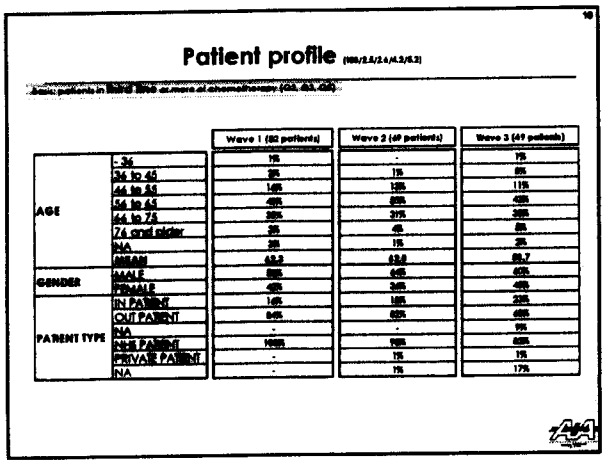
2nd line





Metastatic Colorectal Cancer

3rd line and more



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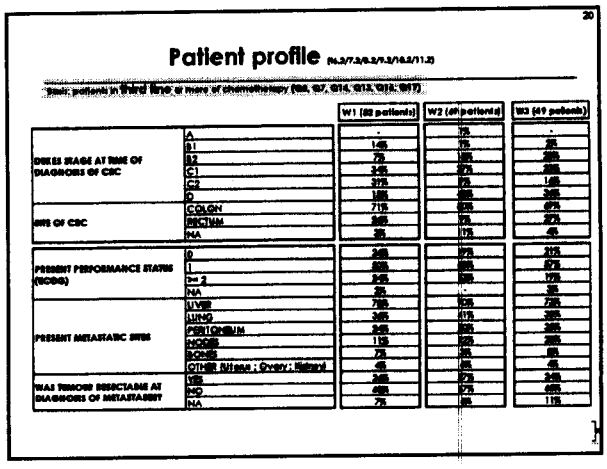
Patient profile (NN/2.5/2.6/4.3/5.2)

Basic: patients in third line or more of chemotherapy (G5, G6, G8)

		Wave 1 (82 patients)	Wave 2 (49 patients)	Wave 3 (49 patients)
AGE	- 36	1%	-	2%
	36 to 45	3%	1%	8%
	46 to 55	14%	18%	11%
	56 to 65	43%	55%	43%
	66 to 75	35%	31%	35%
	76 and older	5%	4%	2%
	NA	3%	1%	3%
	MEAN	62.2	62.8	59.7
GENDER	MALE	59%	64%	45%
	FEMALE	41%	36%	49%
PARENT TYPE	IN PATIENT	16%	18%	22%
	OUT PATIENT	84%	82%	69%
	NA	-	-	9%
	NHS PATIENT	100%	98%	88%
	PRIVATE PATIENT	-	1%	3%
	NA	-	1%	17%



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Patient profile (N.3/7.3/8.3/9.3/10.2/11.2)

Basic: patients in third line or more of chemotherapy (G6, G7, G10, G12, G13, G15, G17)

		W1 (82 patients)	W2 (49 patients)	W3 (49 patients)
DUKES STAGE AT TIME OF DIAGNOSIS OF CRC	A	-	2%	-
	B1	14%	9%	8%
	B2	7%	18%	28%
	C1	34%	27%	28%
	C2	37%	9%	14%
	D	10%	35%	20%
SITE OF CRC	COLON	71%	53%	69%
	RECTUM	26%	9%	27%
	NA	3%	12%	4%
PRESENT PERFORMANCE STATUS (ECOG)	0	24%	12%	31%
	1	50%	39%	57%
	>= 2	24%	39%	12%
	NA	2%	-	2%
PRESENT METASTATIC SITES	LIVER	78%	76%	73%
	LUNG	36%	41%	39%
	PERITONEUM	24%	20%	20%
	NODES	11%	10%	20%
	BONES	7%	2%	8%
	OTHER (Ulcer ; Ovary ; Retro)	4%	2%	4%
WAS TUMOR RESECTABLE AT DIAGNOSIS OF METASTASES?	YES	24%	12%	24%
	NO	69%	37%	69%
	NA	7%	8%	11%