**Background:** We report updated overall survival (OS) data from study NO16966, which compared capecitabine plus oxaliplatin (XELOX) vs 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX4) as first-line therapy in metastatic colorectal cancer.

**Methods:** NO16966 was a randomised, two-arm, non-inferiority, phase III comparison of XELOX vs FOLFOX4, which was subsequently amended to a 2 x 2 factorial design with further randomisation to bevacizumab or placebo. A planned follow-up exploratory analysis of OS was performed.

**Results:** The intent-to-treat (ITT) population comprised 2034 patients (two-arm portion, n = 634; 2 x 2 factorial portion, n = 1400). For the whole NO16966 study population, median OS was 19.8 months in the pooled XELOX/XELOX-placebo/XELOX-bevacizumab arms vs 19.5 months in the pooled FOLFOX4/FOLFOX4-placebo/FOLFOX4-bevacizumab arms (hazard ratio 0.95 (97.5% CI 0.83–1.09)). FOLFOX4 was associated with more grade 3/4 neutropenia/ granulocytopenia and febrile neutropenia than XELOX, and XELOX with more grade 3 diarrhoea and grade 3 hand-foot syndrome than FOLFOX4.

**Conclusion:** Updated survival data from study NO16966 show that XELOX is similar to FOLFOX4, confirming the primary analysis of progression-free survival. XELOX can be considered as a routine first-line treatment option for patients with metastatic colorectal cancer.

**Keywords:** 5-fluorouracil/folinic acid; capecitabine; colorectal cancer; overall survival; oxaliplatin

---

**Patients and Methods**

The methods of this trial have been described in detail previously (Saltz et al, 2008; Cassidy et al, 2008a). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients participating in the study. Approval of the protocol was...
bevacizumab (7.5 mg kg\(^{-1}\) every third week) or placebo was added of day 15. The FOLFOX4 regimen has been previously described daily for 2 weeks as a 3-week cycle. The first dose of capecitabine was given in the evening of day 1 and the last dose on the morning of day 15. The FOLFOX4 regimen has been previously described (de Gramont et al, 2000). After amendment of the study protocol, bevacizumab (7.5 mg kg\(^{-1}\) every third week) or placebo was added to XELOX, and bevacizumab (5 mg kg\(^{-1}\) every second week) or placebo to FOLFOX4. Bevacizumab or placebo was given as a 30- to 90-min intravenous infusion on day 1 of each cycle before oxaliplatin. Treatment was continued until disease progression or for 48 weeks, whichever came first (study treatment phase). Patients who completed the 48-week treatment phase without disease progression were eligible to continue treatment until progression (post-study treatment phase). Patients whose tumour became operable, and for whom resection was performed, were allowed to enter the post-study treatment phase.

Assessments

Tumour assessments (CT scan, MRI) were performed within 28 days before starting study treatment and repeated after every two XELOX cycles and every three FOLFOX4 cycles (i.e., every sixth week in both arms), and at the end of treatment. After completion of study treatment, patients were followed every 3 months until disease progression and/or death.

Patients were evaluated for adverse events during therapy and until 28 days after the last study drug dose. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3. Predefined adverse events of special interest for chemotherapy were: grade 3/4 neutropenia/granulocytopenia; grade 3/4 neurosensory toxicity; grade 3/4 diarrhoea; grade 3/4 vomiting/nausea; grade 3/4 stomatitis and grade 3 hand-foot syndrome.

Statistical analysis

The intent-to-treat (ITT) patient population included all patients who underwent randomisation and signed the informed consent form. The eligible patient population (EPP) was the ITT population minus patients who did not receive at least one dose of study drug, and those patients who violated major protocol inclusion/exclusion criteria. As the results for the EPP population were the same as for the ITT population, ITT data only will be presented in this paper. The safety population included all patients receiving at least one dose of study drug.

Overall survival was defined as the time from the date of randomisation to the date of death. Patients who were not reported as having died at the time of the analysis were censored using the date they were last known to be alive. Overall survival was analysed using a Cox model and presented as Kaplan–Meier estimates with hazard ratios (HRs) and 97.5% confidence intervals (CIs).

The primary analysis of NO16966 was event driven and was performed on 31 January 2006 when 1200 progression-free survival events had occurred in the EPP; this approach ensured 90% power at an \( \alpha \) level of 2.5 (Saltz et al, 2008). A further planned follow-up analysis of OS was performed at the time of the 4-month safety update.

As the study was not powered for formal testing of non-inferiority for OS, the OS analysis is exploratory and the results described by Kaplan–Meier estimates with HRs and 97.5% CIs. An additional exploratory analysis of OS was performed to control for any possible crossover effects of FOLFOX in patients who received XELOX as their first-line regimen. In this analysis, patients in the XELOX arms who received FOLFOX4 or similar regimen as second-line therapy were censored.

RESULTS

Patient population

Between July 2003 and May 2004, 634 patients were randomised in the two-arm portion of the study. Between February 2004 and February 2005, a further 1400 patients were randomised in the 2 \( \times \) 2 factorial part of the study. Overall, 2034 patients made up the ITT population (Figure 1). The baseline demographic and clinical characteristics were well balanced between treatment arms (Table 1).

Treatment exposure and second-line therapy

The median dose intensities (ratio of dose received to dose planned) of 5-FU, capecitabine, oxaliplatin and bevacizumab were \( \geq 0.89 \) in all treatment arms. The median number of cycles administered was 11 (range 1–24) in the FOLFOX4/FOLFOX4-placebo group, 12 (range 1–25) in the FOLFOX4-bevacizumab group, 7 (range 1–18) in the XELOX/XELOX-placebo group and 8 (range 1–17) in the XELOX-bevacizumab group.

There were no major imbalances between the treatment groups with respect to the use of second-line therapy: XELOX-containing arms (65%) and FOLFOX4-containing arms (70%). The agents most commonly used were: irinotecan (56% with FOLFOX4 vs 53% with XELOX); 5-FU (41% vs 34%); capecitabine (19% vs 14%); cetuximab (20% vs 18%); and bevacizumab (10% vs 10%).

Overall survival

The OS data as at 31 July 2008 in the ITT population are shown in Table 2. The corresponding Kaplan–Meier curves for OS are shown in Figure 2.

For the whole NO16966 study population, median OS was 19.8 months in the pooled XELOX/XELOX-placebo/XELOX-bevacizu-mab arms vs 19.5 months in the pooled FOLFOX4/FOLFOX4-placebo/FOLFOX4-bevacizumab arms, with a corresponding HR of 0.95 (97.5% CI 0.85–1.06).

In the pooled XELOX/XELOX-placebo arms, median OS was 19.0 vs 18.9 months in the pooled FOLFOX4/FOLFOX4-placebo arms, with a corresponding HR of 0.95 (97.5% CI 0.83–1.09).

In the XELOX-bevacizumab arm, median OS was 21.6 vs 21.0 months in the FOLFOX4-bevacizumab arm, with a corresponding HR of 0.95 (97.5% CI 0.78–1.15).
Clinical Studies

In the XELOX arm, median OS was 18.8 vs 17.7 months in the FOLFOX arm, with a corresponding HR of 0.87 (97.5% CI 0.72 – 1.05). FOLFOX or a similar regimen was given to 8% of patients in the pooled XELOX arms as second-line therapy (XELOX, n = 15, XELOX-placebo, n = 38, XELOX-bevacizumab, n = 29). After censoring these patients, the median OS was 18.9 months in the pooled XELOX/XELOX-placebo arms and 18.9 months in the pooled FOLFOX/FOLFOX-placebo arms, with a corresponding HR of 0.94 (97.5% CI 0.82 – 1.08), and 21.6 months in the XELOX-bevacizumab arm and 21.0 months in the FOLFOX-bevacizumab arm (HR = 0.93; 97.5% CI 0.76 – 1.13).

Safety

For the updated safety assessment of XELOX vs FOLFOX4, patients in the pooled XELOX/XELOX-placebo (n = 655) and pooled FOLFOX4/FOLFOX4-placebo (n = 648) arms were compared. The updated safety analysis showed that little had changed since the previous analysis (Cassidy et al, 2008a). Predefined adverse events of special interest and key events pooled by body system are presented in Table 3.

In general, XELOX and FOLFOX4 had a similar profile of adverse events. The most common adverse events were gastrointestinal (i.e., diarrhoea, nausea, vomiting and stomatitis) and neurosensory toxicities (i.e., paraesthesia and peripheral neuropathy). However, there were differences between the two regimens in the rates at which key events occurred. FOLFOX4/FOLFOX4-placebo was associated with more grade 3/4 neutropenia/granulocytopenia (44%) and febrile neutropenia (5%) than XELOX/XELOX-placebo (7 and <1%, respectively). Conversely, XELOX/XELOX-placebo was associated with more hand-foot syndrome (all-grade, 31 vs 11%; grade 3, 6 vs 1%) and diarrhoea (all-grade, 66 vs 61%; grade 3/4, 20 vs 11%) than FOLFOX4/FOLFOX4-placebo, although the rate of grade 4 diarrhoea was 1% with both regimens. Rates of grade 3/4 neurosensory toxicity were similar with both regimens (17%). Cardiac disorders were reported in 6 (1%) XELOX/XELOX-placebo recipients and 9 (1%) FOLFOX4/FOLFOX4-placebo recipients. The addition of bevacizumab did not alter the similarities and differences in safety profiles between XELOX and FOLFOX4 (Table 4).

Treatment-related mortality up to 28 days after the last treatment dose was documented in 11 (1.7%) FOLFOX4/FOLFOX4-placebo patients and in 15 (2.3%) XELOX/XELOX-placebo patients. The respective 60-day all-cause mortality rates were 2.3% (n = 15) and 3.4% (n = 22).

DISCUSSION

The primary efficacy analysis of study NO16966 showed that XELOX is non-inferior to FOLFOX4 in terms of progression-free survival, OS and overall response rate in the first-line treatment of patients with metastatic colorectal cancer (Cassidy et al, 2008a). This updated analysis of OS again demonstrates that XELOX and FOLFOX4 have similar efficacy and supports the primary efficacy findings. It is also notable that both XELOX and FOLFOX4 were similar in terms of OS after the addition of bevacizumab.

Overall survival is the most clinically meaningful and objective measure of efficacy in patients with cancer. However, potential differences between study treatments can be masked by second-line and later lines of chemotherapy when this end point is used (Di Leo et al, 2004). In study NO16966, there were no restrictions regarding crossover or salvage therapies after the completion of study treatment. It is therefore possible that crossover to the alternate study treatment was a confounding factor in the present analysis. To allow for this, we performed a separate analysis in which all patients randomised to XELOX and who received FOLFOX as second-line therapy were censored. The results were consistent with those obtained in the ITT population and again support the similar efficacy of XELOX vs FOLFOX4.

The question of whether or not capecitabine is non-inferior to 5-FU/FA when given in combination with oxaliplatin in metastatic colorectal cancer has now been addressed in six different randomised phase III trials (Diaz-Rubio et al, 2007; Porschen et al, 2007; Rothenberg et al, 2008; Cassidy et al, 2008a; Comella et al, 2009; Ducreux et al, 2011), of which NO16966 is the largest.
The other five studies, which involved 300–600 patients each, were largely supportive of NO16966. In three of the studies, the efficacy of XELOX or OXXEL was shown to be similar to that of 5-FU/FA-oxaliplatin regimens (Rothenberg et al., 2008; Comella et al., 2009; Ducreux et al., 2011), whereas the remaining two were inconclusive with regard to non-inferiority (Díaz-Rubio et al., 2007; Porschen et al., 2007). Since the completion of the phase III trials, three separate meta-analyses of relevant studies comparing capecitabine or 5-FU/FA plus oxaliplatin in patients with metastatic colorectal cancer have been performed (Arkenau et al., 2008; Cassidy et al., 2008b; Cuppone et al., 2008). Even though each meta-analysis included a different selection of phase II and III studies, the outcomes were very similar with respect to both progression-free survival (HR/relative risk 0.98–1.04) and OS (1.02–1.04). Thus, there is now strong evidence to support the non-inferiority of capecitabine when used in combination with oxaliplatin vs infusional 5-FU-based oxaliplatin regimens in the treatment of patients with metastatic colorectal cancer, both in the first- and second-line settings.

It is therefore likely that other considerations, such as tolerability profile, convenience, patient preference and cost, will assume greater importance when selecting the fluoropyrimidine backbone of a chemotherapy regimen. With regard to tolerability, both XELOX and FOLFOX have a similar profile of adverse events, but XELOX is associated with more grade 3 diarrhoea and hand-foot syndrome, whereas FOLFOX is associated with more grade

### Table 1

Baseline patient characteristics (ITT population)

| Characteristic                | FOLFOX4 (n = 317) | FOLFOX4-placebo (n = 351) | FOLFOX4-bevacizumab (n = 349) | XELOX (n = 317) | XELOX-placebo (n = 350) | XELOX-bevacizumab (n = 350) |
|------------------------------|------------------|--------------------------|--------------------------------|----------------|------------------------|---------------------------|
| Gender                       |                  |                          |                                |                |                        |                           |
| Male                         | 204 64           | 186 53                   | 205 59                         | 194 61         | 205 59                 | 213 61                    |
| Female                       | 113 36           | 165 47                   | 144 41                         | 123 39         | 145 41                 | 137 39                    |
| Age, years                   |                  |                          |                                |                |                        |                           |
| Median                       | 62               | 60                       | 60                             | 61             | 61                     | 61                         |
| Range                        | 24–83            | 26–83                    | 19–82                          | 24–84          | 18–83                  | 18–86                      |
| ECOG performance status      |                  |                          |                                |                |                        |                           |
| 0                            | 163 51           | 211 60                   | 198 57                         | 160 50         | 207 59                 | 207 59                     |
| 1                            | 154 49           | 138 40                   | 147 43                         | 157 50         | 143 41                 | 142 41                     |
| 2                            | 0               | 0                        | 0                              | 0              | 0                      | 1<1                        |
| Primary tumour site          |                  |                          |                                |                |                        |                           |
| Colorectal                   | 17 5             | 25 7                     | 28 8                           | 30 9           | 30 9                   | 32 9                       |
| Colon                        | 200 63           | 232 66                   | 223 64                         | 204 64         | 233 67                 | 236 67                     |
| Rectal                       | 100 32           | 94 27                    | 98 28                          | 83 26          | 87 25                  | 82 23                      |
| Stage at first diagnosis      |                  |                          |                                |                |                        |                           |
| Local regional               | 144 45           | 141 40                   | 128 37                         | 133 42         | 138 39                 | 122 35                     |
| Metastatic                   | 173 55           | 210 60                   | 221 63                         | 184 58         | 212 61                 | 228 65                     |
| Number of metastatic sites   |                  |                          |                                |                |                        |                           |
| 0                            | 1                | 0.3                      | 1                             | 1              | 0                      | 0                          |
| 1                            | 118 37.2         | 142 40.5                 | 150 43.0                       | 127 40.1       | 155 44.3               | 134 38.3                   |
| 2                            | 121 38.2         | 122 34.8                 | 132 37.8                       | 106 33.4       | 112 32.0               | 121 34.6                   |
| 3                            | 47               | 14.8                     | 65 18.5                        | 44 12.6        | 55 17.4               | 58 16.6                     |
| ≥4                           | 30               | 9.5                      | 21 6.0                         | 22 6.3         | 29 9.1                | 25 7.1                      |
| Alkaline phosphatase         |                  |                          |                                |                |                        |                           |
| Abnormal                     | 135 43           | 147 42                   | 146 42                         | 132 42         | 149 43                 | 156 45                     |
| Normal                       | 182 57           | 201 58                   | 199 58                         | 183 58         | 200 57                 | 191 55                     |
| Previous adjuvant therapy    |                  |                          |                                |                |                        |                           |
| No                           | 234 74           | 266 76                   | 261 75                         | 229 72         | 259 74                 | 274 78                     |
| Yes                          | 83               | 26                       | 85 24                          | 88 25          | 88 28                  | 91 26                      |

Abbreviations: ITT = intent-to-treat; ECOG = Eastern Cooperative Oncology Group; FOLFOX4 = infused fluorouracil, folinic acid and oxaliplatin; XELOX = capecitabine and oxaliplatin.

### Table 2

Overall survival by treatment subgroup (ITT population)

| Treatment subgroup comparison | No. of events | Median time to event (months) | Hazard ratio (97.5% CI) |
|-------------------------------|---------------|-----------------------------|------------------------|
| FOLFOX4/FOLFOX4-placebo/      | 847           | 19.5                        | 0.95 (0.85–1.06)       |
| FOLFOX4-bevacizumab           | 820           | 19.8                        |                        |
| XELOX/XELOX-placebo/          | 573           | 18.9                        | 0.95 (0.83–1.09)       |
| XELOX-bevacizumab             | 546           | 19.0                        |                        |
| FOLFOX4/FOLFOX4-placebo/      | 274           | 21.0                        | 0.95 (0.78–1.15)       |
| XELOX-bevacizumab             | 274           | 21.6                        |                        |
| FOLFOX4                        | 284           | 17.7                        | 0.87 (0.72–1.05)       |
| XELOX                          | 266           | 18.8                        |                        |

Abbreviations: ITT = intent-to-treat; CI = confidence interval; FOLFOX4 = infused fluorouracil, folinic acid and oxaliplatin; XELOX = capecitabine and oxaliplatin.

The other five studies, which involved 300–600 patients each, were largely supportive of NO16966. In three of the studies, the efficacy of XELOX or OXXEL was shown to be similar to that of 5-FU/FA-oxaliplatin regimens (Rothenberg et al., 2008; Comella et al., 2009; Ducreux et al., 2011), whereas the remaining two were inconclusive with regard to non-inferiority (Díaz-Rubio et al., 2007; Porschen et al., 2007). Since the completion of the phase III trials, three separate meta-analyses of relevant studies comparing capecitabine or 5-FU/FA plus oxaliplatin in patients with metastatic colorectal cancer have been performed (Arkenau et al., 2008; Cassidy et al., 2008b; Cuppone et al., 2008). Even though each meta-analysis included a different selection of phase II and III studies, the outcomes were very similar with respect to both progression-free survival (HR/relative risk 0.98–1.04) and OS (1.02–1.04). Thus, there is now strong evidence to support the non-inferiority of capecitabine when used in combination with oxaliplatin vs infusional 5-FU-based oxaliplatin regimens in the treatment of patients with metastatic colorectal cancer, both in the first- and second-line settings.

It is therefore likely that other considerations, such as tolerability profile, convenience, patient preference and cost, will assume greater importance when selecting the fluoropyrimidine backbone of a chemotherapy regimen. With regard to tolerability, both XELOX and FOLFOX have a similar profile of adverse events, but XELOX is associated with more grade 3 diarrhoea and hand-foot syndrome, whereas FOLFOX is associated with more grade
Clinical Studies

62

62

vs FOLFOX4-placebo from NO16966 in the present paper.

et al Ducreux

et al 3/4 neutropenia and febrile neutropenia (Rothenberg et al, 2008; Ducreux et al, 2011). This is supported by the updated safety data from NO16966 in the present paper.

Table 3 Adverse events of special interest to chemotherapy and key events pooled by body system (treatment-related and unrelated)

| Body system | All-grade | Grade 3/4 | All-grade | Grade 3/4 |
|-------------|-----------|-----------|-----------|-----------|
|              | No. %     | No. %     | No. %     | No. %     |
| All events   | 644 99    | 506 78    | 649 99    | 468 72    |
| Gastrointestinal disorders | 603 93    | 167 26    | 606 93    | 216 33    |
| Blood/lymphatic disorders | 448 69    | 318 49    | 312 48    | 104 16    |
| Infections/infestations | 292 45    | 66 10     | 210 32    | 45 7      |
| Events of special interest | | | | |
| Neurosensory toxicity | 515 80    | 107 17    | 534 82    | 114 17    |
| Diarrhoea | 394 61    | 74 11     | 429 66    | 133 20    |
| Nausea/vomiting | 452 70    | 47 7      | 464 71    | 52 8      |
| Stomatitis | 242 37    | 13 2      | 140 21    | 8 1       |
| Neutropenia/ granulocytopenia | 379 59    | 282 44    | 180 28    | 46 7      |
| Febrile neutropenia | — —     | 31 5      | — — 6 < 1 |
| Hand-foot syndrome | 70 11    | 8<1 1b    | 201 31    | 40b 6<1  |

Abbreviations: FOLFOX4 = infused 5-fluorouracil, folinic acid and oxaliplatin; XELOX = capecitabine and oxaliplatin. *Pooled term that includes burning sensation, dysesthesia, hyper or hypoesthesia, neuropathic pain, neuropathy, peripheral neuropathy, neurotoxicity, paraesthesia, peripheral (sens)motor neuropathy, (chronic) polyneuropathy, sensory disturbance or loss, skin burning sensation, temperature intolerance, neuralgia, peroneal nerve palsy, autonomic neuropathy.

In terms of convenience, XELOX requires fewer planned office visits than the FOLFOX regimens because oxaliplatin is administered every 3 weeks (rather than every 2 weeks) and because

3/4 neutropenia and febrile neutropenia (Rothenberg et al, 2008; Ducreux et al, 2011). This is supported by the updated safety data from NO16966 in the present paper.

Figure 2 Overall survival for FOLFOX4/FOLFOX4-placebo/FOLFOX4-bevacizumab vs XELOX/XELOX-placebo/XELOX-bevacizumab (A), FOLFOX4/FOLFOX4-placebo vs XELOX/XELOX-placebo (B), FOLFOX4-bevacizumab vs XELOX-bevacizumab (C) and FOLFOX4 vs XELOX (D) (ITT population).

Table 4 Adverse events of special interest to chemotherapy and key events pooled by body system (treatment-related and unrelated)

| Body system | All-grade | Grade 3/4 | All-grade | Grade 3/4 |
|-------------|-----------|-----------|-----------|-----------|
|              | No. %     | No. %     | No. %     | No. %     |
| All events   | 340 99    | 289 85    | 351 99    | 266 75    |
| Gastrointestinal disorders | 320 94    | 94 28     | 325 92    | 132 37    |
| Blood/lymphatic disorders | 229 67    | 159 47    | 125 35    | 44 13     |
| Infections/infestations | 164 42    | 31 9      | 137 39    | 21 6      |
| Events of special interest | | | | |
| Neurosensory toxicity | 281 82    | 61 18     | 296 84    | 64 18     |
| Diarrhoea | 219 64    | 44 13     | 224 64    | 77 22     |
| Nausea/vomiting | 235 69    | 25 7      | 252 71    | 38 11     |
| Stomatitis | 141 41    | 12 4      | 102 29    | 7 2       |
| Neutropenia/ granulocytopenia | 189 55    | 138 40    | 70 20     | 25 7      |
| Febrile neutropenia | — —     | 15 4      | — — 4     | 1 1       |
| Hand-foot syndrome | 47 14    | 6b 2b     | 141 40    | 42b 12b   |

Abbreviations: FOLFOX4 = infused 5-fluorouracil, folinic acid and oxaliplatin; XELOX = capecitabine and oxaliplatin. *Pooled term that includes burning sensation, dysesthesia, hyper or hypoesthesia, neuropathic pain, neuropathy, peripheral neuropathy, neurotoxicity, paraesthesia, peripheral (sens)motor neuropathy, (chronic) polyneuropathy, sensory disturbance or loss, skin burning sensation, temperature intolerance, neuralgia, peroneal nerve palsy, autonomic neuropathy.

*Grade 3 events only.
capcitabine is taken orally. This is supported by resource use data from NO16966, which showed that the need for drug administration visits, central venous access and patient travel and time were reduced with XELOX vs FOLFOX (Scheithauer et al, 2007). When costs were assigned to these data, the total direct costs of both regimens were similar, whereas the indirect costs of XELOX were considerably less than those of FOLFOX (Garrison et al, 2007). Similar observations were made in a cost comparison of capcitabine vs 5-FU± oxaliplatin based on a retrospective analysis of a US medical claims database (Chu et al, 2009).

In conclusion, updated survival data from study NO16966 show that XELOX is similar to FOLFOX, confirming the primary analysis of progression-free survival. XELOX can be considered as a routine first-line treatment option for patients with metastatic colorectal cancer.

ACKNOWLEDGEMENTS

Financial support for this research was provided by Roche. In addition to the investigators in the author list, we acknowledge the following investigators who also participated in this trial: Australia: S Begbie, I Burns, P Gibbs, D Goldstein, P Mainwaring, J McKendrick, M Michael, N Pavlakis, T Price, M Schwartz, J Shapiro, B Stein, G Van Hazel; Austria: J Thaler; Brazil: C Andrade, G Ismael, A Malzyner; Canada: J-P Ayoub, S Berry, R Burke, P Dube, B Findlay, C Fitzgerald, A Gurjal, D Jonker, L Kaizer, P Pfeiffer; Czech Republic: D Feltl, I Kocakova, M Kuta; Denmark: B Nielsen, P Pfeiffer; Finland: P Bono, P Kellokumpu-Lehtinen, S Pyrhoenen; France: F-X Caroli-Bose, B Coudert, C Debridgode, J-P Delord, G Des Guetz, J-Y Douillard, E Francois, G Freyer, C Garnier, M Gil Delgado, F Goldwasser, F Husseini, P Michel, S Negrier, X Pivot, P Rougier; Germany: M Clemens, A Hochhaus, T Hoehler, S Kanzler, S Kubicka, F Kullmann, L Mantovani, W-H Schmigiel, H-J Schmoll, R Voigtmann; Guatemala: CE Hernandez-Monroy, LM Zetina Toache; Hong Kong: A Chan; Hungary: M Dank, I Lang, T Pinter, M Szucs; Ireland: D Fennelly, M Keane, J Kennedy, S O'Reilly; Israel: A Beny, A Hubert, A Sella, S Stemmer; Italy: C Boni, S Brugnatelli, S Cascinu, FP Conte, A Contu, S Monfardini, R Rosso, S Salvagni, A Soberbo; Republic of Korea: YS Park; Mexico: G Calderillo, E Leon; New Zealand: B Robinson; Norway: L Bakstaks, T Guren, H Soerbye; Panama: E Diaz-Correa; Portugal: S Barroso, P Cortes; Russian Federation: VP Kharchenko, M Lichinitser, GM Matlibas, V Moiseenko; South Africa: G Cohen, C Kukat, J Raats, C Slabber, D Vorobiof; Spain: JE Ales-Martinez, A Anton Torres, J Aparicio, E Aranda, A Cervantes, P Escudero, J Felix, C Fernandez-Martos, R Garcia-Carbonero, P Garcia-Alfonso, E Gonzalez Flores, C Gravalos, J Maurel, M Navarro-Garcia, F Rivera, R Salazar, J Sevilla, J Taberner; Sweden: B Glimelius, H Letocha, U Loenn, D Pedersen; Switzerland: M Bornier, A Roth; Taiwan: T-Y Chao, P-M Chen, AL Cheng, T-S Yang; Thailand: S Chakrapere-Sirisuk, AN Kiattikornjathada, A Sookprasert; Turkey: G Demir, E Goker; United Kingdom: E Bessell, P Chakraborti, F Coxon, D Cunningham, S Falk, F Daniel, R Glynnes-Jones, M Hill, T Iveson, A Maraveyas, T Maughan, D Rea, L Samuel, C Topham; United States: N Abramson, B Amin, B Bhaskar, L Campos, R Castillo, V Chang, P DeSimone, P Eisenberg, JA Ellerton, T Ervin, G Frenette, J Fuloria, D Vorobiof, D Reardon, R Mena, J Neidhart, J Pennacchi, E Poplin, C Redfern, R Reiling, M Saleh, L Schwartzberg, W Sikov, A Solky, P Stella, S Thomas, R Vivacqua, R Yanagihara. Support for third-party writing assistance for this manuscript, furnished by Miller Medical Communications, was provided by F. Hoffmann-La Roche Ltd.

REFERENCES

Arkenau HT, Arnold D, Cassidy J, Diaz-Rubio E, Douillard JY, Hochster H, Martoni A, Grothey A, Hinke A, Schmieg W, Schmoll HJ, Porsch R (2008) Efficacy of oxaliplatin plus capcitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. J Clin Oncol 26: 5910 – 5917

Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figuer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirze´n F, Saltz L (2008a) Efficacy of oxaliplatin plus capcitabine or infusional fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the MCRC. Presented at the ASCO GI Cancers Symposium: Orlando, Florida, USA, 25 – 27 January (abstract 341)

Chu E, Schumian KL, Zelt S (2009) Costs associated with complications are lower with capcitabine than with 5-fluorouracil in patients with colorectal cancer. Cancer 115: 1412 – 1423

Comella P, Massidda B, Filippelli G, Farris A, Natale D, Barberis G, Maiorino L, Palmeri S, Condemi G, Southern Italian Cooperative Oncology Group (2009) Randomised trial comparing biweekly oxapilatin plus oral capcitabine versus oxapilatin plus i.v. bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italian Cooperative Oncology Study 0401. J Cancer Res Clin Oncol 135: 217 – 226

Cuppone F, Bria E, Sperduti I, Di Maio M, Carlini P, Milella M, Cognetti F, Terzoli E, Giannarelli D (2008) Capcitabine (CAF) versus 5-fluorouracil (FU) in combination with oxapilatin (OX) as 1st-line chemotherapy (CT) for advanced colorectal cancer (ACRC): meta-analysis of randomised clinical trials (RCT). J Clin Oncol 26: 192s (Suppl; abstract 4056)

de Gramont A, Figuer A, Seymour M, Homzer M, Hmisi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braid F, Wilson G, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxapilatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938 – 2947

Diaz-Rubio E, Taberner J, Gomez-Espana A, Massuti B, Sastre J, Chaves M, Abad A, Currado A, Queralt B, Reina J, Maurel J, Gonzalez-Flores E, Aparicio J, Rivera F, Losa F, Aranda E, Spanish Cooperative Group for the Treatment of Digestive Tumors Trial (2007) Phase II study of capcitabine plus oxapilatin versus continuous infusion fluorouracil plus oxapilatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 25: 4224 – 4230

Di Leo A, Buyse M, Bleiberg H (2004) Is overall survival a realistic primary end point in advanced colorectal cancer studies? A critical assessment based on four clinical trials comparing fluorouracil plus leucovorin with the same treatment combined either with oxapilatin or with CPT-11. Ann Oncol 15: 545 – 549

Ducrux M, Benounou J, Hebrard M, Ychou M, Lede G, Conroy T, Adenis A, Simon C, Rebischung C, Bergougnoix L, Kockler L, Douillard JY, GI Group of the French Anti-Cancer Centers (2011) Capcitabine plus oxapilatin (XELOX) versus 5-fluorouracil/leucovorin plus oxapilatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer 128: 682 – 690

Garrison L, Cassidy J, Saleh M, Lee F, Mena R, Fuloria J, Chang V, Ervin T, Stella P, Saltz L (2007) Cost comparison of XELOX compared to...
FOLFOX4 with or without bevacizumab (bev) in metastatic colorectal cancer. *J Clin Oncol* 25: 18S (Suppl, abstract 4074)

Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 19: 2282–2292

Porschen R, Arkenau H-T, Kubicka S, Greil R, Seufferlein T, Freier W, Kretzschmar A, Graeven U, Grothey A, Hinke A, Schmieg W, Schmoll HJ, AIO Colorectal Study Group (2007) Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin Oncol* 25: 4217–4223

Rothenberg ML, Cox JV, Butts C, Navarro M, Bang YJ, Goel R, Gollins S, Siu LL, Laguerre S, Cunningham D (2008) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. *Ann Oncol* 19: 1720–1726

Saltz L, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sírén F, Cassidy J (2008)

Efficacy and safety of bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 26: 2013–2019

Scheithauer W, Cassidy J, Figer A, Wong R, Koski S, Lichinitser M, Yang T, Clarke S, Díaz-Rubio E, Garrison L (2007) A comparison of medical resource use for 4 chemotherapy regimens as first-line treatment for metastatic colorectal cancer (MCRC): XELOX vs. FOLFOX4 ± bevacizumab (A). *J Clin Oncol* 25: 18S (Suppl, abstract 4098)

Twelves C, Wong A, Nowacki MP, Abt M, Burris III H, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulas V, Husseini F, Jodrell D, Koralewski P, Kröning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schüller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J, Scheithauer W (2005) Capectabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 352: 2696–2704

Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P, Xeloda Colorectal Cancer Study Group (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 19: 4097–4106