Upfront FOLFOXIRI + bevacizumab followed by fluoropyrimidin and bevacizumab maintenance in patients with molecularly unselected metastatic colorectal cancer

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Background: The addition of bevacizumab (BEV) to standard doublet chemotherapy improves outcomes compared with chemotherapy alone in patients with metastatic colorectal cancer (mCRC). The OPAL study examined the effect of BEV + FOLFOXIRI followed by 5FU/LV and BEV maintenance on progression-free survival (PFS) in patients with previously untreated unresectable mCRC.

Methods: Eligible patients had histologically confirmed mCRC, ECOG performance status ≤1 and were 18–70 years old. Patients received up to 12 cycles of FOLFOXIRI + BEV q2w (induction phase) followed by up to ≤40 cycles of 5FU/LV + BEV q2w (maintenance phase). Median PFS was the primary end point; secondary end points included response, OS, secondary resection rate, safety and prognostic value of pharmacogenetic profiling.

Results: Ninety-seven patients were enrolled. Of these, 90 received study medication and formed the safety population: 64 males; median age 58 (range 28–71) years; ECOG performance status 0/1 in 54%/46% patients; and liver only disease in 35 patients. Relative dose intensities were 79–85% for all four drugs. The incidence of adverse events (AEs) was as previously reported and there were no new safety signals. In total, 87 serious AEs occurred in 39 patients (43%). Median PFS was 11.1 months (95% CI 9.4–12.0) and did thus not meet the primary objective of 12 months. Median OS was 32.2 months (95% CI 22.6–36.9). Fifty-two patients were pharmacogenetically profiled.

Conclusions: FOLFOXIRI + BEV was feasible in this molecularly unselected mCRC patient population, showing a high efficacy in terms of survival, overall response and secondary resection rate. Pharmacogenomic profiling revealed no clinically relevant marker.

Colorectal cancer (CRC) is the second (in women) and third (in men) most commonly diagnosed malignancy and one of the leading causes of cancer deaths (Malvezzi et al, 2014). Around one quarter of patients with CRC present with metastatic disease (mCRC) at the time of diagnosis (synchronous disease), and up to 40% of patients will develop metastases during the course of their
disease, resulting in the relatively high overall mortality rate associated with CRC.

Several drugs as single agent or in various combinations and sequences are available for mCRC, including fluoropyrimidines (5FU, capecitabine), irinotecan, oxaliplatin, the vascular endothelial growth factor (VEGF) antibody bevacizumab, the epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab for RAS wild-type patients, the VEGF receptors 1 and 2 fusion protein alibezert and the multi target tyrosine kinase inhibitor regorafenib (Van Cutsem et al, 2014). Notably, median overall survival (OS) can now be as long as 30 months in molecularly or clinically selected patients with current treatment regimen (Douillard et al, 2013; Heinemann et al, 2014; Loupakis et al, 2014; Venook et al, 2014).

Besides chemotherapy doublets in combination with an antibody, triplet chemotherapy has been established combining fluoropyrimidines, oxaliplatin and irinotecan in first-line mCRC (Sougakos et al, 2006; Falcone et al, 2007; Ychou et al, 2008). The FOLFOXIRI regimen demonstrated a superior overall response rate (ORR), secondary resection rate, progression-free survival (PFS) and OS compared with FOLFIRI (Falcone et al, 2007).

Intensification of first-line therapies with a four-drug combination, including a chemotherapy triplet (fluoropyrimidine, oxaliplatin, irinotecan) and a monoclonal antibody, seems to be a promising approach in terms of increasing the number of patients potentially amenable for secondary local ablation and/or inducing a relevant, long-lasting tumour response. Thus the exploratory phase II OPAL study was performed applying up to 6 months of induction treatment with FOLFOXIRI and bevacizumab followed by up to 18 months of maintenance treatment with 5FU/LV and bevacizumab.

To evaluate the prognostic value of single-nucleotide polymorphisms (SNPs) in the VEGF pathway, an exploratory translational project was performed in a subset of 52 patients (Gerger et al, 2011; Hansen et al, 2012; Loupakis et al, 2013).

**PATIENTS AND METHODS**

**Patient eligibility.** Patients were eligible for inclusion if they were aged between 18 and 70 years; had a histologically confirmed mCRC with at least one radiographically measurable lesion, which was not primarily resectable; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1; and adequate hepatic, renal and bone marrow function. Patients were ineligible if they had a history of previous chemotherapy for mCRC or had uncontrolled severe organ or metabolic dysfunction. The trial was approved by the institutional review board and the competent authority (Paul Ehrlich Institut) and registered (NCT00940303/ EudraCT number: 2008-001180-11). All patients provided written informed consent before study entry.

**Study design and treatment.** This was an open-label, single arm, multicentre phase II trial evaluating the efficacy and tolerability of FOLFOXIRI and bevacizumab in first-line mCRC and correlating efficacy with pharmacogenomic data in a subgroup of patients. Safety data were assessed after 20 patients had been treated for at least two cycles and again upon completion of induction treatment.

Induction treatment with FOLFOXIRI and bevacizumab was administered with oxaliplatin at a dose of 85 mg m⁻² IV over 2 h (day 1), irinotecan at a dose of 165 mg m⁻² IV over 1 h (day 1), LV at a dose of 200 mg m⁻² IV over 2 h (day 1), 5FU at a dose of 3200 mg m⁻² IV over 48 h (days 1–3) and bevacizumab at a dose of 5 mg kg⁻¹ IV over 30–90 min (day 1) in a biweekly schedule for a maximum of 12 cycles followed by an obligatory maintenance with 5FU/LV and bevacizumab (same dose as used in the induction phase with or without dose reductions) for up to 2 years (Masi et al, 2010; Loupakis et al, 2014). Premature entry into maintenance treatment phase was possible after completing at least six cycle of induction treatment in case of repeated treatment delays or—at the discretion of the investigator—due to toxicity reasons leading to permanent discontinuation of oxaliplatin and irinotecan. Treatment was applied until the occurrence of secondary resection, progressive disease (PD), unacceptable toxicity or withdrawal of consent. Radiographic assessment of response was carried out every 8 weeks until PD or withdrawal for any reason.

**Translational pharmacogenomic analyses.** Pharmacogenomic analyses of SNPs of the VEGF pathway (for VEGF-A, VEGFR 1–3, PDGFR beta, HIF 1 alpha, Neuropilin) and determination of KRAS status (codons 12, 13 and 61) were performed in a subgroup of patients after obtaining separate consent. The main focus of pharmacogenetic analysis was the prediction of the added effect of bevacizumab. Therefore promising candidate SNPs were chosen from recent analyses (Lambrechts et al, 2013). DNA was extracted from white blood cells for SNP analysis and from paraffin-embedded tumour tissue for KRAS analysis. For extraction, QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) was used. Tumour samples were macrodissected before extraction to ensure sufficient tumour DNA, within the analysed sample. Primers for SNP analysis were applied according to the work summarised by Lambrechts et al (2013). Results were correlated with PFS and OS. Because of ethical and legal requirements, the extracted DNA had to be destroyed after the preliminary planned analyses were performed. Therefore, extended RAS (KRAS exon 4 and NRAS exons 2–4) and BRAF mutational testing could not be performed.

**Dose adjustments.** A new treatment cycle was scheduled if the neutrophil count was ≥ 1500 mm⁻³, the platelet count was ≥ 75000 mm⁻³, if treatment-related diarrhoea and/or abdominal cramps were fully resolved to baseline or grade 0 and no loperamide had been administered during the last 24 h and all relevant non-haematological toxic effects were grade ≤ 1 (NCI CTC AE v 3.0). Dose reductions were based on the toxicity in the preceding cycle and were performed in 25% steps for 5FU, irinotecan and oxaliplatin. Treatment was held for grade 3 non-haematological adverse events (AEs; including alopecia, nausea or vomiting), until resolution to grade ≤ 1, and resumed at a 25% reduction of doses of all three drugs, and discontinued for grade 4 non-haematological adverse. In case of a drug-specific AE, for example, peripheral neuropathy for oxaliplatin solely, the suspected drug was reduced or discontinued.

**Study evaluations.** Pretreatment evaluation included a complete medical history, physical examination, routine haematology, biochemistry and urine analyses and computed tomography (CT) scans of the chest and abdomen. Haematological (including platelet and differential) analyses, serum chemistry and urine dipstick were obtained at day 1 in each cycle. Subjective symptoms, physical examination results, vital signs (including blood pressure), performance status and all adverse reactions were recorded before each treatment cycle according to NCI CTC AE v 3.0. CT scans were performed every 8 weeks (four cycles) during treatment and afterwards every 12 weeks to assess disease status. ORR and PFS were evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST; Therasse et al, 2000). Archival tissue and 5 ml blood at baseline were obtained for pharmacogenomic analyses in patients giving separate consent.

**Statistical methods.** The primary end point was median PFS according to RECIST measured from the start of treatment. The sample size calculation was based on an assumed median PFS of 12 months for FOLFOXIRI and bevacizumab followed by a bevacizumab-based maintenance therapy to show an improvement.
of median PFS in comparison to a supposed true value of 8.9 months of a three-drug regimen in molecularly unselected first-line mCRC patients. This resulted in a sample size of 87 patients (one-sided alpha-level of 5%, power 80%, drop-out rate 10% and follow-up 36 months). An interim analysis was performed 18 months after inclusion of the first patient. As this was an exploratory study, no adjustment of $P$-values or formal statistical interim analysis methodology were applied. Baseline patient characteristics, response and toxic effects were described using summary statistics. The Kaplan–Meier-method was used to analyse the primary end point and censored event times. 95% Confidence intervals (CIs) were given for all the calculated estimates.

### RESULTS

#### Patients' characteristics

Between July 2009 and July 2011, a total of 97 patients were screened at 16 German study sites. Seven patients were not included owing to violation of selection criteria. Baseline characteristics are summarised in Table 1. Twenty-six female and 64 male patients with median age of 58 years (range 28–71 years) and ECOG PS score of 0/1 in 54%/46%, respectively, were analysed. Site of primary tumour was rectal in 35 (39%) patients. Prior adjuvant treatment was administered in 7 patients (8%), single agent fluoropyrimidine in 5 and fluoropyrimidine and oxaliplatin in 2 patients, respectively.

#### Study treatment

A total of 1342 cycles was administered. Patients received a median of 12 cycles of bevacizumab (range 1–52) and 11.5 cycles of FOLFOXIRI (range 1–12). Relative dose intensities (mean ± s.d.) were 85 ± 14% for bevacizumab, 85 ± 16% for oxaliplatin, 83 ± 16% for irinotecan and 79 ± 15% for 5FU. The mean study duration was 23 months, including a mean treatment duration of 8 months and a mean follow-up duration of 15 months thereafter.

Overall, 29 patients (32%) had to be dose reduced. Study drug(s) were temporarily withdrawn in 43 (48%) patients. Reason for discontinuation of study treatment were PD in 36 (41%), toxicity in 14 (16%), complete remission in 5 (6%), withdrawal of consent in 1, death in 1 and other in 31 patients (mainly patient request or secondary resection).

Colony-stimulating factors were administered in 13 patients (14%).

| Characteristics | N  | %   |
|-----------------|----|-----|
| Gender          |    |     |
| Female          | 26 | 29  |
| Male            | 64 | 71  |
| Median age, years (range) | 58 (28–71) |

#### ECOG performance status

| Status            | N  | %   |
|-------------------|----|-----|
| 0                 | 49 | 54  |
| 1                 | 41 | 46  |
| Primary rectal tumours | 35 | 39 |
| Multiple metastatic sites | 51 | 57 |
| Liver             | 39 |     |
| Lung              | 27 |     |
| Peritoneal        | 9  |     |
| Lymph node        | 28 |     |
| Other (bone, spleen, pleura) | 8  |     |
| Liver metastases only | 35 | 39 |
| Prior adjuvant treatment | 7  | 8   |

#### Pharmacogenetically and KRAS defined subgroups

With regard to the optional participation in the translational part of the trial, overall, 64 patients (74%) received second-line treatment. Patients progressing during maintenance with 5FU/LV and bevacizumab ($n = 19$) were reinduced with oxaliplatin ($n = 6$), irinotecan ($n = 12$) or both ($n = 1$) in combination with bevacizumab ($n = 8$) or EGFR antibodies ($n = 3$). Further salvage treatment contained cetuximab in 15 patients and panitumumab in 18 patients.

#### Toxicity

Treatment was generally well tolerated in an outpatient setting (Figure 3). AEs are summarised in Table 3. The most frequent AEs of CTC grade 3/4/5 were leucopenia and neutropenia (26%), diarrhoea (11%), nausea (9%), vomiting (8%) and venous thromboembolism (6% of patients).

In total, 87 serious AEs occurred in 39 patients (43%). Twenty-four of the 87 SAEs (28%) were assessed by the investigators as related to study medication. Besides 2 patients, suffering from portal vein thrombosis and pulmonary embolism, respectively, all patients recovered from their related SAEs at the end of the study.

A total of 44 patients died during participation in the study, 1 patient during the treatment period and 43 patients during the survival follow-up. Two of these fatal cases were reported as AEs (hepatic failure and infected neoplasm). The investigators assessed both events as unrelated to study treatment.

| Table 2. Efficacy according to RECIST 1.0 and resection rate |
|------------------------------------------------------------|
| Efficacy | N  | %   |
| Complete response | 7  | 8   |
| Partial response  | 51 | 57  |
| Stable disease    | 20 | 22  |
| Progressive disease or death | 7  | 8   |
| No data on tumour status | 5  | 6   |
| Secondary resection rate | 24 | 27  |
| R0 resection rate | 16 | 18  |

#### Table 1. Patients' characteristics

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| Secondary resection rate  | 24 | 27  |
| R0 resection rate         | 16 | 18  |

| Efficacy | N  | %   |
|----------|----|-----|
| PFS, months | 11.1 | 9.4–12.0 |
| OS, months  | 32.2 | 22.6–36.9 |

Abbreviation: CI = confidence interval; OS = overall survival; PFS = progression-free survival.

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blood and tissue was available from 52 patients (58% of the whole study population). Despite one failure in KRAS analysis owing to insufficient tumour content in the tissue block, all analyses could be performed as planned and are displayed in Supplementary Table S1. For VEGFR2_FLK_KDR_305_C_T, the median OS was 18.7 months (95% CI: 16.8–32.2 months) for polymorphism CT and 30.1 months (95% CI: 19.5–36.9 months) for polymorphism TT (P = 0.0380). The other SNPs were not associated with OS in univariate analyses.

Patients with KRAS-mutated tumours (codon 12, 13 or 61, n = 26) had a significantly shorter OS for 21.7 months compared with 36.9 months (P = 0.027) in patients with KRAS wild type (n = 25). Because of ethical and legal requirements, the extracted DNA had to be destroyed after the preliminary planned analyses were performed. Therefore, an extended KRAS and NRAS analysis could not be performed in these patients. Importance of extended RAS and BRAF mutational analyses for mCRC was not known by the time of study design.

**DISCUSSION**

Four-drug regimens with 5FU/LV, irinotecan, oxaliplatin and a monoclonal antibody have been evaluated in single-arm phase 2 trials and have shown an ORR ranging from 77% to 89% and a PFS of 9.5–13.1 months (Masi et al, 2010; Assenat et al, 2011; Fornaro et al, 2013). Recently, the results of the phase 3 randomised TRIBE trial comparing FOLFIRI and bevacizumab with or without oxaliplatin were reported, showing a significantly increased PFS of 12.1 vs 9.7 months (HR 0.75; 95% CI 0.62–0.90); P = 0.003) and OS with 29.8 vs 25.8 months (HR 0.80; 95% CI 0.65–0.98); P = 0.03), in favour of FOLFOXIRI and bevacizumab (Loupakis et al, 2014; Loupakis et al, 2015). ORR with FOLFOXIRI and bevacizumab was 65%.

Despite the common differences between phase 2 and 3 trials, particularly in terms of patient selection, the efficacy results of FOLFOXIRI and bevacizumab in the OPAL study mirror the results of the recently reported TRIBE trial. Notably, the OPAL trial did not seem to have a better patient population, with regard...
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CONFLICT OF INTEREST

AS has received honoraria from Roche, Sanofi, Bayer, Amgen and Merck Serono and research funding from Roche and Sanofi. CB has received honoraria from Merck Serono, Roche, Sanofi and Bayer and research funding from Roche and Merck Serono. EB is an employee of Ecrion Acunova, the contract research organisation that was in charge of analysing the study results. JS has received honoraria by Roche, Sanofi, Lilly, Amgen, Bayer, Merck-Serono, Pfizer and Abbott and research funding from Lilly, Roche and Amgen. CCS has received honoraria from Roche, Amgen and Sanofi. BH has received honoraria from Amgen, Bayer, Merck Serono, Roche and Sanofi and research funding from Roche. The remaining authors declare no conflict of interest.

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