Epidemiology and natural history of central venous access device use and infusion pump function in the NO16966 trial

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Background: Central venous access devices in fluoropyrimidine therapy are associated with complications; however, reliable data are lacking regarding their natural history, associated complications and infusion pump performance in patients with metastatic colorectal cancer.

Methods: We assessed device placement, use during treatment, associated clinical outcomes and infusion pump performance in the NO16966 trial.

Results: Device replacement was more common with FOLFOX-4 (5-fluorouracil (5-FU) + oxaliplatin) than XELOX (capecitabine + oxaliplatin) (14.1% vs 5.1%). Baseline device-associated events and post-baseline removal-/placement-related events occurred more frequently with FOLFOX-4 than XELOX (11.5% vs 2.4% and 8.5% vs 2.1%). Pump malfunctions, primarily infusion accelerations in 16% of patients, occurred within 1.6–4.3% of cycles. Fluoropyrimidine-associated grade 3/4 toxicity was increased in FOLFOX-4-treated patients experiencing a malfunction compared with those who did not (97 out of 155 vs 452 out of 825 patients), predominantly with increased grade 3/4 neutropenia (53.5% vs 39.8%). Febrile neutropenia rates were comparable between patient cohorts ± malfunction. Efficacy outcomes were similar in patient cohorts ± malfunction.

Conclusions: Central venous access device removal or replacement was common and more frequent in patients receiving FOLFOX-4. Pump malfunctions were also common and were associated with increased rates of grade 3/4 haematological adverse events. Oral fluoropyrimidine-based regimens may be preferable to infusional 5-FU based on these findings.

Fluoropyrimidines form the foundation of the vast majority of chemotherapy regimens used in the treatment of metastatic colorectal cancer (mCRC), and they can take the form of intravenous 5-fluorouracil (5-FU); by continuous or bolus infusion or oral formulations (capecitabine). Fluoropyrimidine-based regimens include XELOX (oral capecitabine plus infusional oxaliplatin), FOLFOX (infusional leucovorin (LV), 5-FU and oxaliplatin) and FOLFIRI (infusional LV, 5-FU and irinotecan), each of which has a well-established role in the management of patients with mCRC. These regimens are now included in the key

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CVAD use and infusion pump function in mCRCEvidence-based practice guidelines in Europe and the United States (Van Cutsem et al, 2010; NCCN, 2013).

The preferred 5-FU administration schedule for the FOLFOX or FOLFIRI regimens is intravenous infusions of either 22 or 46 h duration. Patients receiving these regimens usually require placement of a central venous access device (CVAD), as treatment involves repeated and prolonged infusions. Catheter insertion requires skilled personnel, and it is usually performed under local anaesthesia, taking ~30–50 min, on average, to complete (Gann and Sardi, 2003; Shen-Gunther et al, 2003). Central venous access device placements are often associated with complications such as infections and venous thrombosis, resulting in antibiotic use, hospitalisation and CVAD replacements (Deboureau et al, 2009; Beckers et al, 2010). A number of other complications have been observed, including insertion-related problems (McGee and Gould, 2003) and catheter sheath formation (Xiang et al, 1998). Previous studies have reported CVAD-associated complications in 8–15% of patients with CRC (Martoni et al, 2006; Inaba et al, 2007; Kawamura et al, 2008). In a randomised phase II study of patients with advanced CRC treated with XELOX or FOLFOX (utilising protracted infusion of 5-FU and oxaliplatin), venous line complications occurred in 15% of FOLFOX-treated patients, which resulted in suspension or cessation of treatment (Martoni et al, 2006). The INT-0153 study compared the clinical efficacy of continuous infusion 5-FU (CIFU) plus levamisole vs bolus 5-FU/LV plus levamisole in the adjuvant treatment of patients with stage III and high-risk stage II colon cancer, and found that nearly twice as many patients discontinued CIFU/levamisole than those who discontinued bolus 5-FU/LV/levamisole (106 out of 460 vs 64 out of 459, respectively), despite significantly higher rates of grade 4 toxicities in the bolus arm (5% vs 39%). The main adverse events observed were haematological and gastrointestinal in nature. Early treatment discontinuation in the CIFU arm was more often associated with non-life-threatening adverse events, such as hand–foot syndrome, or events associated with the delivery and administration of CIFU, such as pump therapy logistics, pump malfunctions, CVAD-associated thrombosis and catheter-related neck pain (Poplin et al, 2005).

There is, presently, a paucity of data on the natural history of CVADs and CVAD-associated complications from large studies of patients with mCRC. Moreover, data regarding the performance and reliability of infusional pumps have not been prospectively reported in the scientific literature. Herein, we report the largest prospective evaluation of CVAD placement and use during treatment, and of CVAD-associated clinical outcomes. Data were obtained from the NO16966 trial, which was a phase III, randomised investigation into the comparative efficacy of XELOX and FOLFOX-4 in the front-line treatment of patients with mCRC. When used, CVADs were placed in patients receiving XELOX as the result of the oxaliplatin component of the regimen.

### Patients and Methods

#### Study Design

The design of the NO16966 study and the patient population have been described previously (Cassidy et al, 2008). Based on the results of the pivotal trial evaluating bevacizumab in mCRC, the trial design was amended after patient accrual had begun (Saltz et al, 2007). The amended trial used a 2 × 2 factorial design and randomised patients to either FOLFOX-4 or XELOX in combination with bevacizumab or placebo (Cassidy et al, 2008). The primary endpoint was progression-free survival. During the study, data were prospectively collected regarding CVAD placements (but not the specific type of CVAD) or CVAD removals and/or replacements, and adverse events associated with CVAD insertion, removal and replacement (graded according to the National Cancer Institute Common Terminology Criteria, version 3.0 (National Cancer Institute, 2006); available for initial placements only). Central venous access device placement was at the discretion of the investigator. Data were prospectively collected on the presence of an infusion pump malfunction during a treatment cycle, as well as start and stop times associated with individual infusions of 5-FU. Adherence to oral capecitabine was assessed by pill counts at the time of patient clinic visits.

NO16966 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 obtained from an independent ethics committee or the institutional review board of each site.

#### Patients

The entire NO16966 trial population, including patients treated with bevacizumab or placebo, was used for this evaluation. The safety population includes all randomised patients who received at least one dose of any component of the study regimens. Patients were recruited between July 2003 and February 2005.

#### Statistical Analyses

Analyses were derived from the safety population and included patients with available CVAD data. Patients were grouped into cohorts consisting of the total safety population or subsets, dependent on the specific analyses performed: time to first CVAD placement (in patients with a first placement after treatment start); time from first placement to first replacement (in patients with a first removal); and time from first placement to second replacement (in patients with a second removal).

Incidence rates for each cohort were compared between the XELOX and FOLFOX-4 regimens using the Pearson’s χ²-test. Median times to each endpoint (± s.e.) were estimated using the Kaplan–Meier method, and the distributions were compared using the log-rank test. As the patient cohorts selected could have been subsets of the total safety population, results of statistical tests are provided for descriptive purposes only.

Central venous access device-associated complications and adverse events, along with incidence rates, were summarised in terms of those reported after CVAD placement on the baseline case report form (CRF), and those reported during treatment after CVAD removal/replacement on a treatment cycle-specific CRF. Progression-free survival and overall survival among patients treated with FOLFOX-4 who experienced a pump malfunction during treatment were compared with those who did not using the Kaplan–Meier method. The total number of patients experiencing ≥1 grade 3/4 adverse events of relevance to fluoropyrimidine therapy were pooled and compared using the χ²-test. Only the highest grade reported per adverse event and patient was included for statistical analyses. Pump malfunction data were recorded for 5-FU infusions only, and therefore relate only to patients treated with FOLFOX-4.

Multivariate logistic regression analyses explored the potential independent association between study treatment (FOLFOX-4 vs XELOX) and the risk of CVAD-associated adverse events post-implantation/insertion and with respect to the FOLFOX-4 patients alone, the association of pump malfunctions and risk of grade 3/4 adverse events of special interest for fluoropyrimidines/neutropenia.

Cox proportional hazard regression models were performed for progression-free survival and overall survival, and logistic regression analyses were performed for overall response rate.

The additional covariates used in the multivariate logistic and the Cox regression analyses included age (<65 vs ≥65 years), gender, baseline ECOG performance status (0 vs 1/2), number of metastatic sites at baseline (<2 vs ≥2 organs) and infusion duration (<22 vs ≥22 h). The hypothesis testing of all covariates was two-sided at α = 0.025.

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RESULTS

Patient characteristics. The patient baseline demographics for the NO16966 trial has been described previously (Cassidy et al., 2008). Patient demographics and disease characteristics of the cohorts used to analyse CVAD-related complications and pump malfunctions were generally comparable both to the overall population of the study and to each other (Supplementary Tables 1 and 2). The disposition of patients and availability of the derived data regarding CVAD placement are outlined in Figure 1.

CVAD placement. Initial CVAD placement data were available for 1341 out of 1998 patients (67%, Table 1). Central venous access devices were placed in 1194 patients (60%) on/before the treatment start date, with 147 (7%) having a CVAD placed after treatment start.

While CVADs were placed on/before the treatment start date in 797 patients receiving FOLFOX-4 and 397 patients receiving XELOX, placements were performed after treatment start in 91 and 56 patients receiving FOLFOX-4 and XELOX, respectively. For patients with a first CVAD placement after treatment start, the time to first CVAD placement was shorter in patients receiving FOLFOX-4 compared with those receiving XELOX. The median time to first placement was 13.0 days after treatment start (95% confidence interval (CI): 10–15 days) for patients treated with FOLFOX-4, and 81.0 days after treatment start (95% CI: 60–109 days) for patients treated with XELOX (log-rank test  \( P<0.0001 \); Figure 2 and Supplementary Table 3).

CVAD removal/replacement. A higher proportion of patients treated with FOLFOX-4 required a CVAD replacement after removal of their first CVAD than those treated with XELOX (125 out of 888 (14.1%) vs 23 out of 453 (5.1%) patients, respectively). Kaplan–Meier survival analyses estimated the median times to replacement to be similar in the analytic cohorts (Figure 3 and Supplementary Table 3). A similar result was observed for the subpopulation of patients with a first replacement

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**Figure 1. Distribution of patient data.** Abbreviations: BL = baseline (placement on/before the start of treatment); Post-BL = post-baseline (placement after the start of treatment).
Table 1. CVAD placement data for patients treated in the NO16966 study (patients in the safety population who had placement data)

| Patients, n (%) | FOLFOX-4, n = 888* | XELOX, n = 453* |
|----------------|-------------------|----------------|
| First placement on/before treatment start, n = 797 |                         |             |
| First removal on/after date of first placement | 156 (19.6) | 70 (15.1) |
| First replacement on/after date of first removal | 118 (14.8) | 43 (9.5) |
| Second removal on/after date of first replacement | 53 (6.6) | 23 (5.1) |
| Second replacement on/after date of second removal | 33 (4.1) | 8 (1.8) |

Abbreviations: CVAD = central venous access device; FOLFOX-4 = 5-fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin.

*Patients with first placement data.
*Regardless of whether the first placement was on/before or after the treatment start date.
*Patients with a first removal.
*Patients with a first replacement.
*Patients with a second removal.

| Median, days (95% CI) | Log-rank test P |
|-----------------------|-----------------|
| FOLFOX-4 ± bevacizumab/placebo | 13 (10–15) | < 0.0001 |
| XELOX ± bevacizumab/placebo | 81 (60–109) |             |

Figure 2. Kaplan–Meier curve of time to first CVAD placement among patients with first CVAD placements after treatment start, treated with FOLFOX-4 ± bevacizumab/placebo or XELOX ± bevacizumab/placebo (patients in the safety population who had placement data).

Figure 3. Kaplan–Meier curve of time from first CVAD placement to first CVAD replacement among patients with first replacement (after first removal), treated with FOLFOX-4 ± bevacizumab/placebo or XELOX ± bevacizumab/placebo (patients in the safety population who had placement data).

after a first removal treated with chemotherapy alone: no significant differences were seen regardless of chemotherapy regimen or use of bevacizumab. Second replacements were uncommon and occurred mainly in patients treated with chemotherapy alone (data not shown).

CVAD-associated complications and adverse events. Adverse events associated with CVAD placement and use were relatively uncommon, and the majority of events were associated with placement. More than 80% of patients with CVAD placements had their first CVAD-related adverse event within 120 days after initial placement (Figure 4). Central venous access device-associated adverse events after initial placement occurred in 138 out of 1998 patients with a baseline placement (6.9%). Catheter/insertion site events were the most frequent events, occurring in 129 out of 1998 patients (6.5%), and were associated with the catheter site in 154 out of 169 (91.1%) of all cases. Common adverse events in this category included pain, haematoma and haemorrhage. Central venous access device-associated adverse events occurred more frequently at baseline placement with FOLFOX-4 compared with XELOX (11.5% vs 2.4%; Table 2). Adverse events associated with CVAD removal or replacement were also more frequent in patients receiving FOLFOX-4 than in those receiving XELOX (8.5% vs 2.1%, respectively; Table 3). The most common adverse events were equally distributed between CVAD site infections and other local complications. These events included central line/site infection, catheter site cellulitis, catheter thrombosis and catheter-related complications that were not otherwise specified. The CVAD-associated adverse event rates for FOLFOX-4 versus XELOX plus bevacizumab were similar to those for chemotherapy alone (data not shown). Multivariate logistic regression analyses confirmed that treatment was independently associated with the
The most common issue was related to accelerated delivery of 5-FU, frequently than reusable, programmable pumps. Time (Figure 5). Disposable, single-use pumps malfunctioned more, the malfunction rate was consistent across cycles (1.3–4.9%) and over treatment cycles. Pump malfunctions during 5-FU infusion occurred in 16% of patients treated with FOLFOX-4. The malfunction rate was consistent across cycles (1.3–4.9%) and over time (Figure 5). Disposable, single-use pumps malfunctioned more frequently than reusable, programmable pumps.

Among the group of patients experiencing a pump malfunction, the most common issue was related to accelerated delivery of 5-FU, with 61% of patients who experienced a pump malfunction having an infusion duration of <22 h vs 11% of patients without a pump malfunction (Table 4). The majority of patients not experiencing a malfunction (88%) had an infusion duration of 22–24 h vs 31.8% in patients experiencing a pump malfunction.

The rates of grade 3/4 adverse events specifically related to fluoropyrimidine treatment in patients with FOLFOX-4 who experienced a pump malfunction compared with those who did not are shown in Table 5. Overall, there was a trend towards increased adverse events in patients who experienced a malfunction (97 out of 155 (64.3%) vs 42 out of 825 patients; \( \chi^2 \)-test; \( P = 0.00729 \)). The incidence of grade 3/4 neutropenia was significantly higher in FOLFOX-4, FOLFOX-4 ± bevacizumab/placebo and XELOX, XELOX ± bevacizumab/placebo compared with FOLFOX-4, FOLFOX-4 ± placebo and XELOX, XELOX ± placebo groups. The study protocol allowed for the use of disposable, single-use pumps or for reusable, programmable pumps for the 5-FU infusion according to investigator’s choice and site preference. The pump type was recorded; however, more detailed information on the manufacturer or model was not collected. Disposable and reusable pumps were used equally across treatment cycles. Pump malfunctions during 5-FU infusion occurred in 16% of patients treated with FOLFOX-4. The malfunction rate was consistent across cycles (1.3–4.9%) and over time (Figure 5). Disposable, single-use pumps malfunctioned more frequently than reusable, programmable pumps.

Table 2. Adverse events reported after CVAD placement on the baseline CRF page in >0.1% of patients treated with FOLFOX-4 or XELOX (patients in the safety population who had placement data).

| Adverse event, n (%) | FOLFOX-4, n = 990 | XELOX, n = 1008 |
|---------------------|-------------------|------------------|
| Total patients with ≥1 adverse events | 114 (11.5) | 24 (2.4) |
| General disorders and administration site conditions | 106 (10.7) | 23 (2.3) |
| Catheter site pain | 59 (6.0) | 14 (1.4) |
| Catheter site haematoma | 34 (3.4) | 5 (0.5) |
| Catheter site haemorrhage | 21 (2.1) | 2 (0.2) |
| Catheter site erythema | 3 (0.3) | 1 (0.1) |
| Catheter site swelling | 2 (0.2) | 1 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 5 (0.5) | 1 (0.1) |
| Pneumothorax | 2 (0.2) | 1 (0.1) |
| Injury, poisoning and procedural complications | 2 (0.2) | 0 (0) |
| Procedural nausea | 2 (0.2) | 0 (0) |
| Nervous system disorders | 2 (0.2) | 0 (0) |
| Dizziness | 2 (0.2) | 0 (0) |

Abbreviations: CRF = case report form; CVAD = central venous access device; FOLFOX-4 = 5-fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin.

Figure 4. Cumulative incidence of CVAD-related complications (patients in the safety population who had placement data).

Figure 5. Percentages of pump malfunctions by pump type (safety populations for the FOLFOX-4, FOLFOX-4 ± placebo and FOLFOX-4 ± bevacizumab groups).
Table 4. Treatment infusion duration for infusions with and without a pump malfunction (safety populations for the FOLFOX-4, FOLFOX-4 + placebo and FOLFOX-4 + bevacizumab groups)

| Duration | Malfunction, n = 559 infusions | No malfunction, n = 21 497 infusions |
|----------|---------------------------------|--------------------------------------|
| <12 h, n (%) | 22 (3.9) | 58 (0.3) |
| 12–14 h, n (%) | 1 (0.2) | 20 (0.1) |
| 14–16 h, n (%) | 4 (0.7) | 16 (0.1) |
| 16–18 h, n (%) | 35 (6.3) | 114 (5.5) |
| 18–24 h, n (%) | 96 (17.2) | 427 (20.0) |
| 24–32 h, n (%) | 183 (32.7) | 1800 (84.4) |
| 22–24 h, n (%) | 178 (31.8) | 18851 (87.7) |
| >24 h, n (%) | 27 (4.8) | 148 (0.7) |
| >26 h, n (%) | 13 (2.3) | 63 (0.3) |

Abbreviation: FOLFOX-4 = 5-fluorouracil + oxaliplatin.

Table 5. Grade 3/4 adverse events specifically related to fluoropyrimidine treatment across all cycles of patients treated with FOLFOX-4, based on the presence of a pump malfunction (patients in the safety population who had placement data)

| Adverse events, n (%) | Malfunction, n = 155 | No malfunction, n = 825 |
|-----------------------|----------------------|-------------------------|
| Total patients with ≥1 adverse events | 107 (69.0) | 496 (60.1) |
| Gastrointestinal disorders | 25 (16.1) | 157 (19.0) |
| Diarrhoea | 15 (9.7) | 103 (12.5) |
| Nausea | 7 (4.5) | 38 (4.6) |
| Vomiting | 7 (4.5) | 39 (4.7) |
| Stomatitis (all) | 3 (1.9) | 20 (2.4) |
| Blood and lymphatic system disorders | 91 (58.7) | 361 (43.8) |
| Neutropenia | 83 (53.5) | 328 (39.8) |
| Febrile neutropenia | 12 (7.7) | 33 (4.0) |
| Granulocytopenia | 1 (0.6) | 4 (0.5) |
| Skin and subcutaneous tissue disorders | 2 (1.3) | 12 (1.5) |
| Hand–foot syndrome | 2 (1.3) | 12 (1.5) |
| Infections and infestations | 0 (0) | 6 (0.7) |
| Neutropenic sepsis | 0 (0) | 5 (0.6) |
| Neutropenic infection | 0 (0) | 1 (0.1) |

Abbreviation: FOLFOX-4 = 5-fluorouracil + oxaliplatin.

**Table 4**

### Table 4: Treatment Infusion Duration for Infusions with and Without a Pump Malfunction (Safety Populations for the FOLFOX-4, FOLFOX-4 + Placebo, and FOLFOX-4 + Bevacizumab Groups)

| Duration | Malfunction, n = 559 infusions | No Malfunction, n = 21,497 infusions |
|----------|---------------------------------|--------------------------------------|
| <12 h, n (%) | 22 (3.9) | 58 (0.3) |
| 12–14 h, n (%) | 1 (0.2) | 20 (0.1) |
| 14–16 h, n (%) | 4 (0.7) | 16 (0.1) |
| 16–18 h, n (%) | 35 (6.3) | 114 (5.5) |
| 18–24 h, n (%) | 96 (17.2) | 427 (20.0) |
| 24–26 h, n (%) | 13 (2.3) | 63 (0.3) |

### DISCUSSION

The NO16966 trial is the largest patient population from a randomised phase III clinical study to provide data regarding the use of CVADs. Based on this study, it is clear that CVAD-associated complications, the requirement for CVAD replacement and the occurrence of pump malfunctions during treatment were common. Of note, patients treated with XELOX ± bevacizumab/placebo required fewer subsequent replacements and experienced fewer CVAD-associated adverse events than those treated with FOLFOX-4 ± bevacizumab/placebo. As such, differences in CVAD-associated complication rates between patients treated with FOLFOX-4 plus bevacizumab or XELOX plus bevacizumab appear to result from the continued repeated use of infusional 5-FU associated with the FOLFOX-4 regimen.

Thrombosis and infections are well-known complications of CVADs. However, in the NO16966 study, we observed lower or comparable rates of thrombosis compared with 1–18% in several other studies involving CVADs (where patients did not receive prophylaxis against thrombosis) (Verso et al, 2005; Karthaus et al, 2006; Fagnani et al, 2007; Ng et al, 2007; Araújo et al, 2008; Surov et al, 2008; Biffi et al, 2009; Starling et al, 2009; Beckers et al, 2010; Cavanna et al, 2010; Barbetakis et al, 2011; Kriegel et al, 2011; Saber et al, 2011). We also observed lower or comparable rates of infection than the 2.4–5.8% previously reported rates (Karthaus et al, 2006; Fagnani et al, 2007; Ng et al, 2007; Beckers et al, 2010; Cavanna et al, 2010; Barbetakis et al, 2011), although even lower infection rates of 0.4–2.5% have also been reported in some studies (Araújo et al, 2008; Biffi et al, 2009). Consistent with our findings, adverse events have been reported to occur relatively early following CVAD placement (Fagnani et al, 2007; Inaba et al, 2007; Ng et al, 2007; Cavanna et al, 2010; Saber et al, 2011). In the INT-0153 study (Polpin et al, 2005), catheter-related complications and pump issues (logistics and malfunctions) may have adversely impacted the delivery of CIP, and the authors speculated that this may, in part, explain why CIPU did not improve clinical outcomes when compared with bolus 5-FU.

Pump malfunctions during FOLFOX-4 treatment were relatively common in NO16966 and occurred in a relatively high proportion of patients (16%), with malfunctions reported in 1.3–4.9% of patients across treatment cycles. The majority of malfunctions were observed for disposable pumps; however, programmable pump malfunctions constituted ~20% of the total malfunctioning pumps. Shorter infusion times were associated with malfunctions in approximately two-thirds of infusions. Fluoropyrimidine-induced cytotoxicity is known to be both dose- and schedule-dependent (The Meta-Analysis Group In Cancer, 1998; Lamont and Schilsy, 1999). These pharmacological properties raised questions regarding the potential association of altered drug delivery by pump malfunctions and risk for...
adverse events as well as efficacy outcomes. Increased rates of grade 3/4 adverse events specifically related to fluoropyrimidines (predominantly neutropenia) were observed in patients who experienced a pump malfunction. Nevertheless, clinical efficacy outcomes appeared to be comparable regardless of malfunction.

The strength of the present analysis comes from the fact that the NO16966 trial included the largest patient population, to date, that provided data on the use of CVADs in mCRC. However, one of the main limitations of this analysis relates to the fact that information on the specific types of catheters used was not collected. Presumably, the catheter type/insertion for both regimens was based on local standards of care, and as a result, the specific type of catheter may have impacted on the subsequent incidence of adverse events. However, it should be noted that the overall incidence and pattern of onset of adverse events were comparable to those previously reported in the literature. Another potential limitation of our analysis was that CVAD-associated adverse events were only reported during the study treatment period. All other events were collected together regardless of whether they were caused by a CVAD, underlying cancer clinical state, study treatment regimens or other reasons. The other potential reasons for CVAD-associated adverse events were tracked using general adverse event CRFs throughout the study treatment period and for an additional 4 weeks after discontinuation of study treatment. Of note, the rate of hand–foot syndrome was similar in both arms.

Treatment with the oral fluoropyrimidine, capecitabine, effectively avoids many of the resource issues associated with CVADs. A medical resource utilisation companion study to the NO16966 trial showed that the number of drug administration visits and CVADs placed was reduced with XELOX vs FOLFOX-4, despite the addition of intravenous oxaliplatin and bevacizumab (Scheithauer et al., 2007). A separate United States cost minimisation analysis of NO16966 reported that the total estimated indirect costs for XELOX without bevacizumab were $1300 less than for FOLFOX-4 without bevacizumab, and $3100 less for XELOX with bevacizumab than FOLFOX-4 with bevacizumab. The estimated indirect costs for XELOX were $1500–$1700 less than for FOLFOX (Garrison et al., 2007). Similarly, a cost minimisation analysis of XELOX vs FOLFOX-6 showed that XELOX is associated with significantly reduced mean disease management costs compared with FOLFOX-6 (€12918 vs €17226; P < 0.001). Patients treated with XELOX also spend less time at the hospital than patients treated with FOLFOX-6 (Conroy et al., 2010; Perrocheau et al., 2010). A review of 4973 patients in the Thomson Healthcare MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases showed that capcitabine-based therapy was associated with fewer complications than 5-FU-based therapy (Chu et al., 2009). As a result, the mean predicted monthly cost of complications associated with 5-FU plus oxaliplatin was higher than that of those associated with XELOX ($1165, 95% CI: $892–$1595). Notably, no difference in total costs were observed when drug acquisition, administration and complication costs were combined (Chu et al., 2009).

In summary, this study provides additional insights regarding the frequency and nature of CVAD-associated complications that occur during the front-line treatment of patients with mCRC. Our analysis shows that regimens based on an oral fluoropyrimidine (e.g., XELOX) are preferable to infusional 5-FU (e.g., FOLFOX-4) for the treatment of mCRC in the front-line setting with regard to CVAD-associated complications, the need for CVAD replacement, pump malfunctions and CVAD-associated adverse events, all of which adversely impact upon patient well being. These findings also have potentially important implications with respect to adjuvant chemotherapy. The majority (80%) of CVAD-associated adverse events occurred within 120 days of treatment initiation, which is well within the usual 6-month duration of adjuvant chemotherapy. Adjuvant therapy is given with curative intent, but in reality, many patients develop residual disease, recur, relapse despite adjuvant therapy. Only a relatively small proportion of patients, therefore, directly benefit from adjuvant treatment. For this reason, any risk of potentially serious complications should be minimised. Thus, in this setting, oral fluoropyrimidine-based chemotherapy with either the XELOX regimen or capecitabine monotherapy may be a preferred treatment option when compared with FOLFOX-4 or other infusional 5-FU regimens.

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