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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Erbitux

cetuximab

**Procedure No.:** EMEA/H/C/000558/II/0042

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Scientific discussion

## *1.1. Introduction*

Cetuximab is a chimeric monoclonal Immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR). EGFR signaling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR with an affinity higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor and induces the internalization of EGFR, which can lead to down-regulation of the receptor. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).

Erbitux is indicated for the treatment of patients with EGFR-expressing, KRAS (Kirsten rat sarcoma viral oncogene homologue) wild-type metastatic colorectal cancer:

– in combination with chemotherapy

– as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy, and who are intolerant to irinotecan.

Erbitux is also 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.

In all indications, Erbitux is administered once a week as intravenous infusion at a maximum rate of 10 mg/min. The initial dose is 400 mg/m$^2$, and all subsequent weekly doses are 250 mg/m$^2$.

This variation application was submitted by the MAH on the recommendation of the CHMP in follow-up to the assessment of Follow-UP Measure 044 (FUM 044) and the ensuing additional Follow-Up Measures (FU2 044.1 and FU2 044.2). Follow-Up Measure 044 was initiated by the CHMP in September 2009 together with FUM 029 for Vectibix, triggered by findings in a panitumumab (Vectibix) add-on to FOLFOX4 (folinic acid, 5-fluorouracil, oxaliplatin) study showing a negative impact on Progression-Free Survival (PFS) in patients with metastatic colerectal cancer (mCRC) tumours harbouring activating KRAS mutations further to similar earlier findings for cetuximab, also in an mCRC add-on to FOLFOX4 study (OPUS). Assessments followed with the aim to understand the underlying mechanisms behind these findings and also aiming at risk reduction. In the course of these assessments, data suggesting lack of efficacy of cetuximab were reported in combinations of cetuximab with oxaliplatin – fluoropyrimidine regimens (COIN, submitted and assessed) and with the Nordic FLOX (fluoropyrimidine-oxaliplatin) regimen (NORDIC VII, only high level data available).

With this variation application the MAH proposed changes to sections 4.1, 4.5 and 5.1 of the SmPC based on the results of the COIN study. The CHMP considered that the mCRC indication in combination with chemotherapy should be restricted. A new variation will be submitted when the clinical study report of the NORDIC VII trial becomes available with the intention to update the SmPC based on the results of this trial and to reassess the benefit-risk balance of the restricted indication.

## *1.2. Clinical aspects*

The initial indication granted for cetuximab was in mCRC as add-on to irinotecan in patients previously exposed to oxaliplatin and with irinotecan refractory mCRC based on a study (BOND) showing that

irinotecan + cetuximab was more effective than cetuximab alone [cetuximab Overall Response Rate (ORR) 11%, cetuximab + irinotecan 23%]. No KRAS mutation data are available from this trial.

The initial Erbitux mCRC indication was extended to treatment of patients in combination with chemotherapy or as single agent (after oxaliplatin- and irinotecan-based chemotherapy) with variation EMEA/H/C/000558/II/0020 (EC Decision 7 July 2008). Support for the monotherapy indication came primarily from the following trial:

CA225025 (NCIC): randomised, controlled phase III study of cetuximab as single agent in patients who had failed currently available standard chemotherapy regimens

As the most commonly used chemotherapy regimens for mCRC are combinations of fluoropyrimidines with either oxaliplatin or irinotecan, the indication in combination with chemotherapy was supported by the following studies:

EMR 62 202-013 (CRYSTAL): randomised, controlled phase III study of cetuximab in combination with FOLFIRI versus FOLFIRI in patients with mCRC previously untreated for metastatic disease

EMR 62 202-047 (OPUS): randomised, controlled phase II study of cetuximab in combination with FOLFOX versus FOLFOX in patients with mCRC previously untreated for metastatic disease

CA225006 (EMR 62 202-025 or EPIC): randomised, controlled phase III study of cetuximab in combination with standard irinotecan versus irinotecan in patients who had failed oxaliplatin-based therapy for metastatic disease

Updated PFS and Overall Survival (OS) data from CRYSTAL, OPUS and NCIC and updated analyses based on KRAS status from all four studies were included in the Erbitux Product information (PI) with variation EMEA/H/C/000558/II/0035 (EC Decision 28 July 2010). Additional PI changes included in this variation were the following: the requirement for determination of the tumour's KRAS mutation status prior to initiating cetuximab treatment was worded more explicitly, a warning about cardiovascular events was introduced and the warning of increased toxicity in combination with 5-fluorouracil was extended to all fluoropyrimidines.

The data and analyses that resulted in these additional safety changes and the analyses based on KRAS status had been requested by the CHMP as FUM 044. This was requested following the observation that the combination of cetuximab with FOLFOX4 in the OPUS trial impacted results negatively in patients with mutant KRAS tumour status [OS HR: 1.290 (95% CI: 0.873, 1.906), PFS HR 1.720 (95% CI: 1.104, 2.679), ORR HR 0.459 (95% CI; 0.228, 0.924) favouring FOLFOX4 alone (over the cetuximab/FOLFOX4 combination)]. Similar results had been reported in a panitumumab trial in combination with FOLFOX4. In the course of the assessment of FUM 044 and further to CHMP requests for supplementary information (FU2 044.1, FU2 044.2 and the current variation application), the MAH submitted the results of an investigator sponsored trial, the COIN trial.

## *COIN*

The COIN (COntinuous chemotherapy plus cetuximab or INtermittent chemotherapy) study was an open-label, multicentre, 3-arm, randomised (1:1:1), controlled, investigator-initiated phase III, first-line trial that was sponsored by the UK Medical Research Council (MRC) with centres in the United Kingdom and the Republic of Ireland.

## *Methods*

## Treatments

The study comprised the following three arms:

- Arm A: Oxaliplatin-fluoropyrimidine (OxFp) continuous chemotherapy in one of two regimens:

- OxMdG (**Ox**aliplatin **M**odified **d**e **G**ramont: this regimen is similar to FOLFOX4, repeated every 2 weeks, IV): combination of oxaliplatin (85 mg/m² over 2 h), L-folinic acid (175 mg over 2 h), and bolus 5-FU (400 mg/m²) followed by a 46-h infusion of 5-FU (2400 mg/m²)
- XELOX (capecitabine (**XEL**oda) + **Ox**aliplatin, repeated every 3 weeks): combination of IV oxaliplatin (130 mg/m² over 2 h, day 1) and oral capecitabine (1000 mg/m² twice a day [b.i.d.] on days 1 to 14 of each cycle)

- Arm B: continuous OxFp chemotherapy plus cetuximab administered as follows:

Chemotherapy was administered as described for Arm A in combination with infusions of cetuximab given once a week (first infusion 400 mg/m² over 2 h, subsequent infusions 250 mg/m² over 1 h). Cetuximab could be continued if chemotherapy was stopped due to toxicity or patient choice but was to be discontinued on evidence of disease progression or unacceptable toxicity.

- Arm C: intermittent OxFp chemotherapy was administered as described in Arm A for 12 weeks followed by monitoring only until disease progression. Upon progression, treatment was restarted for a new period of 12 weeks. This arm will not be further described and discussed as not being pertinent to cetuximab.

## Objectives

The study intended to compare the efficacy and safety of continuous vs intermittent oxaliplatin-based chemotherapy in first line treatment of mCRC and to investigate the add-on effect of cetuximab to continuous chemotherapy. Continuous chemotherapy was administered in cycles without interruption until progression of disease, unacceptable toxicity or following patient choice. Intermittent chemotherapy was administered in cycles for a total of 12 weeks followed by patient monitoring. Treatment was restarted for another 12 weeks upon progression of disease.

## Endpoints

The primary endpoint was Overall Survival (OS) defined as the interval from randomisation to death from any cause. Patients still alive at data cut-off were censored at the date last seen.

Secondary endpoints included response and Progression-Free Survival (PFS) defined as the interval from randomisation to first evidence of progression or death from any cause. Surviving patients without progression were to be censored at the date they were last seen.

Tumour assessments were made based on radiological scans that were scheduled every 12 weeks. Tumour response was assessed by the investigators according to RECIST without central confirmation.

## *Results*

## Conduct of the study

There were two major protocol amendments:

1) An interim safety analysis resulted in an amendment to the protocol. Patients in Arm B receiving XELOX (1000 mg/m² b.i.d.) plus cetuximab had significantly higher rates of grade ≥3 diarrhoea than those in other treatment groups: cetuximab + XELOX 30% vs XELOX 17% (p <0.001) vs, cetuximab + OxMdG 20%.

The starting dose of capecitabine for patients in Arm B only was reduced from 1000 mg/m² b.i.d. to 850 mg/m² b.i.d. In Arm A, the capecitabine dose remained unchanged at 1000 mg/m² b.i.d. The amendment was implemented after 1775 (73%) patients had been randomised to all arms.

2) The primary endpoint was changed to address the new findings concerning cetuximab, demonstrating KRAS mutations to be a negative predictor of cetuximab efficacy: OS was ascertained separately in patients with wild-type KRAS tumours and in patients with mutant KRAS tumours.

## Numbers analysed

815 patients were randomised to Arm A (279 to OxMdG and 536 to XELOX) and 815 patients were randomised to Arm B. The intention-to-treat (ITT) population thus comprised 1630 patients.

## Baseline characteristics

Baseline demographic and disease characteristics are summarised in the following table.

**Table 1: Baseline characteristics of randomised patients in the COIN study by treatment arm (all randomised patients and subgroup of patients with wild-type KRAS tumours**

| Characteristic | All patients | | *KRAS* wild type population | | *KRAS* mutant population | |
|---|---|---|---|---|---|---|
| | Cetuximab + OxFp (Arm B) | OxFp (Arm A) | Cetuximab + OxFp (Arm B) | OxFp (Arm A) | Cetuximab + OxFp (Arm B) | OxFp (Arm A) |
| Total patients | 815 | 815 | 362 | 367 | 297 | 268 |
| Choice of OxFp chemotherapy | | | | | | |
| XELOX | 66% | 66% | 68% | 65% | 66% | 71% |
| OxMdG | 34% | 34% | 32% | 35% | 34% | 29% |
| Sex | | | | | | |
| Male | 67% | 64% | 70% | 67% | 65% | 63% |
| Female | 33% | 36% | 30% | 33% | 35% | 37% |
| Age | | | | | | |
| Median | 63 years | 63 years | 64 years | 63 years | 64 years | 63 years |
| ≥ 65 years | 47% | 45% | 50% | 44% | 46% | 50% |
| WHO performance status | | | | | | |
| 0 | 46% | 46% | 47% | 48% | 45% | 43% |
| 1 | 46% | 46% | 47% | 45% | 45% | 49% |
| 2 | 8% | 8% | 6% | 7% | 9% | 9% |
| Site of primary tumor, rectum | 32% | 30% | 33% | 28% | 31% | 34% |
| Status of primary tumor | | | | | | |
| Resected | 52% | 55% | 52% | 59% | 58% | 59% |
| Unresected or unresectable | 42% | 41% | 41% | 36% | 36% | 36% |
| Local recurrence | 6% | 5% | 7% | 5% | 6% | 5% |
| Metastases | | | | | | |
| Metachronous | 29% | 31% | 31% | 34% | 29% | 31% |
| Synchronous | 70% | 68% | 68% | 64% | 71% | 67% |
| Liver only | 24% | 21% | 24% | 25% | 25% | 16% |
| Liver and others | 51% | 54% | 52% | 49% | 52% | 56% |
| Non-liver | 24% | 24% | 22% | 25% | 23% | 26% |
| Number of metastatic sites | | | | | | |
| 1 | 37% | 35% | 36% | 38% | 38% | 31% |
| 2 | 38% | 40% | 38% | 38% | 39% | 43% |
| >2 | 24% | 25% | 24% | 23% | 23% | 35% |

WHO = World Health Organization

## Outcomes and estimation

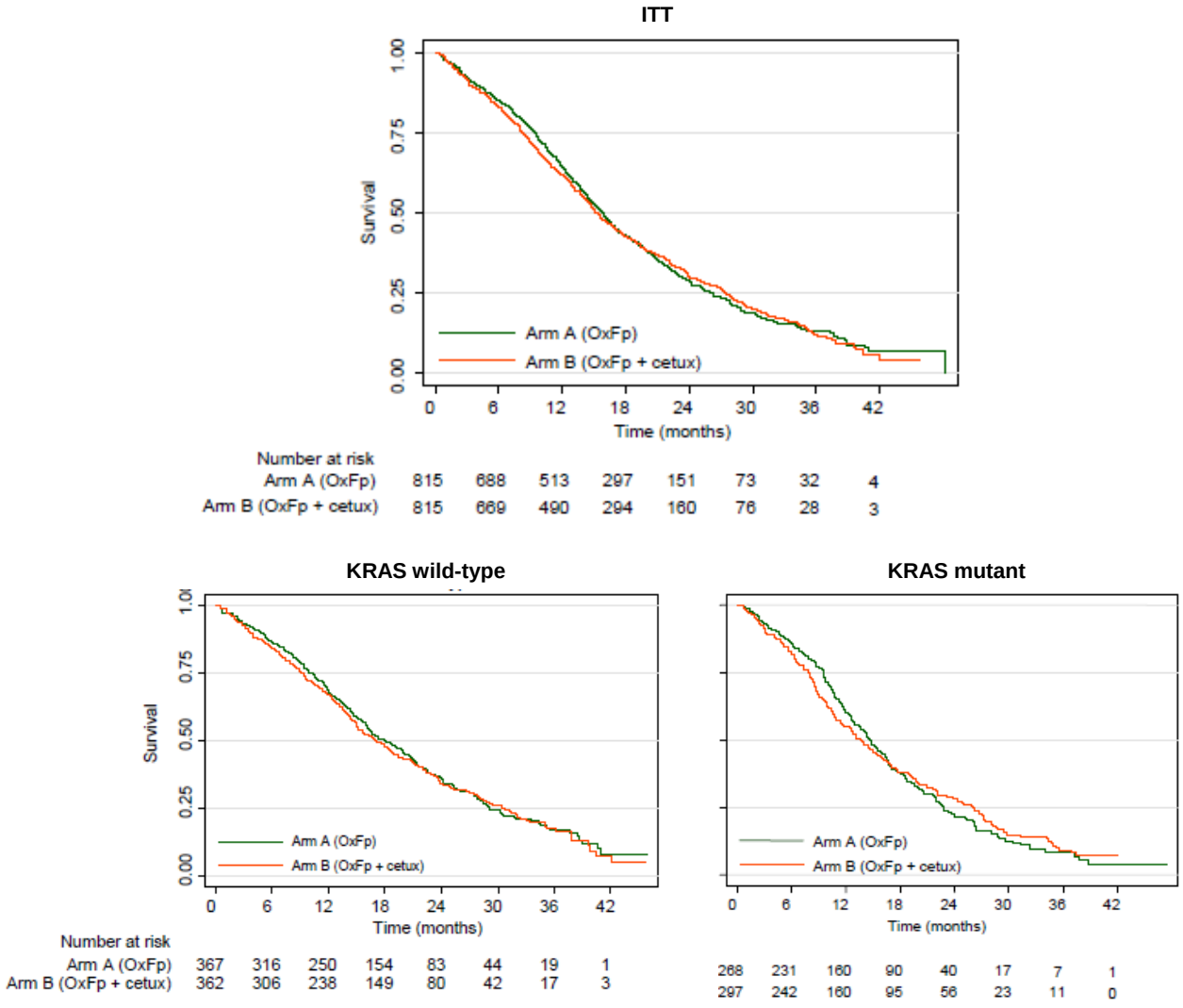
### Primary endpoint: Overall Survival

Results in terms of Overall Survival are summarised in the following figure and table.

**Table 2: Overall Survival in overall population and by KRAS mutation status**

| | ITT | | KRAS wild type | | KRAS mutant | |
|---|---|---|---|---|---|---|
| | OxFp + cet | OxFp | OxFp + cet | OxFp | OxFp + cet | OxFp |
| Total patients | 815 | 815 | 362 | 367 | 297 | 268 |
| No (%) events | 607 (74.5) | 612 (75.1) | 257 (70) | 257 (71) | 234 (78.8) | 219 (81.7) |
| Hazard ratio | 1.009 | | 1.038 | | 0.976 | |
| 95% CI | 0.902, 1.129 | | 0.873, 1.235 | | 0.811, 1.174 | |
| Log-rank p-value | 0.874 | | 0.669 | | 0.796 | |
| Median OS (mo) | 15.3 | 15.8 | 17.9 | 17.0 | 13.6 | 14.8 |

**Figure 1: Kaplan-Meier curve of Overall Survival overall and by KRAS mutation status**



Results by type of chemotherapy are summarised in the following table and figure.

**Table 3: Overall Survival by OxFp regimen**

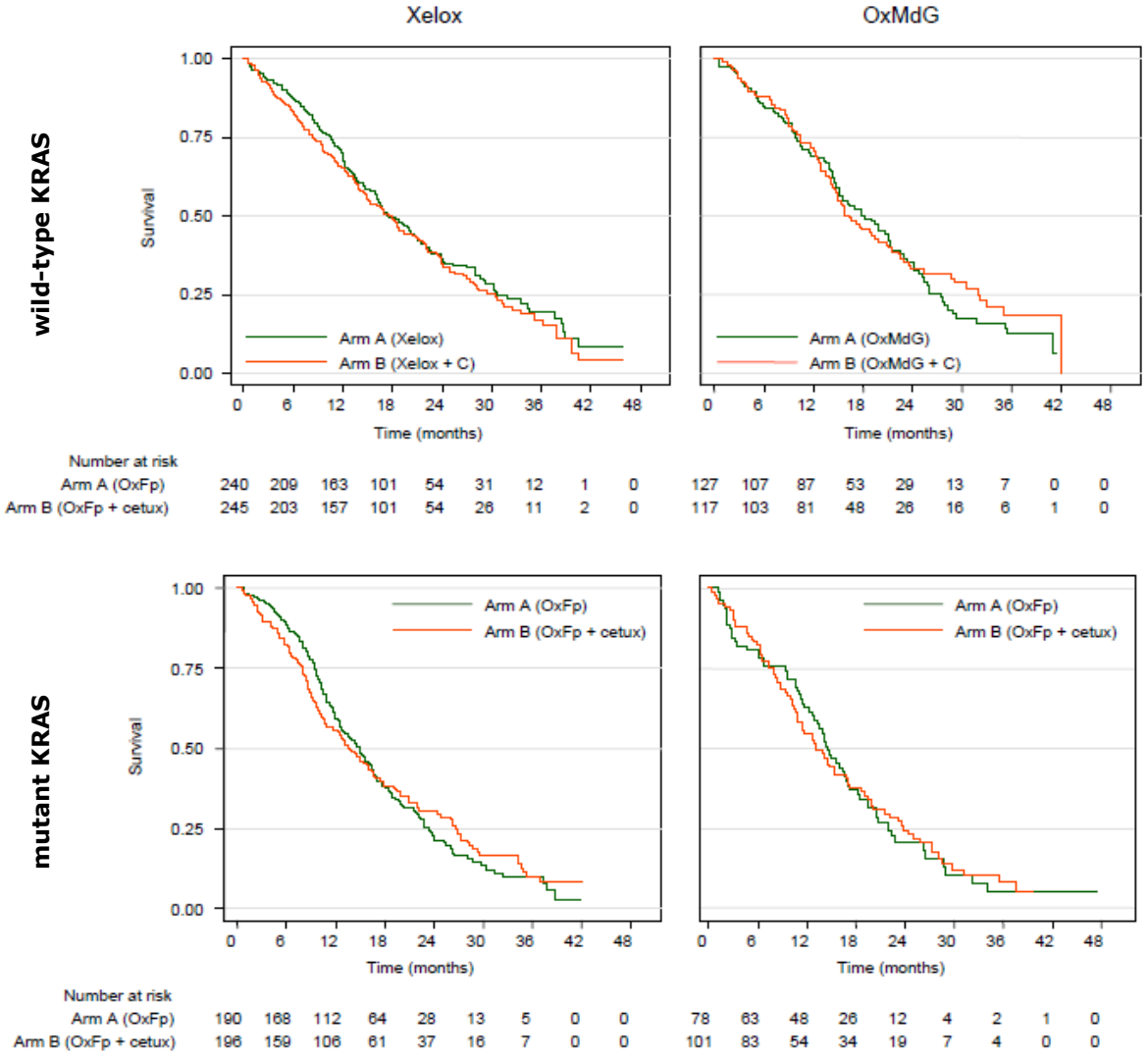
**Wild-type KRAS**

| | Xelox | | | | OxMdG | | |
|---|---|---|---|---|---|---|---|
| Hazard ratio (HR)<br>95% confidence interval; p-value from chi-square test | 1.309<br>(0.915, 1.309) | | P=0.408 | | 0.927<br>(0.723, 1.190) | | P=0.617 |
| | **Arm A** | **Arm B** | **Difference** | | **Arm A** | **Arm B** | **Difference** |
| Median survival time (months) | 17.4 | 17.5 | +0.10 | | 18.2 | 16.3 | -1.87 |
| 2-year survival rate | 36.4% | 35.0% | -1.4% | | 35.3% | 33.3% | -2.1% |

**Mutant KRAS**

| | Xelox | | | | OxMdG | | |
|---|---|---|---|---|---|---|---|
| Hazard ratio (HR)<br>95% confidence interval; p-value from chi-square test | 0.968<br>(0.801, 1.169) | | P=0.775 | | 0.986<br>(0.750, 1.295) | | P=0.931 |
| | **Arm A** | **Arm B** | **Difference** | | **Arm A** | **Arm B** | **Difference** |
| Median survival time (months) | 14.9 | 13.7 | -1.12 | | 14.6 | 13.1 | -1.48 |
| 2-year survival rate | 22.2% | 30.3% | +8.1% | | 21.1% | 24.6% | -3.5% |

**Figure 2: Overall Survival by OxFp regimen**



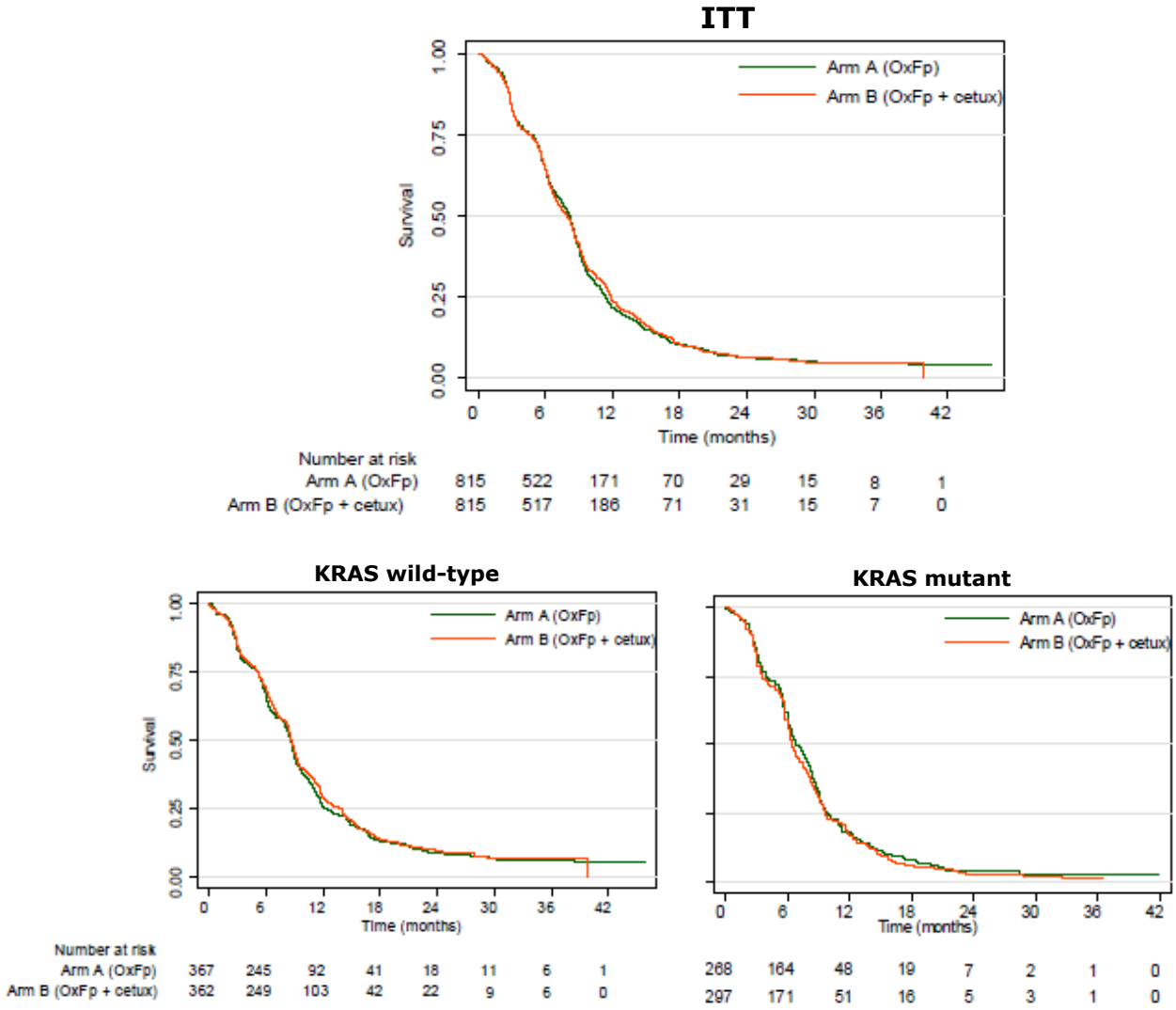
**Secondary endpoint: Progression-Free Survival**

Results in terms of Progression-Free Survival are summarised in the following figure and table.

**Table 4: Progression-Free Survival in overall population and by KRAS mutation status**

| | ITT | | KRAS wild type | | KRAS mutant | |
|---|---|---|---|---|---|---|
| | OxFp + cet | OxFp | OxFp + cet | OxFp | OxFp + cet | OxFp |
| Total patients | 815 | 815 | 362 | 367 | 297 | 268 |
| No (%) events | 749 (91.9) | 755 (92.6) | 324 (89.5) | 331 (90.2) | 284 (95.6) | 256 (95.5) |
| Hazard ratio | 0.982 | | 0.960 | | 1.065 | |
| 95% CI | 0.887, 1.086 | | 0.823, 1.119 | | 0.899, 1.262 | |
| Log-rank p-value | 0.719 | | 0.601 | | 0.464 | |
| Median PFS (mo) | 7.9 | 8.1 | 8.6 | 8.6 | 6.5 | 6.9 |

**Figure 3: Kaplan-Meier curve of Progression-Free Survival overall and by KRAS status**



Results by type of chemotherapy are summarised in the following table and figure.

**Table 5: Progression-Free Survival by OxFp regimen**

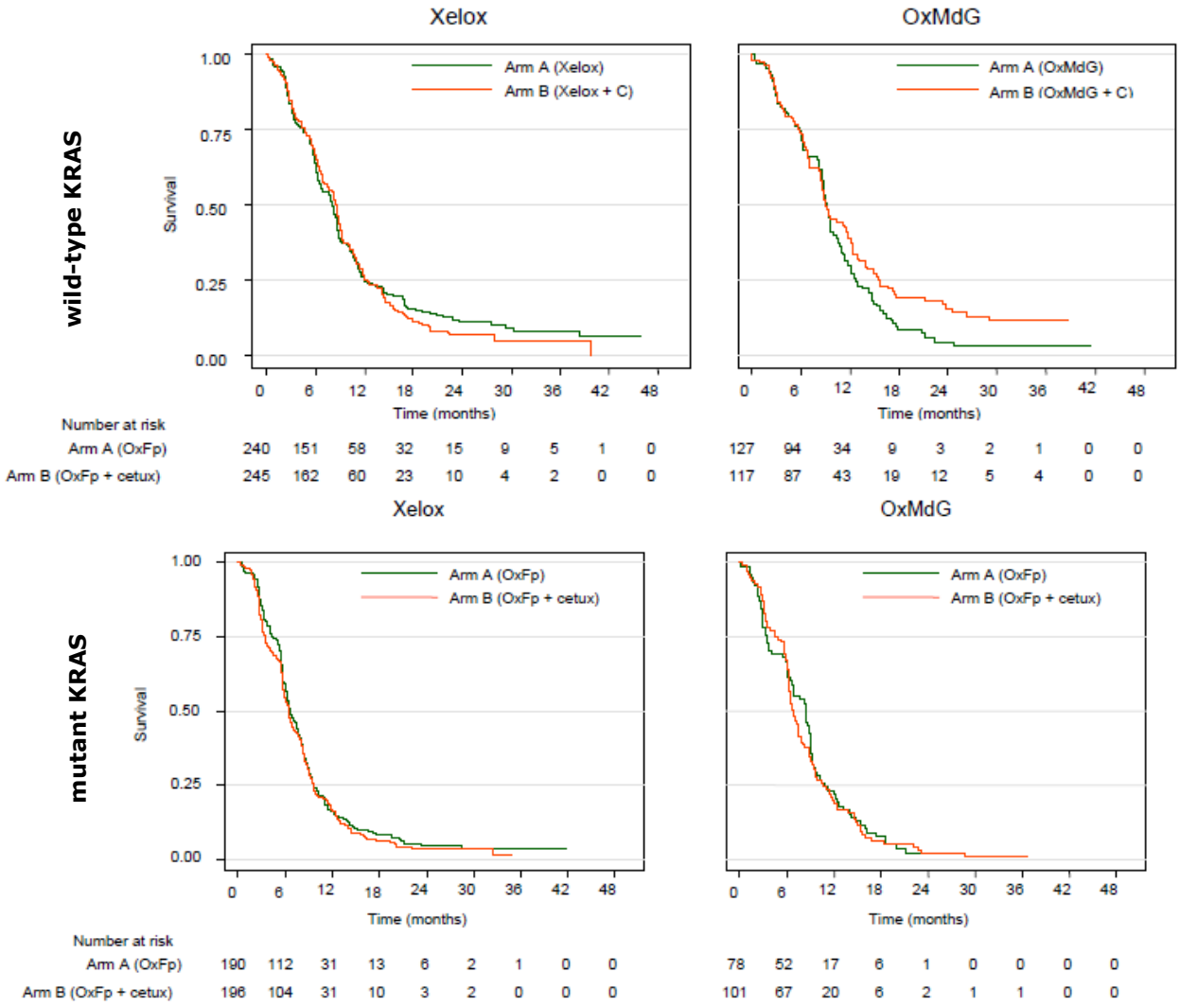
**Wild-type KRAS**

| | Xelox | | | | OxMdG | | |
|---|---|---|---|---|---|---|---|
| Hazard ratio (HR)<br>95% confidence interval; p-value from chi-square test | 1.058<br>(0.876, 1.277) | | P=0.560 | | 0.768<br>(0.587, 1.007) | | P=0.056 |
| | **Arm A** | **Arm B** | **Difference** | | **Arm A** | **Arm B** | **Difference** |
| Median survival time (months) | 8.0 | 8.4 | +0.39 | | 9.2 | 9.0 | -0.16 |
| 2-year survival rate | 10.9% | 6.5% | -4.5% | | 4.4% | 15.5% | +11.1% |

**Mutant KRAS**

| | Xelox | | | | OxMdG | | |
|---|---|---|---|---|---|---|---|
| Hazard ratio (HR)<br>95% confidence interval; p-value from chi-square test | 1.078<br>(0.877, 1.325) | | P=0.475 | | 1.045<br>(0.773, 1.412) | | P=0.775 |
| | **Arm A** | **Arm B** | **Difference** | | **Arm A** | **Arm B** | **Difference** |
| Median survival time (months) | 6.6 | 6.3 | -0.30 | | 8.5 | 6.8 | -1.68 |
| 2-year survival rate | 4.7% | 3.5% | -1.2% | | 1.9% | 2.1% | +0.17% |

**Figure 4: Overall Survival in patients with wild-type KRAS tumours by OxFp regimen**



**Secondary endpoint: Overall Response Rate**

Results in the wild-type and KRAS patient population by treatment arm are presented in the following tables.

**Table 6: Response rates in KRAS wild type tumour patients by type of OxFp regimen**

| Characteristic | Cetuximab + OxFp (Arm B) | OxFp (Arm A) | Cetuximab + XELOX (Arm B) | XELOX (Arm A) | Cetuximab + OxMdG (Arm B) | OxMdG (Arm A) |
|---|---|---|---|---|---|---|
| Total patients | 362 | 367 | 245 | 240 | 117 | 127 |
| Overall response rate at 12 weeks | 57% | 49% | 58% | 49% | 54% | 47% |
| Odds ratio (B vs A) | 1.39 p=0.028 | | 1.43 p=0.052 | | 1.30 p=0.303 | |
| Best overall response rate (CR/PR at any time) | 64% | 57% | 62% | 56% | 68% | 59% |
| Odds ratio (B vs A) | 1.35 p=0.049 | | 1.32 p=0.138 | | 1.44 p=0.171 | |

CI = confidence interval, HR = hazard ratio, CR = complete response, PR = partial response. Response was investigator assessed.

**Table 7: Response rates in KRAS mutant tumour population by type of OxFp regimen**

| Characteristic | Cetuximab + OxFp (Arm B) | OxFp (Arm A) | Cetuximab + XELOX (Arm B) | XELOX (Arm A) | Cetuximab + OxMdG (Arm B) | OxMdG (Arm A) |
|---|---|---|---|---|---|---|
| Total patients | 297 | 268 | 196 | 190 | 101 | 78 |
| Overall response rate at 12 weeks | 39% | 42% | 38% | 39% | 41% | 44% |
| Odds ratio (B vs A) | 0.92 p=0.636 | | 0.93 p=0.729 | | 0.88 p=0.687 | |
| Best overall response rate (CR/PR at any time) | 43% | 46% | 41% | 44% | 47% | 51% |
| Odds ratio (B vs A) | 0.88 p=0.449 | | 0.89 p=0.567 | | 0.83 p=0.529 | |

CI = confidence interval, HR = hazard ratio, CR = complete response, PR = partial response. Response was investigator assessed.

## Ancillary analyses

In the course of the assessment of FU2 044.2 and this variation application, the MAH submitted a number of requested ancillary analyses on data from the COIN trial. More specifically, they submitted upon CHMP request subgroup analyses in the ITT, wild-type and mutant KRAS tumour patients, as well as a distribution of events of death and progression in the PFS subgroup analyses (data not shown).

## Analysis performed across trials (pooled analyses and meta-analysis)

An overview of OS results across the four Erbitux combination with chemotherapy trials and separately for wild-type and mutant KRAS tumour patients can be found in the following table.

**Table 8: OS results across Erbitux clinical trials in combination with chemotherapy**

| Characteristic | ITT | | KRAS wild type | | KRAS mutant | |
|---|---|---|---|---|---|---|
| | Cet+ctrl | ctrl | Cet+ctrl | ctrl | Cet+ctrl | ctrl |
| **CRYSTAL (combination with FOLFIRI in first line)** | | | | | | |
| Total patients | 599 | 599 | 316 | 350 | 214 | 183 |
| No (%) events | 487 (81.3) | 502 (83.8) | 242 (76.6) | 288 (82.3) | 188 (87.9) | 156 (85.2) |
| Hazard ratio | 0.878 | | 0.796 | | 1.035 | |
| 95% CI | 0.774, 0.995 | | 0.670, 0.946 | | 0.834, 1.284 | |
| Log-rank p-value | 0.0420 | | 0.0094 | | 0.76 | |
| Median OS (months) | 19.9 | 18.6 | 23.5 | 20.0 | 16.2 | 16.7 |
| **OPUS (combination with FOLFOX4 in first line)** | | | | | | |
| Total patients | 169 | 168 | 82 | 97 | 77 | 59 |
| No (%) events | 124 (73.4) | 125 (74.4) | 55 (67.1) | 71 (73.2) | 61 (79.2) | 45 (76.3) |
| Hazard ratio | 1.015 | | 0.855 | | 1.290 | |
| 95% CI | 0.791, 1.303 | | 0.599, 1.219 | | 0.873, 1.906 | |
| Log-rank p-value | 0.91 | | 0.39 | | 0.20 | |
| Median OS (months) | 18.3 | 18.0 | 22.8 | 18.5 | 13.4 | 17.5 |
| **EPIC (combination with irinotecan in second line)** | | | | | | |
| Total patients | 648 | 650 | 97 | 95 | 49 | 59 |
| No (%) events | 445 (68.7) | 429 (66.0) | 66 (68.0) | 53 (55.8) | 39 (79.6) | 40 (67.8) |
| Hazard ratio | 0.98 | | 1.28 | | 1.28 | |
| 95% CI | 0.85, 1.11 | | 0.894, 1.846 | | 0.813, 2.005 | |
| Log-rank p-value | 0.7115 | | 0.1755 | | 0.2874 | |
| Median OS (months) | 10.7 | 10.0 | 10.9 | 11.6 | 8.4 | 10.7 |
| **COIN (combination with oxaliplatin in first line)** | | | | | | |
| Total patients | 815 | 815 | 362 | 367 | 297 | 268 |
| No (%) events | 607 (74.5) | 612 (75.1) | 257 (70) | 257 (71) | 234 (78.8) | 219 (81.7) |
| Hazard ratio | 1.009 | | 1.038 | | 0.976 | |
| 95% CI | 0.902, 1.129 | | 0.873, 1.235 | | 0.811, 1.174 | |
| Log-rank p-value | 0.874 | | 0.669 | | 0.796 | |
| Median OS (months) | 15.3 | 15.8 | 17.9 | 17.0 | 13.6 | 14.8 |

An overview of PFS results across the four Erbitux combination with chemotherapy trials and separately for wild-type and mutant KRAS tumour patients can be found in the following table.

**Table 9: PFS results across Erbitux clinical trials**

| Characteristic | ITT | | KRAS wild type | | KRAS mutant | |
|---|---|---|---|---|---|---|
| | Cet+ctrl | ctrl | Cet+ctrl | ctrl | Cet+ctrl | ctrl |
| **CRYSTAL (combination with FOLFIRI in first line)** | | | | | | |
| Total patients | 599 | 599 | 316 | 350 | 214 | 183 |
| No (%) events | 298 (49.7) | 322 (53.8) | 146 (46.2) | 189 (54.0) | 117 (54.7) | 92 (50.3) |
| Hazard ratio | 0.851 | | 0.696 | | 1.171 | |
| 95% CI | 0.726, 0.998 | | 0.556, 0.867 | | 0.887, 1.544 | |
| Log-rank p-value | 0.0479 | | 0.0012 | | 0.27 | |
| Median PFS (months) | 8.9 | 8.0 | 9.9 | 8.4 | 7.4 | 7.7 |
| **OPUS (combination with FOLFOX4 in first line)** | | | | | | |
| Total patients | 169 | 168 | 82 | 97 | 77 | 59 |
| No (%) events | 102 (60.4) | 102 (60.7) | 38 (46.3) | 62 (63.9) | 56 (72.7) | 34 (57.6) |
| Hazard ratio | 0.927 | | 0.567 | | 1.720 | |
| 95% CI | 0.702, 1.225 | | 0.378, 0.858 | | 1.104, 2.679 | |
| Log-rank p-value | 0.620 | | 0.0064 | | 0.0153 | |
| Median PFS (months) | 7.2 | 7.2 | 8.3 | 7.2 | 5.5 | 8.6 |
| **EPIC (combination with irinotecan in second line)** | | | | | | |
| Total patients | 648 | 650 | 97 | 95 | 49 | 59 |
| No (%) events | 610 (94.1) | 598 (92.0) | 87 (89.7) | 88 (92.6) | 47 (95.9) | 54 (91.5) |
| Hazard ratio | 0.692 | | 0.773 | | 0.996 | |
| 95% CI | 0.617, 0.776 | | 0.572, 1.044 | | 0.668, 1.485 | |
| Log-rank p-value | <0.0001 | | 0.0954 | | 0.9853 | |
| Median PFS (months) | 4.0 | 2.6 | 4.0 | 2.8 | 2.6 | 2.7 |
| **COIN (combination with oxaliplatin in first line)** | | | | | | |
| Total patients | 815 | 815 | 362 | 367 | 297 | 268 |
| No (%) events | 749 (91.9) | 755 (92.6) | 324 (89.5) | 331 (90.2) | 284 (95.6) | 256 (95.5) |
| Hazard ratio | 0.982 | | 0.960 | | 1.065 | |
| 95% CI | 0.887, 1.086 | | 0.823, 1.119 | | 0.899, 1.262 | |
| Log-rank p-value | 0.719 | | 0.601 | | 0.464 | |
| Median PFS (months) | 7.9 | 8.1 | 8.6 | 8.6 | 6.5 | 6.9 |

Moreover, and similar to what was mentioned for the COIN trial above, the MAH submitted upon CHMP request for all trials subgroup analyses in the ITT, wild-type and mutant KRAS tumour patients, as well as a distribution of events of death and progression in the PFS subgroup analyses (data not shown). Results of PFS and OS by age group and KRAS tumour status in the combination with chemotherapy trials (COIN, CRYSTAL and OPUS), with the exception of the EPIC trial in which KRAS mutation status was little determined, are given in the following table.

**Table 10: PFS and OS by age and KRAS mutation status in COIN, CRYSTAL and OPUS**

| | *KRAS* mutant population | | *KRAS* wild type population | |
|---|---|---|---|---|
| | **PFS** HR (95% CI) | **OS** HR (95% CI) | **PFS** HR (95% CI) | **OS** HR (95% CI) |
| **COIN** | | | | |
| ≤65 years | 0.94 (0.75, 1.18) | 0.87 (0.68, 1.11) | 1.03 (0.84, 1.27) | 1.09 (0.87, 1.38) |
| >65 years | 1.24 (0.96, 1.62) | 1.15 (0.86, 1.53) | 0.85 (0.68, 1.07) | 0.96 (0.74, 1.25) |
| **CRYSTAL** | | | | |
| <65 years | 0.94 (0.64, 1.37) | 0.94 (0.71, 1.25) | 0.65 (0.50, 0.86) | 0.71 (0.57, 0.89) |
| ≥65 years | 1.52 (0.98, 2.35) | 1.13 (0.81, 1.60) | 0.79 (0.54, 1.15) | 0.98 (0.73, 1.30) |
| **OPUS** | | | | |
| <65 years | 1.57 (0.87, 2.82) | 1.16 (0.70, 1.92) | 0.53 (0.31, 0.90) | 0.82 (0.51, 1.32) |
| ≥65 years | 1.90 (0.95, 3.79) | 1.47 (0.78, 2.76) | 0.70 (0.37, 1.35) | 0.84 (0.47, 1.50) |

OS and PFS results by levels of EGFR expression (and KRAS mutation status) are given in the following table.

**Table 11: PFS and OS by levels of EGFR expression and KRAS mutation status in COIN, CRYSTAL and OPUS**

| **Study / Percentage of stained cells** | ***KRAS* mutant population** | | ***KRAS* wild type population** | |
|---|---|---|---|---|
| | **PFS** HR (95% CI) | **OS** HR (95% CI) | **PFS** HR (95% CI) | **OS** HR (95% CI) |
| **COIN** | | | | |
| ≥10% | 1.28 (1.00, 1.63) | 1.10 (0.84, 1.44) | 0.93 (0.74, 1.17) | 0.98 (0.76, 1.27) |
| <10% | 0.87 (0.64, 1.19) | 0.86 (0.61, 1.20) | 0.85 (0.65, 1.11) | 0.91 (0.66, 1.23) |
| **CRYSTAL** | | | | |
| >35% | 1.61 (0.98, 2.66) | 1.50 (1.01, 2.24) | 0.66 (0.44, 1.01) | 0.81 (0.58, 1.13) |
| >20-35% | 0.79 (0.27, 2.28) | 0.93 (0.43, 1.99) | 0.74 (0.35, 1.54) | 0.82 (0.44, 1.55) |
| >10-20% | 0.61 (0.24, 1.52) | 1.75 (0.80, 3.82) | 0.56 (0.30, 1.03) | 0.72 (0.45, 1.15) |
| >0-10% | 0.89 (0.58, 1.37) | 0.73 (0.52, 1.01) | 0.81 (0.57, 1.14) | 0.77 (0.60, 0.99) |
| **OPUS** | | | | |
| >35% | 7.20 (0.91, 57.03) | 2.32 (0.64, 8.43) | 0.65 (0.15, 2.79) | 0.76 (0.23, 2.55) |
| >20-35% | 2.42 (0.59, 9.85) | 0.85 (0.21, 3.51) | 0.31 (0.02, 3.88) | 2.99 (0.56, 16.00) |
| >10-20% | 3.80 (0.36, 40.65) | 142E6 (0.00, ) | 0.18 (0.03, 0.93) | 0.30 (0.08, 1.13) |
| >0-10% | 1.38 (0.81, 2.36) | 1.10 (0.69, 1.74) | 0.60 (0.37, 0.96) | 0.82 (0.54, 1.23) |

## Safety

The Clinical Study Report of the COIN trial submitted included tabulated data of patient exposure (number of cycles, dose intensities, reductions and delays) as well as detailed tables of grade ≥1 and of grade ≥3 toxicities (data not shown).

Grade ≥3 toxicities by treatment arm in the ITT and in wild-type KRAS tumour patients are presented in the following two tables.

**Table 12: Grade ≥3 toxicities by treatment arm, COIN trial, ITT population (N=1830)**

| | Arm A | | | Arm B | | | *p*-value for A vs B | |
|---|---|---|---|---|---|---|---|---|
| | OxMdG | Xelox | P-value | OxMdG | Xelox | P-value | OxMdG | Xelox |
| Platelets | 3% | 3% | P=0.83 | 2% | 3% | P=0.83 | P=0.99 | P=0.99 |
| Haemoglobin | 2% | 1% | P=0.39 | 7% | 3% | P=0.008 | P=0.003 | P=0.038 |
| WBC | 10% | 1% | P<0.001 | 12% | 1% | P<0.001 | P=0.52 | P=0.32 |
| Neutrophils | 31% | 4% | P<0.001 | 31% | 2% | P<0.001 | P=0.90 | P=0.17 |
| Nausea | 5% | 7% | P=0.22 | 6% | 9% | P=0.17 | P=0.58 | P=0.21 |
| Vomiting | 4% | 5% | P=0.38 | 6% | 7% | P=0.77 | P=0.17 | P=0.16 |
| Diarrhoea | 11% | 15% | P=0.11 | 20% | 26% | P=0.031 | P=0.005 | P<0.001 |
| HFS | 3% | 5% | P=0.18 | 6% | 13% | P=0.006 | P=0.026 | P<0.001 |
| Nail changes | 0% | 0% | N/A | 2% | 2% | P=0.99 | P=0.014 | P=0.001 |
| Skin rash | 0% | <1% | P=0.99 | 20% | 20% | P=0.99 | P<0.001 | P<0.001 |
| Per. neuropathy | 23% | 16% | P=0.028 | 14% | 14% | P=0.99 | P=0.005 | P=0.28 |
| Hypomagnes. | 0% | 0% | N/A | 6% | 3% | P=0.086 | P<0.001 | P<0.001 |
| Anorexia | 4% | 6% | P=0.41 | 10% | 8% | P=0.36 | P=0.014 | P=0.14 |
| Alopecia | <1% | <1% | P=0.99 | 0% | <1% | P=0.99 | P=0.32 | P=0.57 |
| Pain | 12% | 14% | P=0.52 | 12% | 13% | P=0.66 | P=0.98 | P=0.81 |
| Stomatitis | 5% | 1% | P<0.001 | 10% | 3% | P<0.001 | P=0.023 | P=0.002 |
| Lethargy | 18% | 18% | P=0.99 | 29% | 24% | P=0.15 | P=0.003 | P=0.023 |
| Vein pain | 0% | 1% | P=0.056 | 0% | 1% | P=0.56 | N/A | P=0.13 |

**Table 13: Grade ≥3 toxicities by treatment arm, COIN trial, wild-type KRAS tumour population (N=729)**

| | Arm A | | | Arm B | | | *p*-value for A vs B | |
|---|---|---|---|---|---|---|---|---|
| | OxMdG | Xelox | P-value | OxMdG | Xelox | P-value | OxMdG | Xelox |
| Platelets | 2% | 3% | P=0.50 | 3% | 2% | P=0.99 | P=0.67 | P=0.78 |
| Haemoglobin | 2% | 1% | P=0.99 | 6% | 3% | P=0.24 | P=0.092 | P=0.34 |
| WBC | 11% | 0% | P<0.001 | 9% | 0% | P<0.001 | P=0.67 | P=0.99 |
| Neutrophils | 35% | 4% | P<0.001 | 25% | 2% | P<0.001 | P=0.096 | P=0.20 |
| Nausea | 5% | 7% | P=0.50 | 6% | 9% | P=0.41 | P=0.59 | P=0.50 |
| Vomiting | 3% | 5% | P=0.59 | 6% | 6% | P=0.99 | P=0.24 | P=0.55 |
| Diarrhoea | 14% | 16% | P=0.54 | 18% | 24% | P=0.22 | P=0.25 | P=0.038 |
| HFS | 4% | 4% | P=0.99 | 6% | 16% | P=0.004 | P=0.56 | P<0.001 |
| Nail changes | 0% | 0% | N/A | 3% | 4% | P=0.99 | P=0.051 | P=0.004 |
| Skin rash | 0% | 0% | N/A | 22% | 24% | P=0.69 | P<0.001 | P<0.001 |
| Per. neuropathy | 25% | 16% | P=0.047 | 13% | 16% | P=0.53 | P=0.022 | P=0.99 |
| Hypomagnes. | 0% | 0% | N/A | 8% | 3% | P=0.091 | P=0.007 | P=0.015 |
| Anorexia | 5% | 6% | P=0.81 | 8% | 9% | P=0.84 | P=0.43 | P=0.22 |
| Alopecia | 0% | 0% | N/A | 0% | 0% | N/A | N/A | N/A |
| Pain | 12% | 13% | P=0.99 | 10% | 15% | P=0.32 | P=0.84 | P=0.59 |
| Stomatitis | 4% | 1% | P=0.045 | 9% | 4% | P=0.061 | P=0.14 | P=0.038 |
| Lethargy | 22% | 19% | P=0.68 | 27% | 22% | P=0.35 | P=0.37 | P=0.57 |
| Vein pain | 0% | 2% | P=0.30 | 0% | <1% | P=0.99 | N/A | P=0.21 |

Data on the number, aetiology and timing of deaths in the ITT and wild-type KRAS tumour population are summarised in the following table.

**Table 14: Summary of deaths, COIN trial**

| | All patients | | | | | | *KRAS*$^{wt}$ patients | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm A | | Arm B | | Both arms | | Arm A | | Arm B | | Both arms | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Disease-related | 567 | 70% | 548 | 67% | 1115 | 68% | 234 | 64% | 233 | 64% | 467 | 64% |
| Treatment-related | 10 | 1% | 10 | 1% | 20 | 1% | 5 | 1% | 3 | 1% | 8 | 1% |
| Other | 31 | 4% | 38 | 5% | 69 | 4% | 15 | 4% | 17 | 5% | 32 | 4% |
| Missing | 4 | <1% | 11 | 1% | 15 | 1% | 3 | 1% | 4 | 1% | 7 | 1% |
| **Total deaths** | **612** | **75%** | **607** | **74%** | **1219** | **75%** | **257** | **70%** | **257** | **71%** | **514** | **71%** |
| Deaths within 60 days of randomisation | 36 | 4% | 43 | 5% | | | 15 | 4% | 16 | 4% | | |
| Deaths within 60 days of first dose | 31 | 4% | 45 | 6% | | | 11 | 3% | 16 | 4% | | |
| All deaths within 30 days of last treatment | 70 | 9% | 94 | 12% | | | 29 | 8% | 41 | 11% | | |
| Treatment-related deaths within 30 days of last treatment | 10 | 1% | 9 | 1% | | | 5 | 1% | 3 | 1% | | |
| **Total** | **815** | **100%** | **815** | **100%** | | | **367** | **100%** 45% | **362** | **100%** 44% | | |

## *Discussion on clinical aspects*

**COIN**

Overall, the COIN study was adequately designed. ORR and Progressive Disease (PD) were defined based on investigators' assessment only, but the primary endpoint was OS. Tumour assessment by scans was undertaken every 12 weeks (in MAH sponsored studies every 8 week). The very late amendment with respect to dose reduction of capecitabine is of note, as it was the result of interim safety analyses showing an increased frequency of diarrhoea with the XELOX+cetuximab combination indicative of a potential negative toxicity interaction of cetuximab with XELOX and possibly partly explaining the deviation in results between OxMdG and XELOX discussed below.

The study population appears typical for studies in this field, but the proportions of patients with synchronous metastasis and 'liver and others' metastatic sites appear high. There are no likely relevant imbalances between treatment arms. In contrast to MAH sponsored studies, life expectancy of at least 12 weeks was not an inclusion criterion and prior adjuvant therapy could have been administered if completed > 1 month prior to enrolment (> 6 months in MAH sponsored studies).

No trend towards an overall survival benefit was detected. The observed median survival was rather short for a first-line CRC study, about 1.5 year. Of importance, compared to prior results showing a negative effect of cetuximab add-on to FOLFOX4 in terms of PFS and OS (see OPUS trial in tables 8 and 9), no negative effect was observed in case of KRAS mutation positive tumours (XELOX HR: 0.97, OxMdG HR: 0.99). However, in the XELOX group, there was an early separation in favour of the control followed by cross-over favouring the cetuximab arm (lower left panel of figure 2). This could be related to early treatment-related "toxic" deaths.

A borderline significant PFS benefit for add-on cetuximab was observed only in the OxMdG arm. Of note, a difference was observed only after the median (upper right panel of figure 4). In OPUS, a negative effect of cetuximab as add-on to FOLFOX4 was seen in patients with KRAS mutant positive tumours (PFS HR 1.7). This was also seen in patients <65 years of age and in good performance status, indicating that toxicity is less likely to be the main driver behind the negative results. Of note, similar results were found in a panitumumab trial when panitumumab was given as add-on to FOLFOX4 (PFS HR 1.3) and in the CAIRO 2 trial, where cetuximab was added to a bevacizumab and XELOX regimen. This apparent negative dynamic interaction between FOLFOX4 and anti-EGFR antibodies was

not confirmed in the COIN trial between cetuximab and OxMdG (similar to FOLFOX4, PFS HR 1.04) or XELOX (PFS 1.08). An possible explanation could be that the COIN study lacked assay sensitivity to show differences in terms of both negative add-on effects (mutant KRAS tumour patients) and positive add-on effects (wild type KRAS tumour patients).

With respect to ORR, borderline significant favourable effects were observed in the wild type KRAS tumour population and of similar magnitude irrespectively of background chemotherapy. In the KRAS mutation positive tumour population no favourable difference in ORR was observed.

In terms of safety, add-on cetuximab resulted in relevant increases in grade ≥3 diarrhoea (both arms), hand-foot syndrome (XELOX), rash (both arms), lethargy (both arms) and anorexia (OxMdG). A lower frequency of neuropathy was reported in the OxMdG arm after cetuximab add-on.

**Pooled analyses of Erbitux mCRC trials and discussion of indication**

The monotherapy indication in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan is not questioned. Cetuximab has shown clinically meaningful activity in terms of OS benefit as last-line therapy in patients with KRAS wild type tumours (NCIC trial).

The indication in combination with irinotecan-based regimens is not questioned either, as cetuximab add-on to FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) in the first line has shown a meaningful prolongation of PFS and OS in patients with wild-type KRAS tumours, while no difference was seen in patients with mutant KRAS tumours (CRYSTAL trial). With regard to cetuximab add-on to irinotecan in irinotecan-naïve and oxaliplatin-exposed patients (second line, EPIC trial), KRAS mutation data are considered non interpretable due to the low percentage (23%) of KRAS status ascertainment (compare patient numbers for the EPIC trial in the ITT, wt and mt KRAS tumour patients in tables 8 and 9). The study did not meet its primary endpoint (OS), but cetuximab showed a positive PFS effect in the full study population (HR 0.7, investigator assessment). Finally, in patients exposed to oxaliplatin and refractory to irinotecan, cetuximab add-on to irinotecan showed an ORR of 23% vs. 11% on cetuximab alone, median PFS 4.1 vs. 1.5 months, $p<0.001$. Thus cetuximab appeared to reverse resistance to irinotecan which is from a mechanistic perspective a very interesting finding. As cetuximab in monotherapy in a similar population has shown a survival benefit over best supportive care, these results are also considered clinically relevant. No KRAS mutation data are available from this trial (BOND).

With regard to the indication in combination with oxaliplatin-based regimens, in three (COIN, CAIRO2, NORDIC VII) out of four (add. OPUS) studies with oxaliplatin-containing chemotherapy regimens, including one add-on to a bevacizumab containing regimen (CAIRO2) and the not yet assessed NORDIC VII trial, of which high level data have nevertheless been reported, there was no add-on activity of cetuximab in terms of time-related endpoints in KRAS wild type tumours. Only in OPUS was there a positive effect in PFS, but not OS, in patients with wild-type tumours.

In two of these trials (OPUS, CAIRO2) a negative add-on effect on PFS and OS was seen in case of mutant KRAS tumours. In addition, similar findings were reported in a panitumumab add-on to FOLFOX trial (PRIME). At least for the OPUS trial, toxicity appears highly unlikely to be the major cause for this apparent negative add-on effect on mutant KRAS tumours and similar findings have not been reported for any irinotecan-containing regimen. The most likely cause is thus a negative dynamic interaction between anti-EGFR antibodies and oxaliplatin in KRAS-mutated tumours. An unexpected relationship between percentage of EGFR positive tumour cells and negative add-on activity of cetuximab has been observed (see table 11), but otherwise no possible explanation to the negative add-on effect has been identified.

Among the fully assessed trials, conflicting results have thus been reported for OPUS and COIN: in OPUS, a clinically relevant add-on effect in terms of PFS was shown in wild type tumours, while a

negative effect was seen in KRAS mutated tumours. In COIN, a statistically marginalpositive effect was observed as add-on to the OxMdG regimen in wild type tumours and no negative effects were detected in KRAS mutated tumours, a fact probably indicative of lack of assay sensitivity. To what extent tumour burden and other baseline factors contribute to this cannot be determined, but it should be noticed that age above 65 is predictive of less add-on activity of cetuximab (see table 10).

## *1.3. Changes to the Product Information*

The MAH proposed the following change to the mCRC indication (new text underlined):

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

- in combination with chemotherapy (for details on certain regimens, see section 5.1),
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

The CHMP considered that a restriction to the indication in combination with chemotherapy was necessary and the finally agreed wording is as follows (new text underlined):

Erbitux 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 FOLFOX4 (for details, see section 5.1),
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

The warning on cardiovascular disorders in SmPC section 4.4 was updated based on the cross-study subgroup analyses indicating potential negative effects in PFS and OS in patients older than 65 years or with poor performance status. These effects had previously (see Variation EMEA/H/C/000558/ II/0035, EC Decision 28 July 2010) been associated with cardiovascular disorders, although no causal relationship with cetuximab could be established. Moreover, the warning against use in patients with unknown KRAS tumour status in section 4.4 of the SmPC and the related information in section 5.1 were expanded based on the updated information available. Finally, information on the interaction with the XELOX combination was added in section 4.5 of the SmPC.Finally, the CHMP requested the MAH to submit the results of the NORDIC VII study as soon as possible with the aim to reassess the benefit risk of the updated mCRC indication in combination with chemotherapy in light of these data. A condition was agreed to be added in Annex II requiring the submission of the NORDIC VII study data as soon as made available.

## *1.4. Conclusions and Benefit / Risk Assessment*

As add-on to irinotecan containing regimens, cetuximab has shown a positive effect in terms of increased ORR and PFS and in the first line trial as add-on to FOLFIRI a favourable effect on OS has been shown. In the EPIC trial (second line post-oxaliplatin and as add-on to FOLFIRI), designed to demonstrate a survival benefit, a beneficial effect in terms of OS could not be shown, but a positive

effect in terms of PFS was shown in the overall population, while efficacy in relation to tumour KRAS status could not be properly assessed due to the small number of patients with KRAS evaluation. In the last line setting (BOND trial), a meaningful prolongation in PFS was observed with the combination of cetuximab and irinotecan, compared with cetuximab alone, in patients that were refractory to irinotecan. Overall, the findings in trials with irinotecan based regimens are considered consistent and favourable.

Overall, the findings in trials with irinotecan based regimens are considered consistent and favourable. However, in patients with metastatic, KRAS wild-type colorectal cancer, the current indication 'in combination with chemotherapy' is too general based on current knowledge. In CAIRO2, an add-on to XELOX + bevacizumab study, no positive effects in terms of time-related endpoints was demonstrated. In this trial, clearly negative effects in patients with KRAS mutation positive tumours were seen; hence the assay sensitivity is not questioned. A restriction of the combination of cetuximab with oxaliplatin-based regimens is thus warranted. With respect to such regimens and as discussed above, there is one trial with favourable results (OPUS) in KRAS wild-type tumours. In this trial cetuximab was administered as add-on to the FOLFOX4 regimen. This is the only combination among oxaliplatin-based regimens which is still considered to be associated with a positive benefit/risk balance based on the currently available information. However, the MAH will submit the results of the NORDIC VII trial (combination with the Nordic FLOX regimen) as soon as made available with a view to reassessing the benefit-risk balance of the restricted indication.