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Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Cetuximab

Proprietary Product Name: Erbitux

Sponsor: Merck Serono Australia Pty Ltd

Date of CER: 20 September 2012

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Contents

List of abbreviations	4
Introduction	6
1.1. Regulatory history	6
1.2. Background	8
2. Contents of the clinical dossier	10
2.1. Scope of the clinical dossier	10
3. Pharmacokinetics	11
3.1. Study CA 225085	11
3.2. Conclusions regarding PK data	14
4. Pharmacodynamics	14
5. Clinical efficacy	14
5.1. Background	14
5.2. Main studies for current submission	15
5.3. Company sponsored studies: pivotal studies CRYSTAL and OPUS	16
5.4. Investigator sponsored trials: COIN study and NORDIC VII	19
5.5. Various other studies	28
5.6. Efficacy across studies	36
5.7. Conclusions regarding efficacy	41
6. Clinical safety	44
6.1. Background	44
6.2. Overview of studies providing safety data	45
6.3. Safety results – general comments	46
6.4. Patient exposure	46
6.5. Summary of safety from individual studies	47
6.6. Adverse reactions (drug-related adverse events)	51
6.7. Withdrawals due to adverse events	51
6.8. Deaths and other serious adverse events	51
6.9. Laboratory abnormalities	51
6.10. Post-marketing experience	51
6.11. Conclusions regarding safety	53
7. Conclusions regarding clinical data	53
8. Recommendation regarding authorisation	53
9. Clinical questions	54

List of abbreviations

Abbreviation	Meaning
ARF	Acute renal failure
BSC	Best supportive care
CCSI	Company Core Safety Information
CECOG	Central European Co-operative Oncology Group
CHMP	(European) Committee for Medicinal Products for Human Use
DIC	Disseminated intravascular coagulation
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FA	Folinic acid
FOLFIRI	Folinic acid + fluorouracil + irinotecan
FOLFOX	Continuous infusional folinic acid + fluorouracil + oxaliplatin
5-FU	5-fluorouracil
HACA	Human anti-cetuximab antibody
ICSR	Individual case safety reports
IRC	Independent Review Committee
ILD	Interstitial lung disease
K-RAS	Kirsten rat sarcoma
MASCC	Multinational Association of Supportive Care in Cancer
MCC	Metastatic colorectal cancer
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary of Drug Regulatory Affairs
MRC	Medical Research Council
NCIC CTG	National Institute of Canada Clinical Trials Group
NSCLC	Non-small cell lung cancer

Abbreviation	Meaning
ORR	Objective response rate
OxFp	Oxaliplatin + fluoropyrimidine
OxMdG	Infusional 5-FU combined with oxaliplatin
PD	Progression of the disease (PD)
PFS	Progression Free Survival
PPE	Palmar-plantar erythrodysesthesia
PS	Performance status
PMDA	Pharmaceutical & Medical Devices Agency (Japan)
RMP	Risk Management Plan
RPLS	Reversible posterior leukencephalopathy syndrome
SAKK	Swiss Group for Clinical Cancer Research
SCC	Squamous cell carcinoma
SCCHN	SCC of the head and neck
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SRN	Safety Related Notification

Introduction

Cetuximab is an antineoplastic agent, a chimaeric human/mouse monoclonal antibody of the IgG1 subclass, directed at the epidermal growth factor receptor (EGFR).

This is the clinical evaluation of a submission by Merck Serono Australia Pty Ltd to introduce changes to the Product Information of cetuximab (ERBITUX) injection solution; to justify restrictions of indication in mCRC and include PK data in the paediatric population.

The current indications are:

Erbix is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer

- *in combination with irinotecan-based chemotherapy or continuous infusional 5-fluorouracil/folinic acid plus oxaliplatin*
- *as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.*

Erbix is indicated for the treatment of patients with squamous cell cancer of the head and neck

- *in combination with radiation therapy for locally advanced disease*
- *in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.*

The initially approved 1st line broad indication for metastatic colorectal cancer (mCRC) has been restricted late last year by specifying the type of chemotherapy to be used in combination with cetuximab: "*in combination with ~~chemotherapy~~ irinotecan-based chemo-therapy or continuous infusional 5-fluorouracil/folinic acid plus oxaliplatin (see CLINICAL TRIALS)*" (Safety Related Notification to TGA: 1 September 2011).

Dose: Erbitux is administered once a week for all indications. The initial dose is 400 mg cetuximab per m² body surface area. The subsequent weekly doses are 250 mg/m² each.

Administration: Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic agents, and with close monitoring.

Erbitux 5 mg/mL is administered intravenously with an infusion pump, gravity drip, or a syringe pump. For the initial dose, the recommended infusion period is 120 minutes. For the subsequent weekly doses the recommended infusion period is 60 minutes.

1.1. Regulatory history

This section focuses on regulatory history of cetuximab in Australia. Current submission deals primarily with Erbitux use for patients with metastatic colorectal cancer.

Erbitux was first launched in December 2003 in Switzerland.

In Australia Erbitux was originally registered by the TGA for treatment of mCRC in January 2005, and subsequently for treatment of locally advanced head and neck cancer in combination with chemotherapy in January 2007.

The original indication for mCRC has subsequently undergone several modifications restricting cetuximab use to specific subgroup of patients, based on results of various retrospective subgroup analyses of the previously submitted studies.

One of the significant amendments to mCRC indications was the restriction of the population that derives benefit from treatment to K-RAS¹ wild-type patients only (January 2010). At the same time cetuximab use was extended to 1st line indication in mCRC “*in combination with chemotherapy*”. This broad indication was in place until the recent SRN.

These changes are summarized as follows: “previous CRC indication allowed combination with irinotecan in 2nd line treatment. This is being generalised to combination with chemotherapy and extended to 1st line. Previous 2nd line monotherapy after irinotecan is being reduced to 3rd line after irinotecan and oxaliplatin. Overall, the use of cetuximab is restricted to K-RAS-wild type disease.”

Changes to mCRC indications introduced via SRN in September 2011 are described above.

1.1.1. Status in other countries

The sponsor stated that the new data and information provided in this application have only been submitted in a similar format to the European Medicines Agency (EMA). This resulted in changes to the indications for cetuximab for mCRC by specifying the chemotherapy regimens to be used in combination with cetuximab (Erbix SmPC February 2012):

“Erbix is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer

- in combination with irinotecan-based chemotherapy, or*
- in first-line in combination with FOLFOX,*
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.”*

In Switzerland, the original indication for cetuximab in combination with chemotherapy in mCRC was already more specific, and no amendment was required.

In the US and Canada, the application to request a 1st line indication for use in patients with mCRC was under evaluation at the time of this submission.

In New Zealand, a similar process was followed as in Australia, with the changes to indications being introduced as a safety notification, in line with the changes made to the Australian PI.

The sponsor declared that an application for Erbitux in this indication has not been rejected, withdrawn, or repeatedly deferred in either the US or Canada.

On 6 July 2012, the FDA granted approval for cetuximab (Erbitux, ImClone LLC, a wholly owned subsidiary of Eli Lilly and Co) for use *in combination with FOLFIRI for 1st line treatment of patients with K-RAS mutation-negative (wild type), EGFR-expressing mCRC as determined by FDA-approved tests for this use.*

The approved test kit developed by Qiagen (Manchester, England) is a genetic assay; a real time polymerase chain reaction assay detecting 7 different mutations of the K-RAS gene in a tumour specimen.

US regulatory background: Cetuximab, marketed as Erbitux by ImClone, received accelerated approval by the FDA in 2004 to treat late-stage colorectal cancer in patients who had stopped responding to irinotecan-based chemotherapy.

¹ K-RAS is a central down-stream transducer of EGFR signalling. Signal transduction through the EGFR results in activation of wild-type (mutation-negative) K-RAS protein. The K-RAS gene can harbour oncogenic mutations that may result in tumour resistance to therapies that target the EGFR. K-RAS is one of the most frequently activated oncogenes in human cancers. In cells with activating K-RAS mutations, the mutant K-RAS protein is active independent of EGFR regulation. Approximately 40% of colorectal cancer cells express mutated version of K-RAS gene. The mutant K-RAS protein in these cells is thus constitutively activated and not inhibited by cetuximab.

In 2007, the FDA granted regular approval for cetuximab monotherapy “for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based chemotherapy regimens”.

The current FDA indications for Erbitux in mCRC read as follows:

“Erbitux is indicated for the treatment of K-RAS mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests for this use

- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,*
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,*
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.*

Limitations of use: Erbitux is not indicated for treatment of K-RAS mutation-positive colorectal cancer.”

Thus, in the US in mCRC, the cetuximab use as 3rd line monotherapy is approved as in Australia. However, for both 2nd and 1st line indications, the combinations with irinotecan are only approved. Cetuximab is specifically excluded in patients with codon 12 or 13 K-RAS mutations.

1.2. Background

The summary below outlines the outcome of studies already evaluated by the TGA for mCRC indications and shows the subsequent retrospective analyses that lead to further developments.

The initial approval for mCRC indications was based on 4 studies identified by the sponsor as pivotal; one study investigated cetuximab as a single agent (CA 225025), two studies investigated cetuximab in combination with irinotecan-based chemotherapy (EPIC, and CRYSTAL studies), and one in combination with oxaliplatin-based chemotherapy (OPUS study).

The subsequent changes to the mCRC indications were based on retrospective efficacy and safety analyses of these controlled studies in a subgroup of patients with wild-type K-RAS tumours.

- **NCIC study (CA225025)** cetuximab monotherapy (3rd line)

Addition of standard cetuximab dose to “best supportive care” (BSC) significantly increased PFS and OS (primary endpoint) by small amounts (0.1 months for PFS, and 1.5 months for OS).

The impact of K-RAS status was evaluated retrospectively in about a third of subjects in each treatment group.²

In the K-RAS-evaluable population, cetuximab significantly increased PFS, but not OS. The improvement was confined to the wild type K-RAS subgroup (59% of K-RAS evaluable subjects); median PFS increased from 1.9 months to 3.6 months.

- **EPIC study (CA225006)** cetuximab in combination with irinotecan (2nd line)

Addition of standard cetuximab dose to irinotecan monotherapy did not increase significantly OS (primary endpoint) but significantly increased PFS by a small amount (median 1.4 months). OS was confounded by treatment crossover on progression.

² Sponsor comment: This statement relates to the original study report. As already reflected in the approved Product Information, the impact of K-RAS status was evaluated retrospectively in 69% of patients in the NCIC study.

The impact of K-RAS status was retrospectively evaluated in about a quarter of patients in each treatment group. Unlike in the other trials, cetuximab did not significantly affect PFS or OS in the K-RAS evaluable population or in wild type K-RAS subjects (64% of K-RAS-evaluable subjects).

The 2 other company-sponsored studies that were pivotal in 1st line treatment of EGFR-expressing mCRC investigated cetuximab in combination with irinotecan or oxaliplatin.

- **CRYSTAL study (EMR 62 202-013)** cetuximab in combination with FOLFIRI [5-FU/FA + irinotecan] (1st line)

Addition of standard cetuximab dose to FOLFIRI increased median PFS in the overall population by a small amount (0.9 months) at marginal statistical significance.

The impact of K-RAS status was retrospectively evaluated in about a third of subjects in each treatment group.³

Cetuximab did not significantly affect the PFS in the K-RAS evaluable population; however, in patients with wild type K-RAS tumours (64% of K-RAS evaluable subjects); cetuximab increased PFS (primary endpoint) significantly by a small amount. The data for OS that supported this indication was submitted at the time of the Pre-ADEC phase (ie, after the evaluation phase).

Comment: The latest approval by the FDA of Erbitux combined with FOLFIRI regimen in 1st line treatment for mCRC was based on retrospective analyses according to K-RAS mutation status in tumour samples from patients enrolled in CRYSTAL trial. The retrospective analyses of the 2 supportive studies, CA225025 and OPUS, by tumour K-RAS mutation status, supported cetuximab efficacy in the wild-type subgroup.

- **OPUS study (EMR 62 202-047)** cetuximab in combination with FOLFOX4 [5-FU/FA + oxaliplatin] (1st line)

Addition of standard cetuximab dose to FOLFOX4 (continuous) regimen had no effect on PFS. The primary endpoint was ORR, and did not reach statistical significance in the overall study population.

The impact of K-RAS status was evaluated subsequently in 70% of patients in each treatment group.⁴ Cetuximab did not significantly affect the PFS in the K-RAS evaluable population; however, in patients with K-RAS wild-type tumours.

(57% of K-RAS evaluable subjects) cetuximab significantly increased PFS by a small amount (8.3 vs. 7.2 months), and significantly improved the ORR.

Results for OS were submitted at the time of the Pre-ADEC phase; there was a non-significant improvement for K-RAS wild type tumours.

The subsequent review of the data for mCRC indication generated by Merck Serono and by the independent investigators has provided the evidence of lack of efficacy when cetuximab is used in combination with chemotherapy regimens other than FOLFOX4 and irinotecan.

Review of the data was initiated by the European CHMP in September 2009 following the findings of a negative impact on PFS of a related product panitumumab (Vectibix) added-on to FOLFOX4 therapy in patients with mCRC tumours harbouring activating K-RAS mutations. This was similar to the earlier findings for cetuximab in OPUS study, also add-on to FOLFOX4.

³ Sponsor comment: This statement relates to the original study report. As already reflected in the approved Product Information, the impact of K-RAS status was evaluated retrospectively in 89% of patients in the CRYSTAL study.

⁴ Sponsor comment: This statement relates to the original study report. As already reflected in the approved Product Information, the impact of K-RAS status was evaluated retrospectively in 93% of patients in the OPUS study.

In the course of these assessments, data suggesting lack of efficacy of cetuximab were also reported in investigator sponsored studies involving cetuximab with oxaliplatin/fluoropyrimidine regimens:

- **COIN study** cetuximab in combination with oxaliplatin + fluoropyrimidines (OxFp)
- **NORDIC VII study** cetuximab in combination with the Nordic FLOX regimen (5-FU as a bolus/FA + oxaliplatin).

The investigations by the CHMP resulted in changes to Erbitux European SmPC, including more specific wording for the combination chemotherapy in mCRC indication, and an additional precautionary wording regarding use in patients with K-RAS mutated tumours (February 2012).

In Australia, it was agreed that a 2-step process would follow to implement the relevant changes to the PI:

1. Submit a SRN to make immediate changes to the wording of indication (1 September 2011).
2. Submit a Category 1 application with the supporting data reviewed by the CHMP, which led to the indication changes. This is the subject of the current application.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The sponsor submitted Category 1 application to justify changes to the PI of Erbitux (cetuximab) introduced as SRN for the mCRC indications, and added a new PK data for cetuximab in paediatric population.

The indications for 1st line treatment in mCRC have been narrowed (September 2011) by specifying the type of chemotherapy to be used in combination with cetuximab. The current submission mainly addresses this issue.

A statement describing a negative impact of cetuximab added on FOLFOX4 regimen in mCRC patients with K-RAS mutant tumours has been included for one study in *Clinical Trials* section of the PI.

Two statements have been added in relation to paediatric population; one in the *Pharmacology*, and another in the *Precautions* sections of the PI. These are the result of a company-sponsored Phase I, PK and safety study CA225085 of cetuximab in combination with irinotecan in paediatric population with solid tumours.

Changes to the precautionary statements regarding interstitial lung disease, and addition of a statement on the prevention of skin reactions are proposed for the *Precautions* section of the PI.

The sponsor re-organised the information in relation to AEs of the combination chemotherapy, in the *Adverse Effects* and *Interactions with Other Medicines* sections.

For the current review of the 1st line mCRC indication, the sponsor considered 4 studies; the previously evaluated 2 company sponsored clinical trials and the 2 new investigator sponsored studies.

- The pivotal studies for the 1st line mCRC indication remain those that were initially evaluated by the TGA; the Phase III CRYSTAL and the Phase II OPUS studies.
- The 2 other studies are the COIN and NORDIC VII trials that led to the investigation into the benefit/risk of combination therapy in patients with K-RAS wild type tumours.

A number of published papers “included in the assessment for this submission” also formed part of the dossier, as did articles representing some background reading (total 47 publications).

The 3 PSURs (No: 8, 9, & 10) not previously evaluated by the TGA, and covering the period from 01 October 2008 till 30 September 2011 have been submitted.

EMA SmPC for Erbitux served as a reference label document.

The submitted dossier consisted of 8 volumes of data: Module 1 and Module 2 (1 volume each), and 6 volumes of Module 5.

The Module 2 included the Clinical Overview, but did not contain the Clinical Summary.

Module 5 contained the updated clinical study reports of CRYSTAL and OPUS studies. The sponsor provided reassurance that the updated reports “do not contain any new efficacy information and the current PI already reports the results from later cut-off dates and subgroup analyses by K-RAS tumour status. There was no change to the safety profile of cetuximab in these studies after re-calculations based on the new cut-off dates.”

In summary, the dossier included various data from 3 sponsor-led trials; the CRYSTAL, OPUS studies and the paediatric PK Study CA225085.

The rest of the studies discussed in this application were investigator-sponsored trials for which no study reports were available. These trials were reported with varying degrees of detail; some resulted in published papers that were available in the dossier.

3. Pharmacokinetics

3.1. Study CA 225085

Title: “Phase I Study of Erbitux (Cetuximab) in Pediatric Subjects with Refractory Solid Tumors: Characterization of Serum Pharmacokinetics, Safety, and Efficacy of Cetuximab when Combined with Irinotecan.” (August 2005 - March 2008)

The study was the first evaluation of cetuximab in paediatric and adolescent populations and was conducted as a post-marketing commitment following FDA approval of cetuximab in combination with irinotecan in patients with mCRC.

3.1.1. Design

Phase I, open-label, multicenter (US), PK study involving cetuximab at multiple ascending doses in combination with irinotecan at a fixed dose.

Subjects aged 1-18 years with refractory solid tumours, including tumours of the CNS and non-Hodgkin’s lymphoma, were eligible to participate in the study. Two age groups (Group A: 1-12 years and Group B: 13-18 years) were chosen to be able to distinguish any differences in terms of safety and PKs, between paediatric and adolescent subjects.

3.1.2. Objectives

The primary objective was to establish the MTD and recommended Phase II dose for cetuximab in combination with irinotecan in the studied population.

Secondary objectives included: serum PKs of cetuximab, safety profile and DLT of the combination of cetuximab + irinotecan, preliminary evidence of anti-tumor activity of cetuximab + irinotecan in paediatric and adolescent subjects, and incidence of human anti-cetuximab antibody (HACA) formation in subjects receiving cetuximab.

PK evaluation was based on a single dose PK profile.

The sample size could not be precisely determined in this Phase I dose escalation trial as it also depended on the toxicities observed. It was estimated that approximately 60 subjects; 30 per age group, needed to enter the study.

A total of 46 subjects were treated: 27 in Group A, and 19 in Group B. The PK data set included 23 patients in Group A, and 12 in Group B.

3.1.3. Demographics

The study population consisted of heavily pre-treated paediatric and adolescent patients with advanced solid tumours. Subjects in both groups presented with a variety of tumour types; in Group A 63% had a CNS primary tumor and 37% had a non-CNS primary tumor. In Group B, the respective percentages were 47% and 53%.

The study population was nearly evenly distributed between males and females, with a median age of 8 years (range: 1-12) in Group A, and 16 years (range: 13-18) in Group B. The majority of treated subjects in each age group had PS of > 70-100. A total of 14 (52%) subjects in Group A and 11 (58%) subjects in Group B reported an EGFR-positive tumor.

3.1.4. Treatment

Cetuximab was dose escalated from 75 mg/m² up to 250 mg/m² IV weekly with no initial loading dose, while irinotecan was administered as a fixed dose with a planned starting dose of 20 mg/m² IV x 5 days x 2 weeks.

The studied cetuximab doses were: 75 mg/m², 150 mg/m², and 250 mg/m² as IV infusion over 60 minutes, administered weekly (Days 1, 8, and 15 of a 21 day cycle).

Prior to protocol amendment, irinotecan was administered IV at a dose of 20 mg/m²/day (or per dose escalation) as a 60 minute infusion for 5 days x 2 weeks (separated by 2 days off: Days 1-5 and 8-12), every 21 days. On Days 1 and 8 of each cycle, irinotecan was administered 60 minutes following the completion of the cetuximab infusion.

Following reports of irinotecan-related AEs (2/6 subjects in Group A), the protocol amendment decreased the irinotecan dose, while the dose of cetuximab continued to be escalated per the protocol. The irinotecan dose remained at 20 mg/m² for Group B.

All subjects in both groups were pre-treated with an antihistamine. Concomitant medication use was frequent and typical of subjects with advanced cancers. Palliative and supportive care for disease-related symptoms and for toxicity associated with study therapy was offered to all patients.

Subjects who were receiving antiepileptic medications (phenytoin, phenobarbital, primidone, carbamazepine, and valproic acid) were ineligible. Patients requiring use of gabapentin or levetiracetam were eligible. Subjects who require increasing doses of steroids are ineligible.

3.1.5. DLT (safety results)

A total of 5 subjects experienced AEs during the escalation stage that met the criteria for a DLT; 3 in Group A, and 2 in Group B.

In Group A, the MTD was reached at 16 mg/m² irinotecan IV x 5 days x 2 weeks and 250 mg/m² cetuximab IV weekly.

The DLTs observed in Group A (Grade 3 diarrhoea and Grade 4 neutropenia) occurred at the 2 lower dose levels of cetuximab (75 and 150 mg/m²) and were judged to be related to irinotecan, not to cetuximab. Therefore, the study protocol was amended to allow a dose reduction from the planned dose of 20 mg/m² irinotecan to 16 mg/m² IV x 5 days x 2 weeks. Further dose escalation of cetuximab from 150 mg/m² to 250 mg/m² was feasible and treatment of an additional 9 subjects at the MTD level in Group A was well tolerated without further occurrence of any DLTs.

The dose escalation of cetuximab up to 250 mg/m² IV weekly proved to be feasible in Group B.

The MTD in Group B was reached at 20 mg/m² irinotecan IV x 5 days x 2 weeks and cetuximab 250 mg/m² IV weekly with only 1 irinotecan associated DLT occurring at this dose level. Enrolment in Group B was negatively affected by various factors. Thus, supported by the PK data which suggested that there is no exposure difference between the 2 age groups, the decision was made to treat only a minimum of 6 subjects in Group B at the MTD level, but to forego further expansion of this cohort at the MTD level.

Although single agent irinotecan 20 mg/m² IV x 5 days x 2 weeks is considered to be a standard treatment regimen in paediatric patients, irinotecan doses in combination with cetuximab might have to be adjusted due to an increase in toxicities such as diarrhoea, as observed in adults treated with this combination. All subjects in this study were heavily pre-treated including multiple lines of therapies, potentially contributing to an increased susceptibility to the toxic side effects of irinotecan therapy alone.

Overall, the safety of cetuximab at the standard dose of 250 mg/m² with 16 or 20 mg/m² IV x 5 days x 2 weeks of irinotecan in paediatric and adolescent subjects was similar between the 2 age groups, and consistent with the profile of each of the individual drugs in adult subjects.

3.1.6. PK results

The single dose PK of cetuximab was evaluated based on concentration-time profile up to 168 hours after the start of the cetuximab infusion.

- The results indicate that the PK of cetuximab is nonlinear.
- Cetuximab CL/BSA decreased with increase in dose.
- V_{ss}/BSA was independent of dose.
- The 2 age groups appear to have common distributions within dose, and as such, appear to be comparable.

Results observed for the 13-18 year age group should be interpreted with caution due to the small number of subjects within this age group.

- The recommended Phase 2 dose for cetuximab is 250 mg/m² in combination with 16 or 20 mg/m² irinotecan IV x 5 days x 2 weeks, for both age groups.

PK results indicate that cetuximab clearance decreased from 0.06 to 0.02 L/h/m² in Group A and 0.04 to 0.02 L/h/m² in Group B as the dose increased from 75 to 150 mg/m², similar to the clearance observed in adult subjects (clearance of cetuximab decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m² in adult subjects with SCCHN and those with CRC). At doses > 200 mg/m², the clearance appeared to plateau.

The dose-dependent elimination of cetuximab can be explained by receptor-mediated clearance, where the receptors appeared to be saturated at higher doses. The mean half-life of 250 mg/m² was 110 hours (± 43 hours) and 82 hours (±20 hours) for Group A and Group B, respectively, which is comparable to that in adult subjects at the same dose level (range: 63 to 230 hours). However, the results should be interpreted with caution, since in this study the single-dose PK sampling was only up to 168 hours post-dose, which is shorter than 5 half-lives of cetuximab at this dose level.

Linear regression showed similar results for AUC_{INF}, CL and CL/BSA when the natural log of the parameters were regressed on the natural log of actual dose (mg) and the natural log of dose based on BSA (mg/m²). The estimated β was 1.85 for AUC_{INF}. Results for AUC_{INF} and CL/BSA vs. dose (mg/m²) are presented in the dossier.

Although AUC_{INF} increased greater than proportional to dose and CL/BSA decreased with increasing dose, the 2 age groups appear to have similar PK characteristics and common distributions within each dose.

3.1.7. Other results

A total of 42 subjects who received cetuximab had at least 1 time point analysed for HACA reactivity. Of these, 26 subjects were evaluable for anti-cetuximab antibody; 1 exhibited an anti-cetuximab antibody. This represents a 4% incidence rate, in line with what has been seen in the adult population.

No correlation between the detection of EGFR by immunohistochemical testing and tumor response was observed; however, the number of available samples for correlation was limited.

The combination of cetuximab and irinotecan showed encouraging anti-tumor efficacy in subjects with CNS and non-CNS tumors. Antitumour efficacy results are not discussed in this report.

3.2. Conclusions regarding PK data

The PK CA 225085 study evaluated cetuximab at multiple ascending doses in combination with irinotecan at a fixed dose in paediatric and adolescent patients (n = 46). Overall conclusions:

- Cetuximab in combination with irinotecan was safely administered in paediatric and adolescent subjects with solid tumours.
- The safety profile of the combination was similar between the 2 age groups, and consistent with the known safety profile of each of the individual drugs in adult subjects.
- The MTD for the combination of cetuximab and irinotecan was different between the 2 age groups. However, the recommended Phase II cetuximab dose for both age groups is 250 mg/m² together with irinotecan: 16 or 20 mg/m² IV x 5 days x 2 weeks.
- PK analysis indicated a similar cetuximab exposure profile between the 2 age groups and was comparable to that known for adults.

4. Pharmacodynamics

Samples were not collected for PD analyses in the PK study CA 225085. No other PD data were presented.

5. Clinical efficacy

5.1. Background

Treatment of mCRC has been changing considerably in recent years. Combinations of 5-FU/LV containing both bolus (Roswell Park) and infusional administration (De Gramont schedule) with second active drug, either irinotecan or oxaliplatin, have been accepted as the mainstay of 1st line treatment.

During the last years, the IFL regimen (weekly irinotecan and IV push administration of 5-FU or LV) no longer represents the gold standard of front line treatment of mCRC and was replaced by the combination of irinotecan or oxaliplatin with the infusional 5-FU regimens (FOLFIRI or FOLFOX, respectively).

To investigate the use of cetuximab as an add-on option to currently used chemotherapy regimens in mCRC various studies were analysed for this application. These studies are presented in Table 1.

Table 1. Overview of studies

Study	Indication	Study design	Regimen	Patients ITT/KRAS wt
Trials comparing cetuximab plus irinotecan and infusional 5-FU/FA with irinotecan and infusional 5 FU/FA alone				
EMR 62 202-013 (CRYSTAL)	1st line mCRC	Phase III 2-arm, controlled	cetuximab + FOLFIRI vs FOLFIRI	599/316
Trials comparing cetuximab plus oxaliplatin and infusional 5-FU/FA with oxaliplatin and infusional 5 FU/FA alone				
EMR 62 202-047 (OPUS)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFOX4 vs FOLFOX4	169/82
COIN (IST) OxMdG subgroup	1st line mCRC	Phase III 3-arm, controlled	cetuximab + OxMdG vs OxMdG	281/117
Trials comparing cetuximab plus oxaliplatin and infusional 5-FU/FA with cetuximab plus FOLFIRI				
CECOG CORE 1.2.001 (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFIRI vs cetuximab + FOLFOX6	77/34
CELIM (IST)	neoadjuvant, unresectable liver metastases	Phase II 2-arm, controlled	cetuximab + FOLFIRI vs cetuximab + FOLFOX6	53/NA

Study	Indication	Study design	Regimen	Patients ITT/KRAS wt
Further trials investigating cetuximab plus oxaliplatin and infusional 5-FU/FA				
CECOG CORE 1.2.002 (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab q1w + FOLFOX4 vs cetuximab q2w + FOLFOX4	152/152
EMR 200025-001 (FUTURE) FOLFOX4 arm	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFOX4	150/56
Studies using other oxaliplatin-based regimens				
SAKK (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + XELOX vs XELOX	37/NA
COIN (IST) XELOX subgroup	1st line mCRC	Phase III 3-arm, controlled	cetuximab + XELOX vs XELOX	543/245
EXPERT-C (IST)	neoadjuvant CT then CRT high-risk rectal cancer	Phase II 2-arm, controlled	cetuximab + CAPOX vs CAPOX	83/46
EMR 200025-001 (FUTURE), UFOX arm	1 st line mCRC	Phase II 2-arm, controlled	cetuximab + UFOX	152/40

IST = investigator sponsored trial, KRAS wt = KRAS wild type, mCRC = metastatic colorectal cancer, NA = not available, q1w = weekly, q2w = every 2 weeks

5.2. Main studies for current submission

The CRYSTAL and OPUS studies were previously evaluated by the TGA in the Category 1 application for cetuximab in mCRC indications (submission 2008-03405-3-4). Data on OS for these studies was provided. An addendum to the original version of the study reports has now been included in current submission.

The COIN study, that prompted the review of the benefit/risk profile of cetuximab in mCRC, is the main investigator-sponsored trial discussed in the submission.

The sponsor reviewed the available information from the NORDIC VII study (sponsored by Nordic Colorectal Cancer Biomodulation Group - NCCBG) in the context of 1st line mCRC indication for cetuximab. A brief summary has been included.

Due to the Nordic FLOX regimen used in the study not being registered for cetuximab, and to missing information and lack of final data, a meaningful and complete assessment of the outcome of this study was not deemed possible. The results from this study were, therefore, not considered by the sponsor in the analyses provided.

5.3. Company sponsored studies: pivotal studies CRYSTAL and OPUS

5.3.1. General comments

All patients in CRYSTAL and OPUS studies had previously untreated mCRC. The study designs and key eligibility and exclusion criteria have previously been described in detail.

The sponsor provided reassurance that all Merck-Serono-sponsored clinical trials were carried out in accordance with the Declaration of Helsinki, under Good Clinical Practice and with full ethics committee approval, and the patients provided written informed consents.

5.3.2. Subgroup (K-RAS) analyses

Analyses based on K-RAS status were not prospectively planned in the original protocols for these studies because, at the time of design, no conclusive evidence for potentially predictive biomarkers was available. These studies were subsequently examined for a correlation between K-RAS status and response to cetuximab.

Overall, tumour samples were evaluable for K-RAS analyses from 37% (1250/3369) of subjects in the safety population of the 4 RCTs conducted by sponsor (NCIC, EPIC, CRYSTAL, and OPUS); 62% (779/1250) had K-RAS wild type genes. The proportion of K-RAS wild type tumours ranged from 15% (NCIC study) to 40% (OPUS study). The overall rate was low 23% (779/3369).⁵

In assessing the efficacy results, both the overall patient population data and the K-RAS wild type population results were considered, as the former was the ITT population for these trials.

The OS data from these studies, available at the time of approval, supported the use of cetuximab in addition to chemotherapy in mCRC. The analysis of further tumour samples and subsequent updates to the PFS and ORR results added further weight to the benefits of adding cetuximab to existing chemotherapy regimens in the 1st line treatment of mCRC.

5.3.3. CRYSTAL (EMR 62 202-01) study update: cetuximab + irinotecan and infusional 5-FU/FA (FOLFIRI) vs. FOLFIRI alone

Title: "Open, randomized, controlled, multicenter phase III study comparing 5-FU/FA plus irinotecan plus cetuximab versus 5-FU/FA plus irinotecan as first-line treatment for epidermal growth factor receptor-expressing metastatic colorectal cancer." (August 2004-November 2005)

5.3.3.1. Design

This randomized (1: 1), controlled trial supported the indications of combination therapy with FOLFIRI in the 1st line treatment of wild type K-RAS mCRC patients, based on results of PFS

⁵ Sponsor comment: This information in this paragraph relates to data provided for the previous evaluation. Based on the updated information, the paragraph should read: *Overall, tumour samples were evaluable for K-RAS analyses from 61% (2072/3405) of subjects in the safety population of the 4 RCTs conducted by sponsor (NCIC, EPIC, CRYSTAL, and OPUS); 61% (1267/2072) had K-RAS wild-type genes. Based on the number of patients evaluable for K-RAS analyses, the proportion of K-RAS wild-type tumours ranged from 57% (OPUS study) to 64% (EPIC study), of evaluable patients.*

(primary endpoint). This indication was strengthened by the results of OS data (secondary endpoint).

- Population analysed: (ITT): cetuximab + FOLFIRI n = 599; FOLFIRI n = 599; total n = 1198
- Safety: cetuximab + FOLFIRI n = 600; FOLFIRI n = 602; total n = 1202

5.3.3.2. Study treatments

Modified FOLFIRI regimen (simplified de Gramont + irinotecan) given in 2 weekly cycles. Cetuximab was administered according to the standard regimen.

FOLFIRI was administered IV q. 2 weeks and included: irinotecan (180 mg/m² over 30-90 min on Day 1), FA (400 mg/m² racemic or 200 mg/m² L-form over 2 h on Day 1), and 5-FU (400 mg/m² bolus on Day 1 followed by a 46 h continuous infusion of 2400 mg/m²).

Treatment was continued until occurrence of PD or unacceptable toxicity.

5.3.3.3. Assessments

Tumour assessments were based on radiological scans every 8 weeks. Investigators and a blinded Independent Review Committee (IRC) assessed tumour response according to modified WHO criteria.

Retrospective K-RAS analyses: Of the 1198 patients in ITT population, 88.7% (1063/1198) were evaluable for K-RAS mutation status; of these 62.7% (666/1063) had K-RAS wild-type tumours.

Comments on statistics: All reported p values were 2-sided and were not adjusted for multiple testing. Secondary efficacy analyses were supportive, exploratory, and no confirmatory.

5.3.3.4. Results

In the wild type K-RAS subgroup, PFS was increased by statistically significant 1.5 months (p = 0.001). Of note is the Delegate's comment at the time "in view of marginal significance overall, this result needs confirmation" (ITT p = 0.047).

The updated OS data for K-RAS wild type population were presented at a later date: "The addition of cetuximab to FOLFIRI prolonged median OS time from 20.0 to 23.5 months (HR 0.796, p = 0.0094) compared with FOLFIRI alone."

The sponsor summarized this outcome: "For the first time in a randomized phase III study it has been shown that patients with K-RAS wild-type mCRC have a significantly improved OS when treated first-line with cetuximab plus FOLFIRI compared to FOLFIRI alone. Consistently, progression free survival (primary endpoint) and response rate were as well significantly increased in patients treated with cetuximab."

The PI contains the following statements: "This effect translated into an increase of median overall survival in the K-RAS wild type population of 3.5 months."

"Patients with K-RAS wild tumours and an ECOG performance status of > 2 or who were 65 years of age or older, had no benefit in overall survival time, when cetuximab was added to FOLFIRI."

The current dossier included Clinical Trial Report Addendum dated 27 April 2011; the updated OS data (based on cut-off dates of 31 May 2009) are consistent with those of November 2009.

5.3.4. OPUS (EMR 62 202-047) study update: Cetuximab + oxaliplatin and infusional 5-FU/FA (FOLFOX4) vs. FOLFOX4 alone

Title: "Open, randomized, controlled, multicenter phase II study comparing 5-FU/FA plus oxaliplatin (FOLFOX-4) plus cetuximab versus 5-FU/FA plus oxaliplatin as first-line treatment for EGRF-expressing metastatic colorectal cancer (mCRC)." (July 2005 - March 2006)

5.3.4.1. Design

This randomised (1:1), controlled trial supported the indications for cetuximab in combination with FOLFOX4 (continuous infusional regimen) in 1st line treatment of K-RAS wild mCRC patients, based on PFS (secondary endpoint).

- Population analysed: (ITT) cetuximab + FOLFOX4 n = 169; FOLFOX4 n = 168; total n = 337
- Safety: cetuximab + FOLFOX4 n = 170; FOLFOX4 n = 168; total n = 338

Several cut-off dates have been used in relation to this study. The first cut-off date of 4 August 2006 was the clinical cut-off for the primary efficacy analysis.

The final cut-off date was 30 November 2008. This date represents the clinical cut-off for assessment of OS, new reports of death that counted as DP for further exploratory efficacy analyses, and all safety analyses in this report. The cut-off date for assessment of K-RAS mutation status was 13 July 2009 for this report.

5.3.4.2. Study treatments

All subjects in Group A and B received the FOLFOX4 regimen, consisting of a combination of oxaliplatin with the de Gramont schedule of 5-FU/FA.

Cetuximab was administered according to the standard regimen, and always given first, at least 1 hour before chemotherapy.

FOLFOX4 was given IV q. 2 weeks and included oxaliplatin (85 mg/m² over 2 h on Day 1), FA (200 mg/m² over 2 h on Days 1 and 2), and 5-FU (400 mg/m² bolus followed by a 22 h continuous infusion of 600 mg/m² on Days 1 and 2).

Treatment was continued until occurrence of PD or unacceptable toxicity.

5.3.4.3. Assessments

Tumour assessments were based on radiological scans scheduled every 8 weeks. Investigators and a blinded IRC assessed tumour response according to modified WHO criteria.

Retrospective K-RAS analyses: Of the 337 patients in ITT population, 93.5% (315/337) were evaluable for K-RAS mutation status; of these 56.8% (179/315) had K-RAS wild-type tumours.

Comments on statistics: “With the exception of the test of the null hypothesis of OR = 1 over the entire sample population, all further efficacy analyses were exploratory and P values were not adjusted for the multiplicity of statistical tests.”⁶

The sponsor commented that although the K-RAS subgroup analyses were done retrospectively, the statistical analysis methods were specified prior to respective data cut-off dates where K-RAS data became available.

Regulatory comments: The originally reported benefit for PFS in K-RAS wild-type population was small; median increase of 0.5 months. The analyses conducted with later cut-off data showed improved PFS in K-RAS wild population; 8.3 months vs. 7.2 months; p = 0.0064. Of note is the Delegate’s comment at the time: “In view of lack of effect overall, this result needs confirmation.”

From the regulatory perspective, these PFS results were further supported by an updated OS data (another secondary endpoint) in K-RAS wild population, based on cut-off date of 30 November 2008.

⁶ Bokemeyer C *et al.* Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. *J Clin Oncol* 2009;27(5):663-671. (OPUS trial)

5.3.4.4. Results

The primary analysis of efficacy was performed on the ITT population of 169 subjects treated with cetuximab + FOLFOX4 and 168 subjects treated with FOLFOX4 alone.

- The primary objective, the ORR was not met in the overall population. The PFS time and OS were similar in the 2 treatment groups for the ITT population.
- With the addition of cetuximab to FOLFOX4 in the 1st line treatment of mCRC a clinical benefit was only seen in patients with K-RAS wild type tumors.

The addition of cetuximab to FOLFOX4 in patients with K-RAS wild type tumors led to a significantly longer PFS time, a significantly higher OR and improvement in OS time compared with patients receiving FOLFOX4 alone.

Median OS for K-RAS wild population: 22.8 months (95% CI: 19.3-25.9) and 18.5 months (95% CI: 16.4-22.6), $p = 0.3854$.

In the K-RAS wild-type population, median PFS was 8.3 months in the cetuximab + FOLFOX4 group compared to 7.2 months in the FOLFOX4 alone.

Further analyses are presented demonstrating that the K-RAS wild-type population showed a markedly enhanced reduction of hazard for progression (HR: 0.567; 95% CI: 0.375-0.856) in the cetuximab + FOLFOX4 group compared to the FOLFOX4 alone ($p = 0.0064$).

Subjects with K-RAS mutant status did not benefit from the addition of cetuximab to the FOLFOX4 regimen.

“Somewhat unexpected was the observation that patients whose tumours carried a mutation in K-RAS were more likely to derive a clinical benefit if treated with FOLFOX-4 alone, rather than with cetuximab plus FOLFOX-4.”

In subsequently presented analyses significant treatment effects by K-RAS status interaction were observed for OR and PFS ($p < 0.001$), but not for OS ($p = 0.12$).

The updated OS data were submitted at later date: “In the smaller randomized phase II trial EMR 62 202-047, median OS was prolonged by more than four months (18.5 to 22.8 months) compared to receiving FOLFOX alone in the K-RAS wild-type population.”

The current dossier contains Clinical Trial Report Addendum dated 27 April 2011; the OS data presented there are consistent with those of November 2009⁷.

5.4. Investigator sponsored trials: COIN study and NORDIC VII

5.4.1. COIN study Cetuximab + other oxaliplatin-based regimens

Title: “Continuous chemotherapy + cetuximab or Intermittent chemotherapy.”

The outcome of the COIN study prompted review of the benefit/risk profile of cetuximab in mCRC. In current submission emphasis is being placed on the subgroup of the study investigating: Cetuximab + oxaliplatin and infusional 5-FU/FA (OxMdG) vs. OxMdG alone.

Of interest is also the negative outcome for the comparison of cetuximab + XELOX treatment arm vs. XELOX alone. This resulted in the fluoropyrimidine regimen based on oral capecitabine⁸ being no longer considered by the sponsor as a viable combination with cetuximab.

⁷ Sponsor correction: correct date for OPUS CSR is 16 December 2010

⁸ Capecitabine is a prodrug, which is converted to FU predominantly in tumour cells.

5.4.1.1. Design

Phase III, open-label, multicentre, 3-arm, randomised (1:1:1), controlled study in 2445 patients with inoperable metastatic or locoregional colorectal adenocarcinoma not treated previously for metastatic disease comparing oxaliplatin + fluoropyrimidines (infusional 5-FU/FA [OxMdG] or capecitabine [XELOX]) in combination with cetuximab to the same chemotherapy regimen alone.

The study was sponsored by the Medical Research Council with centres in the UK and Ireland. Cetuximab and an educational grant were provided by the Sponsor. EGFR expression was not an inclusion criterion. The authors of this study⁹ state: "In view of the emerging consensus that EGFR immunohistochemistry was not a reliable predictor of response to EGFR-targeted therapy, all patients irrespective of EGFR status were eligible for the COIN trial. However, all patients were asked to provide a tumour sample for future analysis of EGFR status."

This study in 1st line treatment of advanced CRC investigated different treatment strategies comparing 2 experimental arms with a control arm.

Of interest to current submission is the comparison of arms A and B. The 2nd experimental arm (Arm C) attempted to answer the question: Is intermittent chemotherapy non-inferior? Data for the XELOX regimen and for Arm C are not discussed further.

5.4.1.2. Treatments

Study treatments: Patients in Arms A and B received IV oxaliplatin in combination with either oral capecitabine or infusional 5-FU as the fluoropyrimidine. Patients/clinicians choose OxMdG or XELOX before randomization. Patients in Arm B also received cetuximab.

A total of 815 patients were randomised to each of arms A and B:

- Arm A (control): oxaliplatin + fluoropyrimidine (OxFp) chemotherapy (XELOX/OxMdG).¹⁰ OxMdG (n = 279), and XELOX (n = 536)
- Arm B: cetuximab at the standard approved regimen added to the same chemotherapy schedule. Cetuximab + OxMdG (n = 281) and cetuximab + XELOX (n = 534)
- Arm C used an intermittent schedule of OxFp chemotherapy (OxMdG/XELOX) without cetuximab, and is not considered further in the report.

The chemotherapy regimens included:

- OxMdG (IV q. 2 weeks): combination of L-FA (175 mg over 2 h), oxaliplatin (85 mg/m² over 2 h), and bolus 5-FU (400 mg/m²) followed by a 46-h infusion of 5-FU (2400 mg/m²).

This regimen is comparable with but not identical to both FOLFOX4 and FOLFOX6. The oxaliplatin dose used is the same as that of FOLFOX4 but the infusional 5-FU schedule in the COIN study is comparable to that used in the FOLFOX6 regimen.

- XELOX (q. 3 weeks): combination of IV oxaliplatin (130 mg/m² over 2 h, Day 1) and oral capecitabine (1000 mg/m² BD on Days 1 - 14 of each cycle).

Based on results from an Interim Safety Analysis, the starting dose of capecitabine for Arm B was reduced from 1000 mg/m² BD to 850 mg/m² BD by protocol amendment after 1775 (73%) patients had been randomised to all arms. In Arm A, the capecitabine dose remained unchanged at 1000 mg/m² BD. As a result different regimens were used; for the comparator in Arm A (full-dose XELOX) and for Arm B (dose-reduced XELOX).

⁹ Maughan TS, Adams RA, Smith CG, *et al.* Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011;377(9783):2103-2114. (COIN study).

¹⁰ XELOX = oxaliplatin + oral capecitabine. OxMdG = oxaliplatin + infusional 5-FU/FA

Treatment continued until the occurrence of PD, cumulative toxicity, or patient's choice. Patients were allowed to discontinue one or more agents within the regimen as a result of toxic effects, while continuing on the remaining agent or agents.

5.4.1.3. Endpoints and assessments

The revised primary endpoint was OS in patients with K-RAS wild-type tumours. Secondary endpoints included PFS and response.

One of the primary aims was to determine whether the addition of cetuximab to continuous OxFp chemotherapy resulted in improved OS when compared to continuous combination chemotherapy alone.

After the inclusion of all patients into the study (n =1630 for Arms A and B), and after completion of treatment, in the case of most of the patients, the primary endpoint was changed to address the new findings demonstrating K-RAS mutations to be a negative predictor of cetuximab efficacy. Thus, the primary analysis was restricted to patients with K-RAS wild type tumours.

Tumour assessments were based on radiological scans scheduled at (rather long)¹¹ intervals of 12 weeks. Tumour response was assessed by the investigators according to RECIST criteria without any confirmatory scans.

5.4.1.3.1. Statistical considerations

K-RAS analyses and a protocol amendment that changed the primary analysis population to patients with K-RAS wild type tumours were introduced after the end of enrolment, without adjustment of sample size. All p values were 2-sided and were not adjusted for multiple testing.

An Interim Safety Analysis resulted in an amendment to the protocol, which had a major impact on the conduct of the study in terms of capecitabine dose reductions.

Analyses were focused on patients with K-RAS wild type tumours, as this corresponds to the population for which cetuximab has been approved. Due to the generally small number of patients within the subgroup analyses, these results should be interpreted with caution. This is particularly true for the K-RAS mutant subgroups, which accounted for approximately 40% of the K-RAS evaluable populations.

No adjustments were made for any of the potentially confounding factors; imbalances between the treatment arms within a subgroup with respect to the distribution of the type of fluoropyrimidine treatment, and known prognostic variables such as age, sex, PS, and tumour dissemination.

5.4.1.4. Patient enrolment, characteristics and disposition

Baseline characteristics were well balanced between the 2 treatment arms. The baseline characteristics of patients were indicative of a patient population with a poor overall prognosis as compared to other pivotal trials in mCRC. Approximately $\frac{2}{3}$ were male, the rectum was the site of the primary tumour in about $\frac{1}{3}$ of the patients.

Characteristics in patients with K-RAS wild type tumours were similar to those in the overall population. In the K-RAS wild type population, however, the proportion of patients with unresected or unresectable primary tumours was slightly higher in the combination therapy arm than in the OxFp alone arm (41% vs. 36% patients).

Approximately $\frac{2}{3}$ of the patients or clinicians chose the oral XELOX regimen and $\frac{1}{3}$ the infusional OxMdG regimen.

¹¹ In the pivotal company sponsored trials 8 weekly intervals were generally used.

Patients in the cetuximab containing arm received less 1st line chemotherapy (oxaliplatin and fluoropyrimidines) compared with patients in the control arm; independent of the K-RAS mutation status. This was particularly pronounced in patients treated with XELOX. The cetuximab dose was also reduced in both the XELOX and OxMdG groups.

Overall, in the K-RAS wild type population as well as in the K-RAS mutant population, the dose intensity over the entire treatment period was significantly lower in the cetuximab + XELOX arm vs. XELOX alone arm. Significant imbalances between the treatment groups were recorded as early as the first 12 weeks of treatment, but these became more distinct with prolonged treatment duration, suggesting a cumulative toxicity.

There were also significant imbalances in dose reductions in patients treated with the OxMdG regimen, but these were not as pronounced as those with the XELOX regimen.

K-RAS analyses: Tumour samples from approximately 81% of patients were analysed retrospectively for K-RAS expression, of which 55% were K-RAS wild-type. K-RAS tumour data were available for 1316 (80.7%) of the 1630 patients in arms A and B (ITT population); of which 55.4% (729/1316) had K-RAS wild-type tumours.

Of the 729 patients with K-RAS wild tumours, 362 patients received cetuximab and oxaliplatin + fluoropyrimidines (117 patients OxMdG and 245 patients XELOX), and 367 patients received oxaliplatin + fluoropyrimidines alone (127 patients OxMdG and 240 patients XELOX).

5.4.1.5. Primary efficacy results

In general, the COIN study did not meet its primary endpoint of demonstrating a prolonged survival for the addition of cetuximab to 1st line XELOX/OxMdG vs. XELOX/OxMdG alone in advanced colorectal cancer.

In patients with K-RAS wild type tumours, OS did not differ between treatment groups (median survival 17.9 months in the control group vs. 17.0 months in the cetuximab group; HR 1.04; 95% CI: 0.87-1.23; $p = 0.67$). Similarly, there was no effect on PFS (8.6 vs. 8.6 months, respectively; HR 0.96; 95% CI: 0.82-1.12; $p = 0.60$).

The authors of the published paper (Maughan *et al.*, 2011) noted: The primary analysis cohort, patients with K-RAS wild type tumours contained a prognostically mixed cohorts; it also included some patients with BRAF and NRAS mutant tumours. OS differed by somatic mutation status irrespective of treatment received: BRAF mutant, 8.8 months (IQR 4.5 - 27.4); KRAS mutant, 14.4 months (8.5 - 24.0); all wild type, 20.1 months (11.5 - 31.7).¹²

The addition of cetuximab to OxFp was associated with a borderline significant benefit in terms of response rate in patients with K-RAS wild type tumours. However, there was no improvement in terms of other parameters in patients with K-RAS wild type tumours.

A positive trend in terms of PFS, for K-RAS wild patients, was claimed in favour of the addition of cetuximab to infusional 5-FU combined with oxaliplatin (OxMdG). However, the study was not powered to demonstrate superiority in the OxMdG subgroup.

In patients receiving cetuximab + OxMdG, there was evidence of a positive trend towards a reduction in the risk of progression compared with OxMdG alone, with a HR for PFS of 0.77 (95% CI: 0.59-1.01; $p = 0.056$), but there was no improvement in OS (HR 0.93, 95% CI: 0.72-1.19; $p = 0.617$).

In patients with K-RAS mutant tumours, there was no evidence of an effect on efficacy with the addition of cetuximab to OxFp for any of the efficacy parameters investigated.

¹² Other activating mutations such as those in BRAF and NRAS in colorectal cancers might have similar negative effects on the efficacy of EGRF-targeted therapy.

There were significant dose reductions and delays of capecitabine or oxaliplatin administration mainly due to higher frequency of diarrhoea in cetuximab containing arm. In addition, significantly fewer patients treated with cetuximab received 2nd line therapy.

The outcome of COIN study resulted in the indication changes to the PI (and SmPC) via SRN, with the sponsor stating that treatment with “XELOX will no longer be an option with the revised indications.”

Sponsor comments: The results from the COIN study are difficult to interpret due to various factors:

- Relatively short median OS time of 17.5 months in the total population, which is lower than that observed in company sponsored CRYSTAL and OPUS studies, in which cetuximab was added to 1st line chemotherapy.
- Baseline characteristics of patients, which were indicative of a patient population with a poor overall prognosis.

Of note is the following comment by the authors of the published paper (Maughan *et al.*, 2011): “However, the characteristics of the population were not fundamentally different from those in other trials of EGFR-targeted antibodies so, although contributing to the shorter overall survival, they do not adequately account for the failure to detect the expected improvement with addition of cetuximab.”

- The fact that an amendment was made to the study protocol that reduced the capecitabine in patients randomised to the cetuximab arm only, based on interim safety findings.
- Variation of PFS and OS results according to the fluoropyrimidine-based treatment used.

This is illustrated by the finding of a trend towards a PFS benefit with cetuximab + OxMdG but not with XELOX. One possible explanation for this is the higher number of chemotherapy dose reductions and delays reported in patients receiving cetuximab + XELOX compared with those receiving XELOX alone.

- Imbalances between the treatment arms in the proportion of patients receiving 2nd line treatment, which may have influenced OS.

Fewer patients treated with OxFp + cetuximab received 2nd line treatment compared with those receiving OxFp alone. In both (K-RAS wild and mutant) populations the differences between the treatment arms were more pronounced in patients receiving the OxMdG regimen.

The authors of the published paper commented: “A significant reduction in the use of second-line therapy was also noted in the cetuximab group (56% vs 62%). This finding could be a consequence of the increased toxic effects noted with addition of cetuximab, but by itself is unlikely to account for the absence of survival benefit in view of the lack of overall benefit in progression-free survival and the small difference shown.”

- Possible limitation in the potential to detect significant PFS differences between the treatment arms due to the 12-week tumour assessment schedule and the more frequent visits in the cetuximab-containing arm, leading to a higher likelihood of detecting PD.

5.4.1.6. Summary

The COIN study failed to show an improvement in PFS or OS for patients with K-RAS wild type disease treated with cetuximab + OxFp, compared with OxFp alone, although the addition of cetuximab to OxFp increased ORR.

No trends indicating clinical benefit could be shown for patients who received cetuximab in combination with the XELOX regimen.

A positive trend was shown mainly in the OxMdG subgroup, which is in line with the OPUS trial, for the patient population in which the regimen with continuous administration of 5-FU via an infusion pump was used.

Evaluator's comments:

- The study was underpowered to show superiority in any subgroups.
- The claimed positive trend in PFS for cetuximab + OxMdG arm was based on the calculated HRs; hardly convincing evidence when there was no absolute benefit shown in favour of adding cetuximab to the chemotherapy arm (median PFS of 9.0 months vs. 9.2 months; for cetuximab + OxMdG vs. control, respectively).
- It is difficult to make definite conclusions in relation to the secondary endpoints from COIN study, because of methodological concerns; "because overall survival was the primary outcome measure of the trial, responses were not confirmed by repeat scans and external radiological review was not undertaken." (Maughan et al., 2011)."

Additionally, the OS, for K-RAS wild population was obviously worse in the cetuximab + OxMdG combination group (16.3 months vs. 18.2 months).

For this, rather difficult to interpret trial, the evaluator included a summary of a presentation entitled "2010 ASCO presentation: Identification of potentially responsive subsets when cetuximab is added to oxaliplatin-fluoropyrimidine chemotherapy (CT) in first line advanced colorectal cancer (aCRC): mature results of the MRC COIN trial" by Maughan T.S. et al., and some comments from the authors of the published paper:

5.4.1.6.1. COIN trial summary (presented at ASCO):

- Largest trial of EGFR targeted treatment in 1st line advanced CRC setting
 - Prospective OS analysis by K-RAS status
- > 80% patients genotyped for KRAS, NRAS and BRAF:
 - 42% KRAS mutation; 4% NRAS mutation; 8% BRAF mutation)

The addition of cetuximab to oxaliplatin based chemotherapy was associated with:

For all patients

- Increased non-haematological toxicity
- No change in OS or PFS

For KRAS wild type patients

- Increased non-haematological toxicity
- No change in OS or PFS
- Increased response rate

Predefined subgroup analyses have shown that cetuximab improves PFS and OS (NS) only when used in patients with:

- KRAS wild type tumours
- Limited metastatic disease (0/1 metastatic sites) and
- In combination with infusional 5FU + oxaliplatin

Strong prognostic effect of KRAS, NRAS and BRAF mutation status

The lack of overall benefit may be attributed to:

- Reduced usage of 2nd line therapy in Arm B
- 66% patients chose the combination of capecitabine + oxaliplatin which was not associated with benefit with cetuximab
- 75% of the patient population had > 1 site of disease (?)

The *Interpretation of the COIN trial* by Maughan *et al.*, 2011 and other comments from this publication are presented below:

“This trial has not confirmed the benefit of addition of cetuximab to oxaliplatin-based chemotherapy in 1st line treatment of patients with advanced CRC. Cetuximab increased response rate, with no evidence of benefit in PFS or OS in K-RAS wild type patients, or even in patients selected by additional mutational analysis of their tumours.

The use of cetuximab in combination with oxaliplatin and capecitabine in 1st line chemotherapy in patients with widespread metastases cannot be recommended.

And further comment: One major factor that could affect the benefit of the addition of cetuximab to chemotherapy is the precise nature of the agents used in combination.

The only Phase III trial, in 1st line therapy that showed an OS benefit to date used irinotecan and infusional FU as the chemotherapy backbone. By comparison, the trials using oxaliplatin have not shown improved OS, and this failure has raised the possibility of a negative interaction between oxaliplatin and cetuximab.

A broad set of predefined exploratory analyses have been done in an attempt to understand the results of the COIN trial. The only group for which some evidence of a potential benefit was suggested were those patients who had 3 coincident factors: K-RAS wild-type tumours, treatment with infused FU rather than capecitabine, and a limited distribution of metastatic disease (either 0 or 1 metastatic site vs. 2 or more sites, or liver metastases only vs. more widespread disease).

For patients with K-RAS wild type tumours treated with infused FU, the benefit in PFS (HR for FU-based therapy was 0.77; $p = 0.06$, compared with HR for capecitabine-based therapy of 1.06; $p = 0.56$, p for interaction = 0.07) was consistent with other trials.

This finding again suggests the potential importance of the agents used in combination when using EGFR-targeted therapies.

The results of the *COIN trial* are unexpected, and add to the variance seen in other trials evaluating the use of EGFR monoclonal antibodies in combination with chemotherapy, in 1st line treatment of advanced CRC.

The overall lack of benefit of the addition of cetuximab to oxaliplatin and fluoropyrimidine combinations seen in the *COIN trial*, even in the absence of bevacizumab, is likely to be attributable to the specific toxic effect profile of the combination of the oxaliplatin and capecitabine chemotherapy backbone, with which no benefit was seen in any subgroup when cetuximab was added.

By contrast, in patients treated with oxaliplatin + infusional FU, similar benefits in PFS were seen as in other studies.

Finally, the potent prognostic effect of BRAF, KRAS, and NRAS mutations on the outcome of patients with advanced CRC shows the fundamental importance of these changes, and emphasises the need to stratify future trials for these factors, and to seek specific therapeutic approaches within these molecular subgroups.”

5.4.2. NORDIC VII study

Only “incomplete draft trial report” was available.

5.4.2.1. Design

Phase III, open-label, randomised (1: 1: 1), multicentre trial with 3 parallel groups investigating cetuximab in combination with the Nordic FLOX regimen in 1st line treatment of mCRC. The study compared cetuximab + FLOX given either until DP or intermittently vs. FLOX alone. K-RAS wild-type status was not an inclusion criterion. (May 2005 - May 2009).

5.4.2.2. Treatments

Treatment regimen: The Nordic FLOX regimen is based on 5-FU given as a bolus, FA, and oxaliplatin, and is employed almost exclusively in the Nordic countries.

A total of 571 patients were randomized at 32 centres; the ITT population consisted of 566 patients:

- Arm A: FLOX alone (n = 185)
- Arm B: Cetuximab + FLOX (n = 194)
- Arm C: Cetuximab + intermittent FLOX (n = 187)

Arm C was included to allow comparison of the effect of FLOX as continuous or intermittent chemotherapy when given together with continuous cetuximab.

The Nordic FLOX regimen was administered in cycles of 2 weeks and consisted of oxaliplatin 85 mg/m² over 1 h (30 - 90 min) on Day 1, and 5-FU 500 mg/m² as a bolus infusion (< 5 min), followed 30 min later by bolus FA 60 mg/m² (< 10 min) on Days 1 and 2.

Cetuximab was given at the standard approved regimen. In Arms A and B, treatment was continued until PD or unacceptable toxicity.

“It must be emphasized that the Nordic VII study was performed with the rather unusual Nordic FLOX regimen in which oxaliplatin is given in combination with a bolus 5-FU/FA administration; there is no continuous infusion of 5-FU.”

Patients were followed up until 18 months after last patient was enrolled. Second-line therapy could be given when FLOX or FLOX + cetuximab had failed; patients in Arm A were allowed to receive cetuximab.

5.4.2.3. Objectives

Primary objective: The primary objective was to assess the effect of adding cetuximab to Nordic FLOX in 1st line treatment, independent of K-RAS status. The primary endpoint was PFS. The main comparison was between Arm B and A.

Methodology: Investigators evaluated the overall response every 4th cycle (i.e. 8 weeks) according to RECIST criteria.

Subgroup analyses according to K-RAS mutational status were conducted retrospectively. Sample size was not re-estimated for the retrospective analyses, and no adjustment for multiple testing was applied.

5.4.2.4. Demographics

Demographic characteristics were generally comparable across the 3 treatment groups and typical for patients with mCRC. The overall ITT population had a mean age of 60.5 years (35% aged 65-74 years); 59% patients were male, and 96% had WHO PS of 0 or 1. There were no notable differences between arms A and B in relation to baseline disease information.

K-RAS analyses: K-RAS status was determined in 88% (498/566) of patients in the ITT population; 61% (303/498) in the K-RAS-evaluable population had K-RAS wild-type tumours, and 39% (195/498), had K-RAS mutant tumours.

There were less K-RAS wild type patients in Arm B (57%) than in Arms A and C (63% each). There was also a slight imbalance of patients with BRAF¹³ mutant tumours who usually have a very poor prognosis: overall 20% of the K-RAS wild-type population had BRAF mutations.

5.4.2.5. Results

In the ITT population, median PFS (primary endpoint) was 7.9 months in Arm A, 8.3 months in Arm B; and 7.4 months in Arm C.

There were no statistically significant differences between Arms A and B, or between Arms A and C. Arm B had a statistically significant longer PFS than Arm C (HR 1.39, p = 0.006).

In this study PFS was defined as the time from randomisation to first occurrence of PD or death. Patients alive without documented PD were censored at the data cut-off, regardless of when the last tumour evaluation was performed. This censoring approach differed markedly from that used in company-sponsored trials used for registration purposes. Results cannot be compared due to the lack of sensitivity analyses.

In the ITT population, median OS (secondary endpoint) was 20.4 months in Arm A, 19.7 months in Arm B, and 20.3 months in Arm C. There were no relevant differences between the 3 treatment arms.

There was a high degree of censoring after about 17 months. No information on subsequent therapies is available.

In the K-RAS wild-type population, median OS was 22.0 months in Arm A, 20.1 months in Arm B, and 21.4 months in Arm C. No considerable differences between treatment groups were seen for either of the K-RAS populations.

The sponsor provided the following summary of the study:

In the ITT population, the ORR in patients receiving cetuximab + continuous FLOX* (Arm B) was higher than with continuous FLOX alone (Arm A): 48% vs. 40% patients. Median PFS (primary endpoint) was 8.3 months in Arm B and 7.9 months in Arm A; median OS was 19.7 vs. 20.4 months.

None of the treatment differences in favour of cetuximab for these variables could be considered statistically significantly different, but the overall patterns of results for ORR and PFS were similar to those from the ITT populations of the 2 studies that investigated cetuximab in the 1st line setting in combination with FOLFOX4 (OPUS study), or with FOLFIRI (CRYSTAL study).

Evaluator's comment: The study did not investigate the usual continuous FLOX* regimen, as the 5-FU/FA was given as a bolus. Thus, the NORDIC VII trial cannot be classified as employing the "continuous infusional 5-FU/FA" + oxaliplatin regimen.

In this study, Arm B employed "continuous chemotherapy" as opposed to "intermittent chemotherapy" in Arm C.

In the K-RAS wild-type population, addition of cetuximab to "continuous FLOX" did not result in an improvement compared to FLOX alone for ORR (Arm B 46%, Arm A 44%), PFS (7.8 vs. 8.7 months), or OS (21.0 vs. 22.0 months).

In the K-RAS mutant population, the addition of cetuximab to FLOX resulted in improved ORR (Arm B 49%, Arm A 40%), PFS (9.3 vs. 7.9 months), and OS (21.1 vs. 20.4 months).

¹³ BRAF encodes a protein kinase and is involved in intracellular signalling and cell growth and is principal downstream effector of K-RAS. BRAF mutations are increasingly being investigated in mCRC. K-RAS and BRAF mutations are considered mutually exclusive. Subgroups of patients with BRAF mutations were also analysed in sponsor-led trials, but are not discussed in the submission.

None of the treatment differences in the K-RAS wild type or mutant population could be considered statistically significant; however, the difference for PFS in the K-RAS mutant population was unexpectedly in favour of cetuximab ($p = 0.08$).

Unexpectedly, the difference in response rates between Arms B and A declined from 8% in the ITT population to 2% in the K-RAS wild type population.

The overall efficacy profile for the K-RAS wild type population in this study is inconsistent with findings in other studies.

Nordic VII is the only study so far that indicates some benefit for addition of cetuximab to chemo-therapy compared to chemotherapy alone in the K-RAS mutant population, but not in the K-RAS wild type population. At the moment there is no obvious explanation for these unexpected and inconsistent findings.

5.5. Various other studies

Investigator sponsored studies with cetuximab and various chemotherapy regimens are discussed briefly as the dossier included pooled analyses involving some of these trials. Some of the arguments in favour of oxaliplatin, as a back-bone chemotherapy combined with cetuximab, are also based on the results of these studies. The outcomes of the individual studies are presented in Table 2 and Table 3.

Table 2. CORE and CELIM studies (Base: infusional 5-FU/FA + oxaliplatin). Efficacy of cetuximab and infusional 5-FU/FA + oxaliplatin versus cetuximab + FOLFIRI (CORE 1.2.001, CELIM) and comparison with results from pivotal studies.

Study / endpoint	ITT population (independent of KRAS status)				KRAS wild-type population			
	Cetuximab+ FOLFIRI		Cetuximab + FOLFOX6		Cetuximab+ FOLFIRI		Cetuximab + FOLFOX6	
CECOG CORE 1.2.001								
Number of patients	74		77		28		34	
ORR, % patients [95% CI]	45 [33, 57]		43 [32, 55]		50 [31, 69]		56 [38, 73]	
Odds ratio [95% CI]	0.93 [0.49, 1.77]				NA			
p-value (CMH test)	NA				NA			
Median PFS, months [95% CI]	8.3 [7.4, 8.7]		8.6 [6.3, 9.7]		8.4 [3.2, 11.3]		9.1 [8.3, 11.1]	
Hazard ratio [95% CI]	1.06 [0.74, 1.52]				NA			
p-value (log rank test)	0.7375				NA			
Median OS, months [95% CI]	18.9 [14.7, 23.9]		17.4 [14.9, 22.6]		19.9 [11.9, NA]		22.5 [17.1, 28.9]	
Hazard ratio [95% CI]	0.98 (0.67, 1.44)				NA			
p-value (log rank test)	0.9230				NA			
CELIM	Cetuximab+ FOLFIRI		Cetuximab + FOLFOX6		Cetuximab+ FOLFIRI		Cetuximab + FOLFOX6	
Number of patients	53		53		Not available			
ORR, % patients [95%CI]	57 [42, 70]		68 [54, 80]					
Odds ratio [95% CI]	1.62 [0.74, 3.59]							
p-value	0.23							
Median PFS, months [95% CI]*	10.5 [8.9, 12.2]		11.2 [7.2, 15.3]					
Median OS, months [95% CI]*	35.7 [30.0, 41.5]		29.0 [18.7, 39.3]					
EMR 62 202-013 (FOLFIRI) / EMR 62 202-047 (FOLFOX4)	Cetuximab + FOLFIRI		Cetuximab + FOLFOX4		Cetuximab + FOLFIRI		Cetuximab plus FOLFOX4	
Number of patients	599		169		316		82	
ORR, % patients [95%CI]	46.9 [42.9, 51.0]		45.6 [37.9, 53.4]		57.3 [51.6, 62.8]		57.3 [45.9, 68.2]	
Median PFS, months [95% CI]	8.9 [8.0, 9.5]		7.2 [5.6, 7.7]		9.9 [9.0, 11.3]		8.3 [7.2, 12.0]	
Median OS, months [95% CI]	19.9 [18.5, 21.3]		18.3 [14.8, 20.4]		23.5 [21.2, 26.3]		22.8 [19.3, 25.9]	

CI = confidence interval, CT = chemotherapy, CMH test = Cochran-Mantel Haenszel test, NA = not available, ORR = overall response rate, OS = overall survival, PFS = progression-free survival

* unpublished data, provided by the investigator in confidence

CECOG CORE 1.2.001: see [5.4.1.154-CRC2](#)

CELIM: see [5.4.1.153-CRC2](#)

EMR 62 202-013 (CRYSTAL) and EMR 62 202-047 (OPUS): see [Table 5](#)

Table 3. Efficacies across studies (Base: oral fluoropyrimidine + oxaliplatin). Efficacy of cetuximab + oral fluoropyrimidine + oxaliplatin versus chemotherapy alone

Study / endpoint	ITT population (independent of KRAS status)		KRAS wild-type population	
	Cetuximab+ XELOX	XELOX	Cetuximab+ XELOX	XELOX
SAKK				
Number of patients	37	37	Not available	
ORR, % patients [95%CI]	41 [25, 58]	14 [5, 29]		
Median TTP, months [95% CI]	7.2 [6.0, 8.4]	5.8 [5.0, 8.3]		
Median OS, months [95% CI]	20.5 [15.5, 27.2]	16.5 [14.3, 27.0+]		
COIN				
Number of patients	543	536	245	240
ORR, % patients [95%CI]	51 NA	50 NA	62 NA	56 NA
Odds ratio [95% CI]		1.02 NA		1.32 NA
p-value		0.854		0.138
Median PFS, months [95% CI]	7.4 NA	7.4 NA	8.4 NA	8.0 NA
Hazard ratio [95% CI]		1.037 [0.914, 1.175]		1.058 [0.876, 1.277]
p-value (log-rank test)		0.575		0.560
Median OS, months [95% CI]	15.1 NA	15.6 NA	17.5 NA	17.4 NA
Hazard ratio [95% CI]		1.023 [0.910, 1.150]		1.309 [0.915, 1.309]
p-value (log-rank test)		0.749		0.408
EXPERT-C				
Number of patients	83	81	46	44
ORR (CT), % patients [95%CI]	59 NA	50 NA	70 NA	50 NA
p-value		0.195		0.028
ORR (CRT), % patients [95%CI]	78 NA	71 NA	89 NA	72 NA
p-value		0.195		0.028
PFS rate at 3 years, % patients	71 NA	69 NA	80 NA	77 NA
Hazard ratio [95% CI]		NA		0.62 [0.24, 1.57]
p-value (log rank test)		0.463		0.308
OS rate at 3 years, % patients	86 NA	78 NA	96 NA	81 NA
Hazard ratio [95% CI]		NA		0.27 [0.07, 0.99]
p-value (log rank test)		0.077		0.035

2.5 CRC2 Clinical Overview – Addendum: Update on Efficacy and Safety – January 2012

Study / endpoint	ITT population (independent of KRAS status)	KRAS wild-type population
	Cetuximab+ UFOX	Cetuximab+ UFOX
Number of patients	152	40
ORR, % patients [95%CI]	37.5 [29.8, 45.7]	52.5 [36.1, 68.5]
Median PFS, months [95% CI]	6.6 [5.6, 7.2]	6.8 [5.6, 8.2]
Median OS, months [95% CI]	Results not mature at time of analysis	

CI = confidence interval, CRT = chemoradiotherapy, CMH test = Cochran-Mantel Haenszel test, NA = not available, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, TTP = time to progression

5.5.1. CECOG CORE 1.2.001 study Cetuximab + oxaliplatin and infusional 5-FU/FA vs. cetuximab + FOLFIRI (irinotecan + infusional 5-FU/FA)

5.5.1.1. Design

Phase II, open-label, 2-arm, randomised (1:1), controlled, multicentre trial investigating the efficacy and safety of cetuximab combined with FOLFOX6 or FOLFIRI as 1st line treatment in patients with unresectable, metastatic CRC. EGFR expression was not an inclusion criterion.

A total of 151 patients received either cetuximab in combination with 5-FU/FA + oxaliplatin (FOLFOX6), (Arm A: n = 77); or 5-FU/FA + irinotecan (FOLFIRI), (Arm B, n = 74).

The trial was sponsored by the Central European Co-operative Oncology Group (CECOG); 156 patients were enrolled at 28 centres in Europe and Israel. Cetuximab and a financial grant were provided by Merck KGaA. The study report was not available.

5.5.1.2. Objective

The primary objective was to estimate the difference in 9-month PFS rates between the treatment arms.

5.5.1.3. Treatments

Study Treatments: Cetuximab was administered according to the standard regimen. Chemotherapy regimens were given IV every 2 weeks.

FOLFOX6 included oxaliplatin (100 mg/m² on Day 1), FA (400 mg/m² racemic or 200 mg/m² L-form on Day 1), and 5-FU (400 mg/m² bolus on Day 1 followed by a 46 h continuous infusion of 2400 mg/m²).

FOLFIRI contained irinotecan (180 mg/m² on Day 1) together with 5-FU and FA as described for FOLFOX6.

Patients received 6 months of combination treatment, after which cetuximab was continued. Treatment was discontinued in the case of PD.

5.5.1.4. Assessments

Tumour assessments were based on CT or MRI scans scheduled at baseline, Weeks 6, and 12, and then every 12 weeks. Investigators assessed tumour response according to RECIST criteria.

K-RAS analyses: Subgroup analyses according to K-RAS mutational status were performed retrospectively. Of the 151 patients (ITT population); 77.5% (117/151) were evaluable for K-RAS mutation status; out of these 53.0% (62/117) had K-RAS wild-type tumours.

5.5.1.5. Results

Cetuximab + FOLFIRI vs. cetuximab + FOLFOX6. Conclusions by the authors of the published paper: ¹⁴ “This study confirms that combinations of cetuximab with FOLFOX6 or FOLFIRI are effective and significantly improve clinical outcome in KRAS wild-type compared with K-RAS mutated mCRC.”

“No significant differences in efficacy were found for cetuximab combined with FOLFOX6 or FOLFIRI in the first-line treatment of mCRC.”

A claim in favour of FOLFOX4¹⁵ arm has been made by the sponsor. “In the absence of chemotherapy-alone control arms, the present study was not able to accurately assess the influence of K-RAS mutation status on clinical outcome for cetuximab or chemotherapy-alone as individual treatment components.”¹⁶

5.5.2. CELIM study

5.5.2.1. Design and objective

Phase II, open-label, multicentre, randomised (1:1), controlled trial evaluating the effectiveness of cetuximab and either FOLFOX6 or FOLFIRI in neoadjuvant treatment of unresectable

¹⁴ Ocvirk J *et al.* Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOg trial. *World Journal of Gastroenterology* 2010;16: 3133 - 3143.

¹⁵ Sponsor correction: FOLFOX4 should read FOLFOX6.

¹⁶ Source of this quote: Ocvirk J *et al.* Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOg trial. *World Journal of Gastroenterology* 2010;16: 3133 - 3143.

colorectal liver metastases (technically non-resectable, or ≥ 5 metastases). EGFR expression was not an inclusion criterion.

Study was conducted at 17 centres in Germany and Austria; 111 patients were randomized. The trial was sponsored by the Corporation of Knowledge and Technology Transfer at the Technical University of Dresden (GWT-TUD GmbH). Cetuximab and a financial grant were provided by Merck KGaA.

The primary endpoint was response rate according to RECIST criteria. The authors aimed to address the correlation between tumour response rates and resectability in randomized setting.

5.5.2.2. Treatments

Study treatments: Cetuximab was administered according to the standard regimen. The chemotherapy regimens were given IV every 2 weeks. Treatment was planned for 8 cycles.

FOLFOX6 included oxaliplatin (100 mg/m² on Day 1), FA (400 mg/m² on Day 1), and 5-FU (400 mg/m² bolus on Day 1 followed by a 46 h continuous infusion of 2400 mg/m²).

FOLFIRI contained irinotecan (180 mg/m² on Day 1) together with 5-FU and FA as described for FOLFOX6.

5.5.2.3. Assessments

Tumour assessments were based on CT or MRI scans scheduled every 8 weeks. Investigators assessed tumour response according to RECIST criteria. A retrospective, blinded surgical review of patients with radiological images at both baseline and during treatment was done to assess objectively any changes in resectability.

Resection was intended to be done within 4 - 6 weeks of the last treatment cycle. Patients with unresectable tumours were to continue treatment until PD, and were assessed for resectability every 4 cycles, for a maximum of 2 years. Following resection, patients continued on treatment for 6 cycles.

K-RAS analyses were conducted retrospectively. Of the 106 patients in the ITT population, 88.7% (94/106) patients were evaluable for K-RAS mutation status; out of these, 71.3% (67/94) had K-RAS wild-type tumours.

5.5.2.4. Results

Cetuximab + FOLFIRI vs. cetuximab + FOLFOX6 (results for K-RAS wild population not available): "In our study of patients with colorectal liver metastases, high tumour-response rates were achieved with cetuximab and either FOLFIRI or FOLFOX6. This translated into a high rate of metastasectomy."¹⁷

5.5.3. Further trials of cetuximab + oxaliplatin and infusional 5-FU/FA

5.5.3.1. CECOG CORE 1.2.002 study

Phase II, open-label, 2-arm, randomised (1:1), controlled, multicentre trial investigating the efficacy and safety of cetuximab given weekly or every 2 weeks in combination with FOLFOX4 as 1st line treatment in patients with K-RAS wild-type mCRC.

Patients were enrolled at 22 centres in Europe and Israel; 152 patients received study treatment.

The trial was sponsored by the CECOG. Cetuximab and a financial grant were provided by Merck KGaA. A study report is said to be in preparation.

¹⁷ Folprecht G. *et al.* Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010;11: 38-47.

The primary objective was to assess the ORR of FOLFOX4 + cetuximab given weekly and FOLFOX4 + cetuximab given every 2 weeks.

Study treatments: FOLFOX4 was given IV every 2 weeks (up to 13 cycles).

Cetuximab was given according to the standard weekly regimen (1st infusion 400 mg/m² over 2 h, subsequent weekly infusions 250 mg/m² over 1 h), or every 2 weeks (500 mg/m²; 1st infusion over 2 h, 2nd over 1.5 h, all subsequent infusions over 1 h).

Treatment was continued until occurrence of PD or unacceptable toxicity.

Tumour assessments were based on CT or MRI scans scheduled every 3 months. Investigators assessed tumour response according to RECIST criteria.

K-RAS status was assessed prospectively; only patients with K-RAS wild type tumours were included in the trial (based on a protocol amendment that became effective after 23 patients were already enrolled, whose K-RAS status was assessed retrospectively).

The preliminary study resulted in publication by T. Ciuleanu et al.¹⁸ in 2011; the authors suggesting comparable efficacy and safety results of both regimens.

At the time of analysis median follow up was 12 months; ORR was 51% in Arm A and 63% in Arm B, respectively; the difference between arm B and A being 12% (95% CI: -4%-27%).

Preliminary results for PFS time did not indicate relevant differences between both arms.

5.5.3.2. FUTURE study (EMR 200025-001)

Phase II, open-label, 2-arm, randomised (1:1), controlled, multicentre trial comparing cetuximab + UFOX vs. cetuximab + FOLFOX4 as 1st line treatment for mCRC. EGFR expression was not an inclusion criterion.

A total of 301 patients were randomised and treated: 150 with cetuximab + FOLFOX4 and 151 with cetuximab + UFOX (i.e. UFT + oxaliplatin). Randomisation to treatment was stratified according to whether a patient was considered as high, medium or low risk using Köhne's criteria.¹⁹

The study was conducted in Europe, the Asia-Pacific region, and Latin America. The trial was sponsored by Merck KGaA.

The primary objective was to compare PFS in patients receiving cetuximab + either UFOX or FOLFOX4.

Study treatments: Cetuximab was administered according to the standard regimen.

The UFOX regimen was given in 28-day cycles and included IV oxaliplatin (85 mg/m² over 2 h on Days 1 and 15) and oral UFT divided into 3 daily doses on Days 1-21 inclusive.

UFT is composed of a fixed combination of tegafur (prodrug of 5-FU) and uracil (inhibitor of 5-FU degradation) in a 1:4 molar ratio; the total daily dose was 250 mg/m² tegafur + 560 mg/m² uracil.

The FOLFOX4 regimen was given IV every 2 weeks and included oxaliplatin (85 mg/m² over 2 h on Day 1), FA (200 mg/m² over 2 h on Days 1 & 2), and 5-FU (400 mg/m² bolus followed by a 22 h continuous infusion of 600 mg/m² on Days 1 and 2).

¹⁸ Ciuleanu T *et al.* Cetuximab weekly (q1w) versus every two weeks (q2w) plus FOLFOX4 as first-line therapy in patients (pts) with KRAS wild-type (wt) metastatic colorectal cancer (mCRC). *J Clin Oncol* 2011;29: 494 (February 1 Supplement).

¹⁹ The Köhne's prognostic groups were developed in the era of 5-fluorouracil treatment; also seem to be applicable to patients treated with combination chemotherapy. Diaz *et al.* Analysis of Prognostic Factors and Applicability of Köhne's Prognostic Groups in Patients with Metastatic Colorectal Cancer Treated with First-Line Irinotecan or Oxaliplatin-Based Chemotherapy. *Clin Colorectal Cancer* 2005;5 (3):197 - 202.

Treatment continued until occurrence of PD or unacceptable toxicity.

Tumour assessments were based on radiological scans every 8 weeks. Investigators assessed tumour response according to RECIST criteria.

K-RAS analyses were performed retrospectively. Of the 302 patients (ITT population), 59.6% (180/302) were evaluable for K-RAS mutation status; out of these, 53.3% (96/180) had K-RAS wild-type tumours.

Comments: The study clearly had limitations due to a high rate of major protocol deviations; 15.3% in the FOLFOX arm and 32.9% in the UFOX arm; including 24.3% of patients treated with UFOX for whom it is unclear whether UFT was administered at the planned dose.

Results: The ORR was lower and PFS was shorter in the UFOX arm than in the FOLFOX arm and than in other studies using cetuximab in combination with infusional 5-FU/FA + oxaliplatin.

5.5.4. Studies using other oxaliplatin-based regimens

5.5.4.1. COIN study

Included cetuximab + XELOX (IV oxaliplatin + oral capecitabine) arm - see above.

5.5.4.2. SAKK study

Phase II, open-label, 2-arm, randomised (1:1), controlled, multicentre trial investigating the addition of cetuximab to oxaliplatin and capecitabine (XELOX) as 1st line treatment in patients with unresectable mCRC and immunohistochemical evidence of EGFR expression.

The study was conducted at 9 centres in Switzerland (74 patients). The trial was sponsored and conducted by the Swiss Group for Clinical Cancer Research (SAKK). Merck KGaA provided a financial grant.

The randomized, Phase II designed to select the more promising schedule of the two in terms of response. The primary endpoint was response rate.

Study treatments: Cetuximab was administered according to the standard regimen. Oxaliplatin (130 mg/m²) was given as a 2 h IV infusion on Day 1. Capecitabine was administered orally at a dose of 1000 mg/m² BD as an intermittent regimen (2 weeks of treatment followed by a 1 week rest period).

Chemotherapy was given in 3 weekly cycles. Study treatment was continued for up to 6 cycles or until PD, unacceptable AEs, or surgery.

Tumour assessments were based on radiological scans every 9 weeks during treatment, and every 12 weeks thereafter. An independent response review was conducted by 2 radiologists and 1 medical oncologist; tumour response was assessed according to RECIST criteria.

“Formal statistical comparisons between the arms were not legitimate and not planned in this phase II trial.”

K-RAS analyses: Assessment of K-RAS mutational status was not performed for patients enrolled from June 2004 until October 2005.

Results: Cetuximab + XELOX vs. XELOX.

The study resulted in publication by M. Borner *et al.*²⁰ in 2008; with the authors concluding, that the “Differences in response rates between the treatment arms indicate that cetuximab may improve outcome with XELOX. The correct place of the cetuximab, oxaliplatin and

²⁰ Borner M *et al.* Adding cetuximab to capecitabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the Swiss Group for Clinical Cancer Research SAKK. *Annals of Oncology* 2008;19:1288-1292.

fluoropyrimidine combinations in first-line treatment of MCC has to be assessed in phase III trials.”

The objective PR, after external review and radiological confirmation were: 14% and 41% in the XELOX and in the XELOX + cetuximab arm, respectively. The “low response rate of 14% in the XELOX arm is of concern.”

5.5.4.3. EXPERT-C study

Phase II, open-label, multicentre, 2-arm, randomised (1:1), controlled, multicenter trial investigating the neoadjuvant chemotherapy (CAPOX) followed by chemoradiation, both with or without cetuximab followed by total mesorectal excision in patients with MRI-defined high-risk rectal cancer. Afterwards adjuvant chemotherapy was given with or without cetuximab.

The trial was sponsored by the Royal Marsden NHS Foundation Trust (RMH). Cetuximab and a financial grant were provided by Merck KGaA. Capecitabine was provided by Roche, and oxaliplatin by Sanofi-Aventis. Patients were enrolled at 15 European centres.

The primary endpoint was CR: defined as pathological CR or radiological CR in patients who declined surgery, in K-RAS and BRAF wild-type tumours.

Study treatments. Patients were randomised to receive 4 cycles of oxaliplatin 130 mg/m² on Day 1 with capecitabine 1,700 mg/m² Day 1 - 14 of a 3-week cycle (CAPOX) followed by chemoradiation boost with concurrent continuous capecitabine 1650 mg/m²/day), total mesorectal excision, and 4 cycles of adjuvant CAPOX, or the same regimen with the addition of the standard cetuximab regimen.

Tumour assessments were based on radiological scans scheduled 12 weeks after start of treatment (end of neoadjuvant chemotherapy), after 22 weeks (end of chemoradiation), after the end of the post-operative adjuvant therapy, and during further follow-up every 12 months. Investigators assessed tumour response according to RECIST criteria.

K-RAS analyses: Enrolment to this study started in September 2005; a restriction of the enrolment to patients with K-RAS wild-type tumours and subgroup analyses according to K-RAS mutational status were introduced by a protocol amendment in October 2008.

Of the 164 patients (ITT population); 90.9% (149/164) were evaluable for K-RAS mutation status; out of these 60.4% (90/149) had K-RAS wild-type tumours.

Results for cetuximab + CAPOX + CRT vs. CAPOX + CRT are tabulated in Table 3 above.

5.5.4.4. FUTURE study

Included a treatment arm in which cetuximab was given in combination with the UFOX regimen (IV oxaliplatin + oral tegafur-uracil) - see above.

5.5.4.5. Evaluator’s summary of ‘various other studies’

This heterogeneous group of studies listed above is of little relevance to the current application. The studies are summarized by the sponsor in the Clinical Overview. Overall, the trials were un-evaluable as the study reports were not available.

The studies, some of them that resulted in published papers, were reported with various degrees of detail; for some only preliminary results or tables were available (e.g. EXPERT- C, CECOG CORE 1.2.002 studies).

The population recruited for the studies did not match the targeted population for this application (mostly noted in EXPERT and CELIM studies), or employed cetuximab with a variety of combination chemotherapy regimens; that were inconsistent with the regimens recommended in the indications for cetuximab.

This was particularly noticeable with oxaliplatin-based chemotherapy combinations. The oxaliplatin dose varied depending on the regime used (e.g. FOLFOX4, FOLFOX6, and XELOX); the lowest being for the FOLFOX4 regimen. The significant number of the chemotherapy regimens involved oral fluoropyrimidine; the combinations that are clearly no longer recommended with cetuximab (e.g. combination with XELOX).

The purpose of this application was to support the indication for cetuximab in 1st line treatment in combination with irinotecan-based chemotherapy or continuous infusional 5-FU/FA + oxaliplatin. Very little supportive data could be drawn from the studies presented above under *Various other studies*.

5.6. Efficacy across studies

The sponsor presented efficacy results across a heterogeneous group of studies with cetuximab in addition to irinotecan and a variety of oxaliplatin-based chemotherapy regimens.

The studies used for support of this application employed cetuximab in combination with irinotecan based chemotherapy, and different continuous infusional 5-FU/FA + oxaliplatin regimens (FOLFOX4, OxMdG, and FOLFOX6).

The results of all the studies were presented to highlight the benefit of adding cetuximab to the chemotherapies used. The sponsor concluded from the presented data, that no relevant differences were observed between these regimens.

5.6.1. Efficacy of cetuximab + infusional 5-FU + oxaliplatin vs. chemotherapy alone

- FOLFOX-based therapy in combination with cetuximab demonstrated benefit over FOLFOX alone in patients with K-RAS wild type tumours. (OPUS and subgroup of COIN study and comparison with FOLFIRI regime [CRYSTAL] as a backbone).
- The Phase II OPUS study investigated infusional 5-FU/FA + oxaliplatin with or without cetuximab and showed consistent efficacy results for all endpoints in the K-RAS wild type population.
- The significant increases for ORR and PFS were demonstrated for the addition of cetuximab to FOLFOX4. There was a statistically significant benefit for response (OR 2.55) and PFS (HR 0.57) and a clear benefit of 4.3 months for median OS.
- The increases of ORR, median PFS, and median OS were of the same magnitude as those in the Phase III CRYSTAL study in which cetuximab was added to the FOLFIRI regimen.

This is supported by the results of the COIN study which showed advantages in terms of ORR and PFS in the subgroup of patients treated with OxMdG (infusional 5-FU/FA + oxaliplatin; comparable with FOLFOX4 and FOLFOX6).

- Data from patients treated with the OxMdG regimen in the COIN study supported the findings for response (OR 1.44) and PFS (HR 0.768). There was no benefit for OS in the COIN study.

Overall, the results obtained with cetuximab in combination with infusional 5-FU + oxaliplatin compare well with those from CRYSTAL study in which there was a statistically significant benefit for ORR (OR 2.069), PFS (HR 0.696), and OS (HR 0.796; benefit in median OS of 3.5 months) in the K-RAS wild type population underlining the predictive value of K-RAS in mCRC.

The magnitude of the benefits resulting from addition of cetuximab to the irinotecan-based FOLFIRI regimen was similar to those observed in OPUS study, when cetuximab was added to FOLFOX.

Evaluator's comments: The trials using cetuximab + oxaliplatin-based chemotherapy have not demonstrated convincingly improved OS, and overall the results of the studies combining cetuximab with oxaliplatin-based regimens are inconsistent.

The indications for the 1st line treatment of mCRC for cetuximab, require that the “continuous infusional 5FU/FA + oxaliplatin” regimen is to be used. So far, 2 studies fulfilled these criteria; the OPUS and the COIN study.

OPUS trial: This Phase II study failed to demonstrate the statistically significant survival benefit for the overall, or K-RAS wild type population. The benefits obtained for other efficacy endpoints in K-RAS wild population are described in relevant sections of this report.

The study used FOLFOX4 regimen, which employs “continuous infusional 5FU/FA”.

The evaluator is not aware of any Phase III trial involving oxaliplatin-based chemotherapy regimen and cetuximab that demonstrated the OS benefits in the setting of advanced CRC.

COIN study: The OxMdG regimen (oxaliplatin + infusional 5-FU/FA) is comparable, but not identical to both FOLFOX4 and FOLFOX6. The results from COIN study are difficult to interpret due to methodological considerations and the variation of the outcome (PFS and OS) according to the fluoropyrimidine based treatment regimen. (Refer to section on *Investigator sponsored trials: COIN study (and NORDIC VII)*, above). The study was underpowered to show superiority in any subgroups.

The positive trend claimed for PFS for cetuximab + OxMdG arm is an observation to be acknowledged, but cannot be used to support any efficacy claim for this study, or to be generalised to “cetuximab and oxaliplatin + infusional 5FU/FA regimens”.

Additionally, in the COIN study, the OS for K-RAS wild population was worse in the cetuximab + OxMdG group (16.3 months vs. 18.2 months).

Of note, neither OPUS nor COIN study was powered to show a survival benefit in the K-RAS wild-type population.

A pooled analysis of the results of the OPUS study and the OxMdG subgroup of COIN study treated with infusional 5-FU/FA + oxaliplatin (OxMdG subgroup) has also been also presented.

A benefit of adding cetuximab to standard infusional 5-FU/FA + oxaliplatin in 1st line combination chemotherapy regimens for mCRC has been claimed based on ORR and PFS.

Further statistical argument was presented: “The corresponding ORs and HRs considering data from a total of 423 patients compare well to those observed in the *CRYSTAL trial* (n = 666) in which cetuximab was added to FOLFIRI.”

Evaluator's comment: The presented argument based on pooled data from 2 methodologically vastly different studies is hardly convincing.

Of note, no conclusions could be drawn from any of the secondary endpoints of COIN study because responses were not confirmed by repeat scans, and external radiological review was not undertaken. Pooling these 2 studies for analysis seems meaningless.

As a reminder, in OPUS trial, the net benefit (although statistically significant) in PFS in the K-RAS wild population was only 0.9 months²¹. In the COIN study, barely “a positive trend” in terms of PFS was noted for cetuximab + OxMdG arm.

5.6.2. Efficacy of cetuximab + infusional 5-FU + oxaliplatin vs. cetuximab + FOLFIRI

“A study reported by Tournigand *et al.*²² established that FOLFOX and FOLFIRI, as the most frequently used 1st line chemotherapies, have similar efficacy in the 1st line treatment of patients with mCRC.”

²¹ Sponsor correction: the net benefit in PFS in the K-RAS wild type population was 1.1 months.

Evaluator's comments: The study entitled: "*FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR study*" was conducted in late 90s.

Patients were randomized to FOLFIRI followed on progression by FOLFOX6 (Arm A), or to FOLFOX6 followed by FOLFIRI (Arm B); 113 patients per arm.

The primary endpoint was the second PF time. The response was assessed by CT scans according to WHO criteria subject to external review by at least 2 radiologists.

The study was designed for the 2-sided log-rank test to have 80% power to detect a 20% difference in the proportion of patients without progression at 15 months (60% in Arm A, 40% in Arm B; type 1 error 5%, type 2 error 20%).

Median 2nd PFS was 14.2 months in Arm A vs. 10.9 months in Arm B ($p = 0.64$). Median survival was 21.5 months in 109 patients allocated to FOLFIRI then FOLFOX6 vs. 20.6 months in 111 patients allocated to FOLFOX6 then FOLFIRI ($p = 0.99$).

The authors concluded, that: "both sequences achieved a prolonged survival, and similar efficacy. The toxicity profiles were different." .. "Our study failed to demonstrate that a sequence of first-line irinotecan followed by second-line oxaliplatin, or the reverse sequence beginning with first-line oxaliplatin, was better than the other. RR, PFS first-line, second PFS, and OS did not differ between the two arms with statistical significance. However, our first objective, second PFS, did not provide a good evaluation of the two lines of treatment."

It is not certain if this was equivalence, non-inferiority, or even a superiority trial. From the available data, it is not obvious, if the clinically important effect size (δ) was defined a priori. No firm conclusions could be reached from the GERCOR study.

Based on these results, the 2 investigator-sponsored trials (CECOG CORE 1.2.001²³ and CELIM study²⁴) were conducted to determine whether FOLFOX or FOLFIRI was the better combination partner for cetuximab.

An overall patient population of 882 patients, of whom 441 had confirmed K-RAS wild-type status, was treated with the combination of cetuximab and continuous infusional 5-FU/FA + oxaliplatin in the studies described above.

The efficacy results for the 2 regimens were comparable in both studies, with slight advantages for the FOLFOX-based therapy.

Within the K-RAS wild type population, HRs in general favoured the combination of cetuximab + FOLFIRI over FOLFIRI alone with the exception of OS in patients with ECOG PS2 and in patients who were 65 years of age or older (data not shown).

Evaluator's comment: From the regulatory perspective, data from these 2 investigator-sponsored trials are non-evaluable. Of note, The FOLFOX6 regimen uses slightly higher dose of oxaliplatin than FOLFOX4.

Based on the above data it is not possible to conclude about the equivalence of the 2 chemotherapy regimes, or about the advantage of oxaliplatin-based regimen (FOLFOX6) over FOLFIRI. Refer to comments of the individual studies. Pooling data of the 2 weak studies does not add to the argument.

²² Tournigand C *et al.* FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR study. *J Clin Oncol* 2004; 22: 229-237.

²³ FOLFOX6 vs. FOLFIRI in patients with mCRC

²⁴ FOLFOX 6 vs. FOLFIRI as neoadjuvant treatment in unresectable colorectal liver metastases

The studies (cetuximab + infusional 5-FU + oxaliplatin vs. chemotherapy alone) demonstrated that cetuximab in combination with infusional 5-FU + oxaliplatin were an effective therapy with consistent results across studies and endpoints, and thus confirmed the results observed in the pivotal OPUS study. These findings were independent of the actual continuous infusional 5-FU regimen used, namely FOLFOX4, OxMdG, FOLFOX6, or any other comparable regimen investigated.

The above findings reflect the established clinical practice that considers the most-common FOLFOX-like regimens, which differ with respect to the dosing schedules for oxaliplatin, FA and the 5-FU (bolus and continuous infusional administration), as interchangeable because similar efficacy is observed with these regimens.

This perspective is widely accepted by the oncological community despite the fact that the comparability of different FOLFOX-like regimens was never investigated in a prospective clinical trial; nor is any review article available considering this question. Clinicians however, may consider the use of FOLFOX6 instead of FOLFOX4 due to its convenience for the patient. (The patient has to visit the clinic once more often to receive FOLFOX4 as compared to FOLFOX6.) FOLFOX4 requires 5-FU bolus administration at 2 consecutive days each followed by continuous infusion over 22 hours; FOLFOX6 is applied with only one 5-FU bolus administration followed by a continuous 46 hour infusion of 5-FU.

The comparability of cetuximab + FOLFOX and cetuximab + FOLFIRI is supported by the results of 2 Phase II studies the CECOG CORE 1.2.001 and CELIM studies. Both studies show overall comparable results for FOLFOX in combination with cetuximab and for FOLFIRI in combination with cetuximab. The results are similar to those observed in the pivotal studies; CRYSTAL and OPUS studies for the combination of cetuximab with chemotherapy.

Evaluator's comment: Again, these 2 investigator-sponsored studies are un-evaluable, and it is not possible to draw any firm conclusions on the comparability of FOLFOX6 and FOLFIRI regimens.

5.6.3. Efficacy of cetuximab + oral fluoropyrimidine + oxaliplatin

Efficacy results for the standard weekly cetuximab regimen given in combination with oral fluoropyrimidines (capecitabine in XELOX and CAPOX regimens, UFT in the UFOX regimen) are provided.

Overall, the studies using the XELOX/CAPOX regimen in combination with cetuximab showed different results. The results in studies using XELOX in combination with cetuximab are mixed, possibly due to differences in the duration of therapy.

The 2 studies using capecitabine show a benefit for the addition of cetuximab to chemotherapy alone (SAKK²⁵ and EXPERT-C²⁶ studies), while the COIN study does not support the addition of cetuximab.

The observations reported for the SAKK study suggesting that the addition of cetuximab to XELOX might improve clinical outcome are not supported by the data for those patients in the COIN study who received XELOX, where no significant benefit was observed for the addition of cetuximab even in patients with K-RAS wild-type tumours.

Conversely, data for the addition of cetuximab to CAPOX regimen (reduced capecitabine dose as XELOX regimen in the COIN study) in the EXPERT-C study, showed the addition of cetuximab to confer a significant advantage in terms of ORR in the period of neoadjuvant chemotherapy, as well as during chemoradiation. This observation was coupled with HRs of 0.62 and 0.27 in favour of cetuximab for PFS and OS, respectively.

²⁵ Cetuximab + XELOX vs. XELOX in patients with mCRC

²⁶ Cetuximab + CAPOX + CRT vs. CAPOX + CRT in patients with high risk rectal cancer

In both the SAKK and EXPERT-C studies, tolerability, and thus possibly also efficacy, may have been better because patients were treated with XELOX for a limited duration: 6 cycles (18 weeks) of therapy in the SAKK study, and 2 episodes of 12 weeks each in the EXPERT-C trial. Additionally, in the EXPERT-C study the dose of capecitabine matched the dose used in the COIN study after the amendment, and was thus lower than in the other studies.

In the FUTURE trial²⁷ the ORR was lower and PFS was shorter in the UFOX arm than in the FOLFOX arm, and than in other studies using cetuximab in combination with infusional 5-FU/FA + oxaliplatin.

No firm conclusion on the efficacy of addition of cetuximab to the employed chemotherapies can be drawn, as the study did not include a control group without cetuximab. The study also had clear limitations due to a high rate of major protocol deviations.

In summary, the 2 studies with other chemotherapy backbones involving oral fluoropyrimidines showed less beneficial results for cetuximab. These studies are: COIN study (cetuximab + XELOX) and the FUTURE study (cetuximab + UFOX).

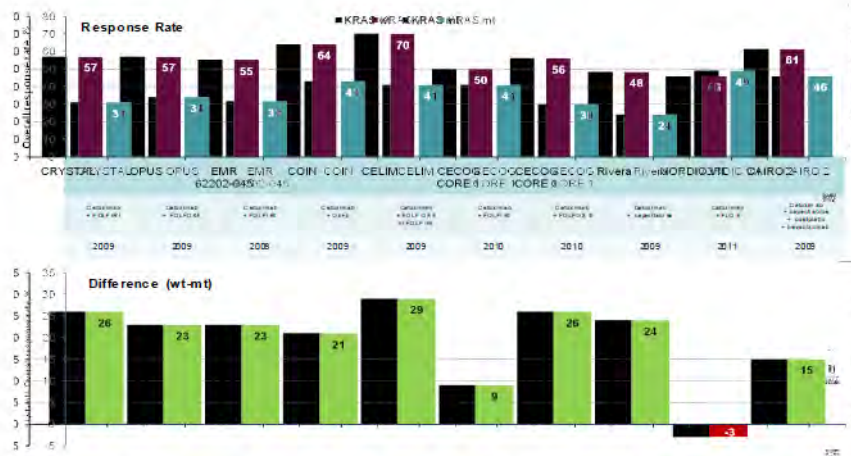
Overall, the results in studies using XELOX in combination with cetuximab are mixed, possibly due to differences in the duration of therapy. No definitive conclusions can be drawn from these studies. The combination of cetuximab with oral fluoropyrimidine regimens may need further investigation.

5.6.4. Evaluator's summary of efficacy across studies

- The sponsor concluded that studies investigating cetuximab in combination with irinotecan-based chemotherapy and continuous infusional 5-FU/FA demonstrate consistent results across studies and efficacy endpoints and support the indication for 1st line mCRC, adapted earlier via the SRN (September 2011).
- Studies investigating cetuximab in combination with continuous infusional 5-FU/FA + oxaliplatin showed that it is an effective therapy with consistent results across studies and efficacy endpoints.
- The overall efficacy profile for the K-RAS wild-type population in these studies is consistent.
- The sponsor supported the above statement with a graphic representation of response rate across 9 different studies (Figure 1).

²⁷ Cetuximab + UFOX vs. cetuximab + FOLFOX4 in patients with mCRC

Figure 1. Response rate in K-RAS wild type and K-RAS mutant populations of cetuximab studies in First-Line Treatment of Metastatic Colorectal Cancer



CRYSTAL: see 5.4.1.150-CRC2; OPUS: see 5.4.1.151-CRC2; EMR 62202-045: A phase I, open-label, multicentre, pharmacokinetic, pharmacodynamic and pharmacogenomic study of the epidermal growth factor receptor targeting antibody cetuximab administered every week or every 2 weeks in the first-line setting in patients with advanced colorectal cancer to determine the recommended dose (not addressed in this documentation, as not considered pivotal to the assessment); see 5.4.1.81-CRC2; COIN: see 5.4.1.152-CRC2; CELIM: see 5.4.1.153-CRC2; CECOG CORE 1.2.001: see 5.4.1.154-CRC2; Rivera (not addressed in this documentation, as not considered pivotal to the assessment): see 5.4.1.155-CRC2; NORDIC VII: see Appendix 6; CAIRO 2 (not addressed in this documentation, as not considered pivotal to the assessment): see 5.4.1.96-CRC2

Evaluator's comment: The sponsor commented that some of the studies presented as a bar graph were not addressed in this submission, as they were “not considered pivotal to the assessment.”

The presented graph is meaningless in the context of the current application. It includes studies with vastly different chemotherapy regimens investigated with cetuximab (e.g. CAIRO 2 study involving capecitabine + oxaliplatin + bevacizumab +/- cetuximab).

- Studies with other chemotherapy backbones including oral fluoropyrimidine regimens showed less beneficial results for cetuximab. Since no definitive conclusions could be drawn from these studies further investigations may be needed.
- The submitted data underline the favourable benefit-risk balance for the addition of cetuximab to continuous infusional 5-FU/FA regimens.
- Overall, the combinations of cetuximab with continuous infusional 5-FU/FA and oxaliplatin or irinotecan showed acceptable and manageable toxicity in the treatment of 1st line mCRC. The corresponding safety profile is adequately reflected in the current PI for cetuximab.

Based on the explanations above, the Sponsor is of the opinion that the chemotherapy regimen used in combination with cetuximab for the treatment of mCRC should be specified to “continuous infusional 5-FU/FA plus oxaliplatin” as per current indications in the PI.

Evaluator's comment: As the outcomes of oxaliplatin-based chemotherapy regimens combined with cetuximab are inconsistent, and in some instances conflicting, much of the argument involved pooling of the data involving methodologically weak studies.

The case for oxaliplatin-based chemotherapy in combination with cetuximab is heavily weighted on a pivotal Phase 2, Opus study, which failed to demonstrate the significant survival benefit.

5.7. Conclusions regarding efficacy

In the context described in this report's overview (above), the indication for cetuximab in combination with chemotherapy regimens for the treatment of mCRC was re-evaluated.

In this submission the 1st line palliative chemotherapy for advanced CRC is addressed, involving the combination of cetuximab with irinotecan-based chemotherapy and continuous infusional 5-FU/FA plus oxaliplatin.

Overall, the results presented for both irinotecan- and oxaliplatin-based combination therapies are not impressive, even in the K-RAS wild type population.

The conclusions, below, are focused on efficacy outcomes from 2 company-sponsored pivotal trials that were previously evaluated by the TGA, and one large NCRI-sponsored [COIN] study, that led to the review of present indications for cetuximab in 1st line indications for mCRC.

The important point to consider in evaluating the outcome of the studies is that the benefits for the targeted population, i.e. patients with K-RAS wild type tumours, was estimated based on retrospective exploratory analyses, and that statistical significance levels (alpha values) were not adjusted for the multiplicity of statistical tests.

The updated data submitted for the CRYSTAL (n = 1198) and OPUS studies (n = 337) is consistent with those data (OS) available previously to the TGA in November 2009.

The COIN study, which is difficult to interpret, basically put into question the combination of cetuximab with oxaliplatin as a backbone of chemotherapy regimens.

The numerous submitted investigator-sponsored studies and the analyses of pooled data are of interest, but cannot be relied on in decision-making.

- Cetuximab added to irinotecan (FOLFIRI) chemotherapy

Cetuximab added to irinotecan (FOLFIRI) chemotherapy provided extra benefit for K-RAS wild population based on the outcome of Phase III CRYSTAL study, and these results are not disputed here. "This was also the first time that the addition of an EGFR antibody therapy to a standard continuous 5-FU-based regimen, in 1st line mCRC treatment, resulted in an overall survival benefit."

The retrospective analysis of patients with K-RAS wild-type tumours demonstrated that the addition of cetuximab to FOLFIRI resulted in a clinically relevant and statistically significant benefit in tumor-related outcomes to the standard irinotecan-based chemotherapy (considered by some as one of the most effective chemotherapy combinations in the initial treatment of CRC). The addition of cetuximab to FOLFIRI prolonged median OS from 20.0 to 23.5 months (p = 0.0094) compared with FOLFIRI alone. Consistently, PFS (primary endpoint) and RR were as well significantly increased in patients treated with cetuximab.

In the wild type K-RAS subgroup, PFS (assessed by an IRC) was increased by statistically significant 1.5 months (p = 0.001). Elderly K-RAS wild type patients and patients with ECOG PS > 2 derived no benefit from cetuximab added to FOLFIRI. For the overall population, PFS benefit reached marginal significance for the cetuximab + FOLFIRI combination group (p = 0.0479), and there was a non-significant benefit for OS in the overall population (p = 0.04).²⁸

To obtain the picture of complexity, the results of another study involving cetuximab in combination with irinotecan, also evaluated previously by the TGA, is mentioned here: Unlike in other trials, cetuximab did not significantly affect PFS or OS in wild type K-RAS subjects in the EPIC study (2nd line therapy comparing cetuximab and irinotecan vs. irinotecan alone).

- Oxaliplatin-based chemotherapy in combination with cetuximab

By comparison, the trials using oxaliplatin-based chemotherapy in combination with cetuximab have not shown improved OS, and this failure has raised the possibility of a negative interaction between oxaliplatin and cetuximab.

²⁸ Sponsor clarification: p = 0.04 indicates statistical significance according to the study criteria for significance.

In the Phase II OPUS study, the addition of cetuximab to FOLFOX4 in patients with K-RAS wild type tumours led to a significantly longer PFS time, a significantly higher OR, and improvement in OS time compared with patients receiving FOLFOX4 alone (NS). The updated analysis with later cut off data showed improved PFS in K-RAS wild population; 8.3 months vs. 7.2 months ($p = 0.0064$). The updated OS data were 22.8 months vs. 18.5 months ($p = 0.39$), respectively for the cetuximab + FOLFOX 4 vs. FOLFOX 4 alone.

The primary objective, the ORR was not met in the overall population. The PFS time and OS were similar in the 2 treatment groups for the ITT population.

Of note, with the exception of the primary efficacy endpoint (OR in ITT population), all further efficacy analyses were considered exploratory, and p values were not adjusted for the multiplicity of statistical testing.

Retrospective analyses of these 2 studies, the CRYSTAL and OPUS trials, supported overall efficacy in patients with the K-RAS wild type subgroup. The OPUS study in particular led to the conclusions that cetuximab should not be used in the treatment of CRC patients whose tumours have K-RAS mutations, or for whom K-RAS tumour status is unknown. In these patients negative effects PFS and OS were seen as add-on to FOLFOX4.

The outcome of the large investigator-sponsored COIN trial (total randomized patients $n = 2245$) is not clear cut. The primary analysis demonstrated that the addition of cetuximab to oxaliplatin-based chemotherapy conferred no benefit in relation to PFS or OS, irrespective of K-RAS mutational status, although RR was significantly improved in patients with K-RAS wild-type tumours. Of note, there was a negative outcome for the comparison of cetuximab + XELOX treatment arm vs. XELOX alone. This resulted in the fluoropyrimidine regimen based on oral capecitabine being no longer considered by the sponsor as a viable combination with cetuximab.

It has been postulated, that the lower dose of capecitabine subsequently administered in XELOX arm may also conceivably have been suboptimal for the treatment of mCRC. "Indeed, closer inspection of the results suggested that patients with K-RAS wild-type tumors who received XELOX + cetuximab derived no additional benefit, whereas those who received infusional 5-FU/oxaliplatin (OxMdG) + cetuximab had prolonged PFS time (HR 0.77, $P = 0.056$) compared with those receiving OxMdG alone."

Additionally, pooled analyses of the results of the OPUS study and the OxMdG subgroup of COIN study treated with infusional 5-FU/FA + oxaliplatin (OxMdG subgroup) have been discussed in the [sponsor's] Overview in support of the oxaliplatin-based combination chemotherapy. These are of interest, but do not add much weight to efficacy data.

- Summary

In summary, the efficacy of oxaliplatin-based regimens in combination with cetuximab had been questioned for 1st line indication of mCRC. This led to review of the data from company-sponsored trials and a number of investigator-led studies.

A number of pooled analyses have also been presented, as well as comparisons with irinotecan-based chemotherapy regimens in combination with cetuximab, capitalizing on similarities in statistical comparisons (e.g. comparable HRs).

In all of the studies, the results for the targeted K-RAS wild population were based on retrospective subgroup analyses, and the studies were not powered to show the difference in the subgroups. When considered with the initial approval for 1st line indication in mCRC, the absolute gains were small, but statistically significant and often clinically meaningful.

Thus, the outcomes of the studies are far from clear-cut, and the results are less convincing for the combination of cetuximab with oxaliplatin based regimens, including "continuous infusional 5-FU/FA + oxaliplatin."

There have been striking inconsistencies in efficacy data of the trials involving cetuximab with oxaliplatin-based chemotherapy, and no survival benefit has been convincingly demonstrated.

- Other developments

The recently published online preliminary results of a “large, phase III, European trial” add further uncertainty to the efficacy of oxaliplatin-based chemotherapy combined with cetuximab. The PETACC8 trial²⁹ was originally designed to compare 12 cycles of FOLFOX4 vs. FOLFOX4 + cetuximab. “In the multicenter randomized study, the combination of FOLFOX4 plus cetuximab (Erbix) did not prolong disease-free survival, compared with FOLFOX alone, even in patients with KRAS wild-type tumours. The disease-free survival rate at 3 years was 75.1% in 791 patients given FOLFOX 4 with cetuximab and 78% in 811 patients in the control group.”

“These preliminary results of the PETACC8 cooperative group trial were presented for the first time on June 29 at the European Society for Medical Oncology (ESMO’s) 14th World Congress on Gastrointestinal Cancer. The disappointing outcome follows a negative report from the North Central Cancer Treatment Group (NCCTG) N0147 trial, which also looked at the benefit of cetuximab added to FOLFOX in the adjuvant colorectal cancer setting (Alberts *et al.* 2012³⁰).”

“The current study specifically looked at patients with K-RAS wild type. These are patients who should, in theory, still be able to respond to an epidermal growth factor receptor (EGFR) inhibitor, such as cetuximab.”

“The probability for a positive result in the final analysis is very low.” “Cetuximab might have a different form of activity on micrometastatic disease compared to that observed in stage IV disease.”

In July 2012 FDA granted approval for cetuximab in combination with FOLFIRI in 1st line treatment of patients with K-RAS mutation-negative (wild type), EGFR-expressing mCRC as determined by FDA-approved tests for this use. Oxaliplatin-based chemotherapy in combination with cetuximab is not approved for mCRC in the US in any line of treatment.

- Conclusion

The evaluator concludes that the submitted data, and overall information available to date, supports cetuximab in combination with irinotecan-based chemotherapy in 1st line indication for mCRC, but does not support the combination with “continuous infusional 5-FU/FA + oxaliplatin.”

6. Clinical safety

6.1. Background

The safety profile of cetuximab is well known and characterised, based on previous RCTs in mCRC, SCCHN, and NSCLC.

“The safety profile in the target mCRC population with K-RAS wild-type tumour status was evaluated in CRYSTAL and OPUS studies. There were no major differences in the safety profile of cetuximab between the K-RAS wild-type population and the overall safety population.”

The evaluator noted that the overview of the K-RAS safety population, based on 4 controlled, randomized studies in mCRC (NCIC, EPIC, CRYSTAL, and OPUS studies), was submitted and included as part of pre-ADEC advice in October 2009 (submission 2008-03405-3-4).

²⁹ “Adjuvant Cetuximab Fails to BOOST FOLFOX in Stage III Colon Cancer” “Oncology STAT”; July 17, 2012 (online).

³⁰ Alberts *et al.* 2012 Effect of Oxaliplatin, Fluorouracil, and Leucovorin With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon Cancer: A Randomized Trial. *JAMA* 2012;13:1383-1393

In the overall safety population (n = 3369) of the 4 RCTs, 37% (1250/3369) of subjects were evaluable for K-RAS status, and of these 62% (779/1250) had tumours with K-RAS wild type genes.

The general conclusions of the safety analysis were very similar to the conclusions stated above by the sponsor (taking into account the low proportion of subjects with K-RAS wild type tumours).

Overall, the frequencies of SAEs, including treatment-related and cetuximab-related SAEs, did not reveal major differences between the 2 populations in these 4 RCTs. Similar conclusions were drawn for AEs leading to discontinuation of cetuximab and/or study treatment. Imbalances in neutropenia were found, but were not considered clinically relevant.

“The profiles of the AE neutropenia and corresponding laboratory variables differed in the safety and K-RAS wild type populations of the studies in which cetuximab was given in combination with chemotherapy. In the K-RAS wild type population, frequencies in the cetuximab groups tended to be higher than in the respective control groups. However, there was no consistent pattern across studies and in study CA225006 (EPIC study) the differences were explained by an additional analysis. It is considered that imbalances may be due to differences in treatment duration or exposure.”

6.2. Overview of studies providing safety data

The current review of safety data involved the following studies supporting the use of cetuximab as an add-on option to continuous infusional 5-FU/FA + oxaliplatin: Table 4.

Table 4. Metastatic CRC trials by infusional 5-FU regimen.

Trial	Patients treated*	Oxaliplatin IV	5-FU bolus IV	5-FU continuous IV infusion	FA	Cycle duration
EMR 62202-47(OPUS) FUTURE CECOG CORE 1.2.002	169 150 70	85 mg/m ² 2 h day 1	400 mg/m ² day 1	600 mg/m ² 22 h	200 mg/m ² days 1+2	2 weeks
COIN	281	85 mg/m ² 2 h day 1	400 mg/m ² day 1	2400 mg/m ² 46 h	175 mg day 1	2 weeks
CECOG CORE 1.2.001 CELIM	77 54	100 mg/m ² 2 h day 1	400 mg/m ² day 1	2400 mg/m ² 46 h**	400 or 200 mg/m ² (RAC or L) day 1	2 weeks

FA = folinic acid, L = L-form, IV = intravenous, RAC = racemic form

* Safety population;

** in CECOG CORE 1.2.001 increase to 3000 mg/m² was allowed

OPUS: see [5.4.1.151-CRC2](#); 4; FUTURE: refer to [Appendix 3](#), CECOG CORE 1.2.002: see [5.4.1.156-CRC2](#);

COIN: see [5.4.1.152-CRC2](#); CECOG CORE 1.2.001: see [5.4.1.154-CRC2](#); CELIM: see [5.4.1.153-CRC2](#);

The data are based on study reports for completed company-sponsored trials and the available and published data for non company-sponsored trials. The review focuses on the overall safety population, as the K-RAS mutation status was not available in all studies.

In all company-sponsored trials, treatment-emergent AEs (during treatment and up to 30 days after last dose of study drug) irrespective of relationship to study treatment are presented. This may not be the case in the other trials. Data comparison across trials has some limitations because of differences in data documentation, analysis and presentation of safety results, i.e. pre-specified AE documentation, different coding dictionaries and versions.

The studies involved in safety analysis included:

- OPUS study and the OxMdG subgroup of COIN - trials that involved comparison of cetuximab and infusional 5-FU/FA + oxaliplatin vs. infusional 5-FU/FA + oxaliplatin alone.

- CECOG CORE 1.2.001 and CELIM studies - trials that compared cetuximab and infusional 5-FU/FA + oxaliplatin vs. cetuximab and FOLFIRI.
- CECOG CORE 1.2.002 and FUTURE studies (FOLFOX arm).

6.3. Safety results – general comments

Based on the additional safety data observed in the above studies, the safety profile of cetuximab in combination with infusional 5-FU + oxaliplatin is unchanged as compared to that reported earlier. However, in the COIN study, a significantly higher incidence of Grade ≥ 3 diarrhoea was observed for patients in the cetuximab + XELOX group (26%) vs. the XELOX alone (15%), leading to frequent dose reductions of both, capecitabine and oxaliplatin and a protocol amendment that defined 850 mg/m² BD as the capecitabine dose for patients treated with cetuximab. The sponsor observed, that in other trials of cetuximab + XELOX or XELIRI similar results for Grade 3/4 diarrhoea was reported; in none of these studies was it reported to be a major issue.

In the 6 selected above studies, 801 patients (safety population) were treated with cetuximab in combination with continuous infusional 5-FU/FA + oxaliplatin. The AEs observed were consistent with the known safety profiles of cetuximab, oxaliplatin and the chemotherapy agents employed. The incidence of the most frequent Grade 3/4 AEs was generally in the same range. The incidence of neutropenia ranged from 24% - 34%.

Neurotoxicities generally reported as Grade 3/4 peripheral neuropathy or peripheral sensory neuropathy are known side effects of oxaliplatin and had an incidence of 1.2% - 6.3%. In the COIN study a higher frequency (14.0%) was reported. The incidence of neurotoxicity was not increased in combination with cetuximab compared to the comparator arm in the randomised controlled trials; OPUS and COIN studies.

The incidence of palmar-plantar erythrodysesthesia (range 0 - 6%) is known for fluoropyrimidines and the increased frequency is a known interaction with cetuximab.

In summary, the safety profile of cetuximab in combination with continuous infusional 5-FU/FA + oxaliplatin is unchanged as compared to that reported earlier. Considering the impact of severe diarrhoea on XELOX administration, a statement on the interaction with capecitabine and oxaliplatin (XELOX) has been included in the PI: "In combination with capecitabine and oxaliplatin (XELOX) the frequency of severe diarrhoea may be increased." (*Interactions with other medicines* section). (submission 2011-02844-3-4)

Furthermore, the statement on cardiovascular disorders was updated to reflect, besides age, the PS: "An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. In some studies association with age ≥ 65 years has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account." (*Precautions* section)

Finally, a statement on the efficacy results in the pivotal CRYSTAL study was added: "Patients with K-RAS wild-type tumours and an ECOG performance status of > 2 or who were 65 years of age or older, had no benefit in overall survival time, when cetuximab was added to FOLFIRI." (*Clinical trials* section)

6.4. Patient exposure

It is not clear, what is the exposure to Erbitux in combination with irinotecan or oxaliplatin-based chemotherapy regimens.

6.5. Summary of safety from individual studies

6.5.1. Pivotal studies

6.5.1.1. OPUS study (Update on safety, January 2012)

The safety population included 338 patients: 169 treated with cetuximab + FOLFOX4 and 168 with FOLFOX4 alone.

The safety outcomes of this pivotal study were already described in previous evaluations. The safety results were generally consistent with the known safety profile of cetuximab and the other treatments used in this trial.

The incidence of most AEs was similar in both treatment groups, except for known side effects of cetuximab. All AEs reported more frequently for the combination treatment with cetuximab + FOLFOX4 compared to FOLFOX4 were known side effects of cetuximab.

The frequency of palmar-plantar erythrodysesthesia syndrome, a known side-effect of 5-FU was increased in combination with cetuximab compared to FOLFOX4 alone (11.2% vs. 4.2%).

The incidence of Grade 3/4 cardiac AEs was higher in patients receiving cetuximab + FOLFOX4 (8/170, 5%) compared with those receiving FOLFOX4 alone (0/168).

Both, the increased frequency of palmar-plantar erythrodysesthesia syndrome and an increased risk of cardiac ischemia including MI and CCF are listed in the PI of cetuximab.

The frequency of SAEs was higher in the cetuximab + FOLFOX4 group than in the FOLFOX4 group (35.9% vs. 25.6%).

In general, the haematotoxicity of oxaliplatin and 5-FU was not aggravated by the addition of cetuximab.

The incidence of neurotoxicity related AEs (composite AEs) was not increased for the combination of cetuximab + FOLFOX4 compared to FOLFOX4 (8.8% vs. 11.9%).

The observed decrease in electrolytes and the increase in liver enzymes were consistent with the current PI.

There were no major differences in the safety profile of cetuximab considering subjects with K-RAS wild type tumours alone. In the K-RAS wild type population, the AE profile including special AE categories (acne-like rash, mucositis, cardiac AEs) was overall consistent with the total safety population. However, a higher incidence of neutropenia was noted in the K-RAS wild population given cetuximab in combination with chemotherapy compared with chemotherapy alone. This may be related to longer treatment duration in the cetuximab + chemotherapy group.

In summary, there were no major differences in the safety profile of cetuximab in combination with FOLFOX4 between the K-RAS wild type population and the overall safety population. The findings were consistent with the current product PI for cetuximab.

6.5.1.2. CRYSTAL study

A total of 1202 patients (safety population) were treated with cetuximab + FOLFIRI (n = 600) and with FOLFIRI alone (n = 602). The safety outcomes of this pivotal study were already well described in previous evaluations.

Evaluation of special composite AE categories including acne-like rash, infusion-related reactions including hypersensitivity reactions, mucositis, and cardiac AEs did not reveal any new findings.

The 5-FU is known to cause coronary vasospasm. The frequencies for Grade 3/4 cardiac AEs of the medical concepts "infarction/ischemia" and "congestive heart failure" were low and slightly

increased for cetuximab + FOLFIRI arm compared to FOLFIRI alone (2.3% vs. 1.2% and 0.7% vs. 0.2%, respectively).

Overall, the safety profile of cetuximab in combination with FOLFIRI in subjects with K-RAS wild type tumours was consistent with that of the total safety population.

In the K-RAS wild type population the frequency of Grade 3/4 neutropenia (documented AE) was increased in cetuximab + FOLFIRI arm vs. FOLFIRI alone (30.6% vs. 23.7%), while this was not seen in the K-RAS mutant population.

The frequency and severity of AEs observed in this study in K-RAS wild type subjects were consistent with the current product labelling of cetuximab. The study did not reveal any new safety findings.

6.5.2. Other studies

6.5.2.1. CA225085 (PK) study

Based upon the overall summary, safety is comparable between the 2 age groups, and the safety profile for the combination was consistent with the individual safety profile of each drug in adult subjects.

PD/relapse was the most common reason for discontinuation of therapy. Of the 4 subjects who discontinued due to study drug toxicity, 3 subjects experienced hypersensitivity (SAE) due to cetuximab (all Group B) and 1 subject discontinued due to Grade 4 pneumonia/sepsis and neutropenia resulting in death (Group A).

The main reasons given for cetuximab dose modifications were AEs, hypersensitivity, and non-hematologic toxicity (Grade 3 diarrhoea). The main reasons for irinotecan dose modifications were delayed non-hematologic recovery (mostly Grade 3 diarrhoea), delayed hematologic recovery, and other reasons.

Deaths: 6 subjects died within 30 days after administration of the last dose of study medication; 5 of PD, and 1 of brainstem glioma, with Grade 4 pneumonia/sepsis/neutropenia. In total, 11 subjects died of their disease (1 unknown cause of death); 35 - 174 days after the last dose of study drug.

All subjects in both age groups reported at least 1 AE. The most frequently reported on-study AEs of any grade (Groups A and B) were: diarrhoea (89% and 79%), vomiting (70% and 74%), abdominal pain (59% and 47%), headache (52% and 63%), and nausea (48% and 84%).

Treatment-related AEs were reported by 96% of the subjects in Group A, and 100% of the subjects in Group B.

There were no Grade 3/4 AEs of acneiform rash. Grade 3 AEs of infusion reaction were reported in 3 subjects (Group B); all were considered related to cetuximab. Two subjects (Group B) reported cardiac AEs that were considered possibly related to study drug (1 Grade 2 bradycardia and 1 Grade 1 tachycardia).

The profile of SAEs in both age groups was related to AEs associated primarily with irinotecan therapy.

Clinical laboratory test abnormalities were few, with most values recorded as Grade 1/2 in both age groups. Grade 4 hypomagnesaemia was recorded in 1 subject (Group A).

6.5.2.2. COIN study

The addition of cetuximab to XELOX regimen resulted in an increase of several types of AEs, including skin rash, lethargy, and GI symptoms, especially diarrhoea. These AEs occurred more frequently in patients treated with cetuximab + XELOX arm, and led to dose reductions and delays of chemotherapy.

The incidence of Grade 3/4 diarrhoea and skin rash was higher in COIN as compared to OPUS study. The COIN trial did not reveal any new safety findings. The hand-foot syndrome (PPE syndrome) is known for fluoropyrimidines, and an increased frequency is known for the combination with cetuximab.

Based on the results from the analyses for efficacy in patients with K-RAS mutant and K-RAS wild type tumours no subgroup analyses for safety were deemed necessary.

A total of 281 patients were treated with cetuximab + OxMdG and 279 patients with OxMdG alone. The following frequencies for AEs (any Grade cetuximab + OxMdG vs. OxMdG) were reported: skin toxicity (93% vs. 49%), GI toxicity (89% vs. 80%), and haematological toxicity (82% vs. 80%).

The most frequently reported ($\geq 5\%$ patients) Grade 3/4 toxicities were: decreased neutrophil (31% vs. 31%), lethargy (29% vs. 18%), diarrhoea (20% vs. 11%), skin rash (20% vs. 0%), peripheral neuropathy (14% vs. 23%), pain (12% vs. 12%), anorexia (10% vs. 4%), and stomatitis (10% vs. 5%), nausea (6% vs. 5%), vomiting (6% vs. 4%), hand-foot syndrome (6% vs. 3%), and hypomagnesaemia (6% vs. 0%).

In general, Grade ≥ 3 diarrhoea occurred with higher frequency with cetuximab + OxFp as compared to OxFp alone (24% vs. 14%). The increased gastrointestinal toxicity (especially diarrhoea) was particularly noticed in the XELOX + cetuximab arm; Grade ≥ 3 diarrhoea occurred in 26% of patients in this treatment arm.

The sponsor compared these results with the OPUS study: Grade ≥ 3 diarrhoea occurred in 8.5% of patients treated with cetuximab + FOLFOX4 and in 5.2% of patients treated with FOLFOX alone; which is a remarkably lower proportion of patients than was reported for the COIN study across all treatment groups.

High gastrointestinal toxicity resulted in dose reductions and delays, per initial protocol, of capecitabine, oxaliplatin, and cetuximab on an individual patient basis, especially in patients treated with XELOX + cetuximab.

The Interim Safety Analysis led to a capecitabine dose reductions: analysis of the toxicity data from the first 804 randomised patients (ITT population) revealed that patients in Arm B receiving XELOX had significantly higher rates of Grade ≥ 3 diarrhoea than those in other treatment groups: cetuximab + XELOX 30% vs. XELOX alone 17% ($p < 0.001$); cetuximab + XELOX 30% vs. cetuximab + OxMdG 20% ($p = 0.002$).

The published paper (T.S. Maughan *et al.* (COIN study) *Lancet Oncol*; June 4, 2011) contains additional information highlighting the seriousness of the capecitabine-based therapy + cetuximab combination: "Among all patients randomly assigned to treatment groups, treatment-related deaths were reported in 10 patients in the control group and 9 in the cetuximab group.

Of the 9 patients taking cetuximab, 8 were in the capecitabine-based therapy + cetuximab subgroup; 7 of the deaths occurred before the capecitabine dose reduction and were predominantly related to GI toxic effects. In the control group, the 10 deaths were split evenly between capecitabine-based and FU-based therapy, with no pattern to the causative toxic effects noted."

In another publication, it is stated: "In this paper, we present toxicity reported during the first 12 weeks of treatment for the first 804 patients randomised into the COIN trial. Grade 3/4 neutropenia was significantly increased in patients receiving infusional 5FU (17% without and

26% with cetuximab) compared with those taking oral capecitabine (2% without and 1% with cetuximab), and this translated into neutropenic sepsis in 4, 5, 1 and 0%, respectively.”³¹

6.5.2.3. NORDIC VII study

All safety analyses were performed on the safety population, i.e. the 568 patients who received at least 1 dose of study medication. The reporting was limited to “drug-related” AEs only.

According to the preliminary study report: “there were no unexpected adverse reactions registered during the study. The overall experience was that adding cetuximab to the Nordic FLOX regimen did not add any severe safety concern.” A comparison of safety data for K-RAS wild-type and mutant population was not available.

“Exposure to chemotherapy seemed to be reduced in terms of duration and dose for patients treated in Arm B as compared to Arm A; chemotherapy exposure in Arm C was expected to be less because of the intermittent regimen. Interestingly exposure to cetuximab is increased in Arm C as compared to arm B cetuximab may have been stopped at the same time as chemotherapy.”

The overall profile of Grade 3/4 toxicities was in line with the known safety profiles of cetuximab and the chemotherapy agents of the FLOX regimen.

Grade 3/4 neutropenia was the most frequent toxicity in all treatment arms and occurred in 48.7% patients in Arm A, 47.2% in arm B, and 49.2% in arm C. Across the treatment arms a high rate of Grade 3/4 febrile neutropenia was found, ranging from 9.4%-12.9%. These rates were higher than those in the OPUS study which employed a continuous infusional 5-FU/FA, oxaliplatin-based regimen (cetuximab + FOLFOX4: 2.4%, FOLFOX4: 1.8%).

The Nordic VII study was performed with the rather unusual Nordic FLOX regimen in which oxaliplatin is given in combination with a bolus 5-FU/FA administration; there is no continuous infusion of 5-FU.

Conclusions: As the Nordic FLOX regimen is not registered for cetuximab, modification of the PI for cetuximab to reflect preliminary results obtained from the Nordic VII study that uses this regimen was not considered appropriate.

As expected, Grade 3 skin reactions were more common in patients receiving cetuximab: Arm A: 1.1%, Arm B 22.8%, Arm C 29.2%; no Grade 4 reactions were reported. Diarrhoea was also more frequent in patients receiving cetuximab: Arm A 9.9%, Arm B 16.6%, Arm C 16.2% (all Grade 3 except 1 patient in Arm C). Sensory neuropathy was more frequent in patients without cetuximab.

6.5.2.4. CELIM study

A total of 109 patients received cetuximab with either FOLFOX6 (group A: n = 54) or FOLFIRI (group B: n = 55).

Toxicity of Grade ≥ 3 occurred in 72% of patients, the most common being skin toxicity and neutropenia. The most frequent Grade 3/4 toxicities (≥ 3 patients) by treatment group (A and B) were: 26% and 40% for skin toxicity, and 24% and 22% for neutropenia. Diarrhoea was reported for 9.3% and 18.2% of patients.

6.5.2.5. CECOG CORE 1.2.001 study

Arm A: (FOLFOX6 + cetuximab) n = 77, and Arm B: (FOLFIRI + cetuximab) n = 74: total n = 151.

The most commonly affected SOCs (Group A and B) were: skin/subcutaneous skin disorders (74.0% and 78.4%), GI disorders (71.4% and 70.3%), blood/lymphatic system disorders

³¹ Adams RA *et al.* Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. *British Journal of Cancer* 2009;100: 251-258.

(58.4% and 44.6%), general disorders/administration site conditions (48.1% and 47.3%), and nervous system disorders (45.5% and 20.3%).

Grade 3/5 AEs were reported in 68.8% of patients in FOLFOX6 + cetuximab group and in 55.4% patients in FOLFIRI + cetuximab group. The most frequent Grade 3/5 toxicities ($\geq 5\%$ of patients in FOLFOX6 group) were: neutropenia (Group A 28.6% vs. Group B 20.3%), diarrhoea (10.4% vs. 13.5%), rash (6.5% vs. 4.1%), and dermatitis acneiform (5.2% vs. 2.7%). There were no Grade 5 AEs related to study medication.

6.5.2.6. CECOG CORE 1.2.002 study

A total of 152 patients with K-RAS wild-type metastatic CRC tumours were randomised to Arm A (cetuximab q 1w + FOLFOX4); n = 75, or Arm B (cetuximab q 2w + FOLFOX4); n = 77.

The most common AEs any grade reported in patients ($\geq 30\%$) in Arm A and B were: rash (63% and 68%), neutropenia (41% and 48%), and diarrhoea (33% and 30%). The most frequent Grade 3/4 AEs reported in patients ($\geq 10\%$) of either treatment group were: neutropenia/neutrophils decreased (32% and 34%), diarrhoea (7% and 10%), and rash (15% and 16%).

6.5.2.7. FUTURE study

FOLFOX4 + cetuximab (n = 150) vs. UFOX + cetuximab (n = 151): total N = 301.

The most frequently reported AEs by SOC ($> 50\%$) were: skin/subcutaneous tissue disorders (79.3% and 88.7%), GI disorders (80.0% and 86.8%), nervous system disorders (68.7% and 69.5%), general disorders/administration site conditions (70.0% and 67.5%), blood/lymphatic system disorders (59.3% and 33.1%), and infections/infestations (52.0% and 39.7%).

The most frequent Grade 3/5 AEs ($\geq 5\%$ for cetuximab + FOLFOX group) by treatment group (cetuximab + FOLFOX4 vs. cetuximab + UFOX) were: neutropenia (28.7% vs. 0%), diarrhoea (9.3% vs. 19.2%), rash (9.3% vs. 6.6%), dermatitis acneiform (8.0% vs. 3.3%), and leukopenia (6.0% vs. 0%), and fatigue (5.3% vs. 0.7%).

6.6. Adverse reactions (drug-related adverse events)

Where information is available from investigator-sponsored trials, it is discussed under summary of individual studies, above.

6.7. Withdrawals due to adverse events

See summary of individual studies above.

6.8. Deaths and other serious adverse events

See summary of individual studies above.

6.9. Laboratory abnormalities

No significant new information available.

6.10. Post-marketing experience

This submission includes 3 PSURs (No: 8, 9 and 10), which have previously not been evaluated by the TGA, together covering the period: 1 October 2008-30 September 2011.

The sponsor stated, that a number of changes to the CCSI have been made during this time; the following have already been implemented in the Erbitux PI:

- Inclusion of AE terms: dehydration, aseptic meningitis.
- Inclusion of “increase in blood pressure” as a symptom of infusion-related reactions.
- Inclusion of the effect of cetuximab on the frequency of certain ADRs of platinum-based chemotherapies (severe leukopenia, severe neutropenia).
- Inclusion of a warning on K-RAS mutations.
- Extension of the interaction with infusional 5-fluorouracil to fluoropyrimidines.

The following changes made to the CCSI are proposed for inclusion in the Erbitux PI via this application:

- Update to the NCI-CTC definition.
- Update to sections containing information on the paediatric population to include the results of a Phase I safety and PK study of cetuximab in combination with irinotecan.
- Update to the warning on interstitial lung disease to include information on the Japanese population.

In the latest PSUR (PSUR No: 10) the following safety issues were considered for close monitoring for possible inclusion in the CCSI. All these have since been included in the CCSI and are listed in the Australian PI.

Erbitux monotherapy

- Deep vein thrombosis.
- Interstitial lung disease.
- Stevens-Johnson syndrome/toxic epidermal necrolysis.

Erbitux in combination with platinum-based chemotherapy

- The effect of Erbitux on the frequency of certain ADRs of platinum-based chemotherapy (subsequent infectious complications following severe leukopenia, severe neutropenia).

Erbitux in combination with fluoropyrimidines

- Increased frequency of cardiac events (cardiac ischaemia including MI, and congestive heart failure).

The sponsor concluded that the safety data reviewed in the PSURs indicate that the benefit-risk balance of Erbitux remains positive. All findings were either adequately covered in the current PI, or are proposed for inclusion via this application.

6.10.1. Risk management plan

The Risk Management Plan (RMP) dated 2 March 2011, has previously been evaluated (submission 2009-02587-3- 4). The Office of Product Review deemed the RMP acceptable, subject to some assurances from the company. In a response letter dated 2 June 2011, the sponsor provided all the requested assurances.

The important potential risks that have been identified include: Interstitial pneumonitis (already in PI), reversible posterior leukoencephalopathy syndrome (RPLS), haemolytic disorders and DIC, transplant rejection, thrombotic thrombocytopenic purpura, ARF, toxic epidermal necrolysis and Stevens-Johnson syndrome (already in PI), and GI perforation. These require on-going monitoring.

6.11. Conclusions regarding safety

The safety findings were presented with the individual studies, and are discussed in this report. No separate, integrated safety report on cetuximab in combination with irinotecan and oxaliplatin based chemotherapy regimens has been provided.

The sponsor concluded: "Overall the combinations of cetuximab with continuous infusional 5-FU/FA and oxaliplatin or irinotecan show acceptable and manageable toxicity in the treatment of first-line metastatic CRC. The corresponding safety profile is adequately reflected in the current product information for cetuximab." The evaluator has no reason to object to these conclusions.

7. Conclusions regarding clinical data

The current submission contains data to provide justification for the current indications for cetuximab as 1st line therapy for mCRC *"in combination with irinotecan-based chemotherapy or continuous infusional 5-fluorouracil/folinic acid plus oxaliplatin."*

The previous, rather broad indications for cetuximab in 1st line therapy for mCRC "in combination with chemotherapy" have been restricted, by SRN in September last year, by specifying the exact regime of chemotherapy to be used.

"The subsequent review of the data for mCRC indication generated by Merck Serono and by the independent investigators has provided the evidence of lack of efficacy, when cetuximab is used in combination with chemotherapy regimens other than FOLFOX4 and irinotecan."

The current evaluation report is based on the review of significant amount of data that sponsor submitted, including the update reports to 2 pivotal studies for the 1st line mCRC indication that were previously evaluated by the TGA; the Phase III CRYSTAL and the Phase II OPUS studies.

Submitted data from the 2 investigator-sponsored studies that led to the review of the benefit/risk of combination therapy in patients with K-RAS wild type tumours, the COIN and NORDIC VII trials were also reviewed, as was large number of published papers.

The evaluator concluded that the submitted data, and overall information available to date, supports cetuximab in combination with irinotecan-based chemotherapy in 1st line indication for mCRC, but does not support the combination with "continuous infusional 5-FU/FA + oxaliplatin." Refer to the section on Conclusions on efficacy, above.

The other significant change to the PI includes addition of statements on paediatric population, based on submitted company-sponsored Phase I, PK study CA225085 of cetuximab in combination with irinotecan in paediatric population with solid tumours; this does not represent any controversial issue.

The other changes proposed to the PI of Erbitux are discussed elsewhere in this report³², and can be adopted with minor changes.

8. Recommendation regarding authorisation

The major part of this submission by Merck Serono Australia Pty Ltd relates to the approval of indications for cetuximab in combination with irinotecan- and oxaliplatin-based chemotherapy in 1st line therapy for mCRC.

- Based on the available information and considering the targeted indications of cetuximab as part of combination palliative chemotherapy in life-threatening disease, the evaluator

³² This Extract from the Clinical Evaluation Report does not include the sections discussing revisions to the PI.

supports cetuximab in combination with irinotecan-based chemotherapy in 1st line indication for mCRC.

- The combination of cetuximab with “continuous infusional 5-FU/FA + oxaliplatin” is not supported in this setting.
- The remaining proposed updates to the PI of Erbitux are approved; conditional upon the sponsor addressing the recommendations relating to the changes to the PI.

9. Clinical questions

None

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