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ORIGINAL ARTICLE

A multicenter, randomized, open-label study to assess the steady-state pharmacokinetics of bevacizumab given with either XELOX or FOLFOX-4 in patients with metastatic colorectal cancer

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Abstract
Purpose To compare the pharmacokinetics (PK) of bevacizumab (BV) at steady-state under two different dosing regimens, 7.5 mg/kg q3w and 5.0 mg/kg q2w, concomitantly with a combination of capecitabine and oxaliplatin (XELOX) and FOLFOX-4 (oxaliplatin in combination with infusional 5-FU/LV), respectively, in patients with metastatic colorectal cancer (mCRC).

Methods Patients were randomized in a 1:1 ratio to either XELOX + BV or FOLFOX-4 + BV. Blood samples for steady-state PK of BV were collected on day 1 of cycle 5 (at the earliest) for XELOX + BV treatment and day 1 of cycle 7 (at the earliest) for FOLFOX-4 + BV treatment.
Results A total of 64 patients were enrolled, of which 37 were eligible for PK analyses. The primary PK parameter of BV, $AUC_{ss(per\ week)}$, was statistically similar between the two dosing regimens with the 90% confidence interval in the commonly used no-effect boundaries of 0.8 and 1.25. The V_{ss} and CL did not differ between the two regimens; $t_{½}$ during the PK cycle was also similar for both arms at approximately 16 days. These results demonstrated no clinically relevant change in BV PK when co-administered with either XELOX or FOLFOX-4. BV in combination with XELOX and FOLFOX-4 was generally well tolerated with no unexpected safety signals and no deaths. Nine patients in the XELOX + BV arm and 15 patients in the FOLFOX-4 + BV arm experienced at least one SAE (most commonly gastrointestinal disorders) which led to dose modification in 7 and 2 patients, respectively, and to premature withdrawal in 9 and 5 patients, respectively. All 64 patients experienced at least one non-serious AE. Laboratory tests and vital signs were unremarkable.
Conclusions No clinically relevant differences in overall steady-state exposure of BV occurred when BV was given 7.5 mg/kg q3w in combination with XELOX or 5.0 mg/kg q2w with FOLFOX-4 in patients with mCRC, and the pharmacokinetics of BV were very similar between the two regimens. No unexpected adverse events or deaths were identified.

Keywords Bevacizumab · Pharmacokinetics · XELOX · FOLFOX-4

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Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies, third to breast cancer and lung cancer in women and third to lung cancer and prostate cancer in men [1]. In use for over 40 years, 5-fluorouracil (5-FU) remains the most active single agent against metastatic colorectal cancer (mCRC), though response rates are usually less than 20% [2]. Intravenous (i.v.) 5-FU in combination with leucovorin (5-FU/LV) became the standard chemotherapy for CRC in the 1980s [2], but when given by repeated bolus injections or short infusions, it is associated with both gastrointestinal and myelosuppressive toxicity, which limits the intensity and duration of treatment. Subsequent trials reported increased response rates with low dose continuous 5-FU infusion as first-line chemotherapy [3]. While less severe acute toxicities are observed, other toxicities associated with chronic exposure of tissues to 5-FU or its metabolites are more frequently observed, such as hand-foot syndrome (HFS) [4].

Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase (TP). After oral administration, capecitabine is first metabolized in the liver by carboxylesterase to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase principally located in the liver and tumor tissue. 5′-DFUR is then catalytically activated to 5-FU by TP, thereby producing higher intratumoral 5-FU concentrations. It is registered globally as first-line monotherapy for patients with mCRC [5].

Oxaliplatin (Eloxatin®) is a platinum (Pt) derivative with a mechanism of action similar to that of cisplatin as well as other Pt compounds. Oxaliplatin has been widely studied in first-line or subsequent therapy settings in patients with advanced CRC, e.g., the FOLFOX-4 (oxaliplatin in combination with infusional 5-FU/LV) regimen [6]. Several studies have been conducted using a combination of capecitabine and oxaliplatin (XELOX) in CRC. Based on study results obtained from a phase I dose-escalation trial [7], the recommended dosing schedule for XELOX regimen was capecitabine 1,000 mg/m^2 twice daily (bid) on days 1 through 14 (followed by 1 week without treatment) with i.v. oxaliplatin 130 mg/m^2 on day 1 in a 3-weekly (q3w) treatment cycle, which has since been shown to be tolerable and feasible in large-scale phase III studies [8–10].

In CRC, one of the most potent and specific angiogenic factors is vascular endothelial growth factor (VEGF). Increased VEGF expression correlates with invasiveness, vascular density, metastasis, recurrence, and prognosis [11]. Bevacizumab (BV, Avastin®), a monoclonal antibody against VEGF, prevents angiogenesis. It is administered i.v. as a combination treatment along with standard chemotherapy drugs for colon cancer. The IFL regimen consisting of irinotecan plus 5-FU/LV was the first to show a survival benefit for the addition of BV to first-line chemotherapy for mCRC [12].

A recent phase 3 trial demonstrated that XELOX is non-inferior to FOLFOX-4 and that BV in combination with chemotherapy (XELOX + BV or FOLFOX-4 + BV) showed PFS improvement compared to chemotherapy alone (XELOX or FOLFOX-4) in first-line treatment of mCRC [9, 11]. In parallel, this independent pharmacokinetic (PK) study was performed. The primary objective of this study was to examine and compare the PK of BV at steady-state under two different dosing regimens, 7.5 mg/kg once every 3 weeks (q3w) and 5.0 mg/kg once every 2 weeks (q2w) in combination with XELOX and FOLFOX-4, respectively.

Materials and methods

Overall study design

This was an open-label, randomized, multicenter study consisting of two treatment regimens. Patients were randomized in a 1:1 ratio to either Arm A (XELOX + BV) or Arm B (FOLFOX-4 + BV). The dosing regimens for this study were as follows:

Arm A (XELOX + BV)

BV at 7.5 mg/kg was administered as an i.v. infusion over 30–90 min, followed by oxaliplatin administered as a 130 mg/m^2-i.v. infusion over 2 h on day 1 in combination with capecitabine administered orally at a dose of 1,000 mg/m^2 bid (equivalent to a total daily dose of 2,000 mg/m^2) with first dose on the evening of day 1 and last dose on the morning of day 15 every 3 weeks.

Arm B (FOLFOX-4 + BV)

BV at 5.0 kg/mg was administered as an i.v. infusion over 30–90 min, followed by oxaliplatin administered as an 85 mg/m^2-i.v. infusion over 2 h on day 1, concomitantly with LV administered as a 200 mg/m^2 infusion over 2 h, followed by 5-FU, administered as a 400 mg/m^2-bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 h on days 1 and 2. Treatment was given in 2-week cycles.

Patients were to receive treatment up to 48 weeks (i.e., 16 cycles for Arm A, and 24 cycles for Arm B), until progressive disease (PD) or unacceptable toxicity was

encountered, or the patient withdrew consent, whichever occurred first. In the absence of disease progression, patients could continue treatment in a post-study treatment phase beyond 48 weeks.

Rationale for BV dosage selection

BV was given at 5.0 mg/kg q2w together with FOLFOX-4 (2-week regimen). To maintain the dose intensity of 2.5 mg/kg/week dosage, the BV dose given with XELOX (3-week regimen) was 7.5 mg/kg q3w. Since BV clearance is slow with a long terminal half-life of approximately 20 days [13], these two regimens should result in identical average concentrations (Cavg) and similar trough concentrations for BV. The predicted exposure to BV, expressed as AUCss (μg day/ml per week), is nearly identical with 7.5 mg/kg q3w and 5.0 mg/kg q2w as shown in Table 1.

Study population

The target population for this study was male or female outpatients, ≥18 years of age, with an ECOG of ≤1, a life expectancy of ≥4 months, and histologically/cytologically confirmed adenocarcinoma of the colon/rectum with metastatic and/or locally advanced disease, who had not previously received systemic treatment for metastatic disease. All women who participated in this study were either postmenopausal, surgically sterilized, or using protective contraception, and all men, for which it was applicable, were using protective contraception.

Approximately 50 patients were planned to be enrolled in this study to ensure that the required 28 evaluable patients were available for the PK analyses. A total of 64 patients were actually enrolled, of which 37 were included in the PK analyses.

Compliance with good clinical practice

This study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study also fully adhered to the principles outlined in the "Guideline for Good Clinical Practice" International Conference of Harmonization (ICH) Triparite Guideline (January 1997) and to the basic principles of good clinical practice as outlined in the US Code of Federal Regulations on the Protection of Human Subjects.

Table 1 Predicted bevacizumab PK parameters at steady-state

PK parameter	Dosing regimens	
	7.5 mg/kg q3w	5.0 mg/kg q2w
C_{avg} (μg/ml)	120	121
$C_{ss,min}$ (μg/ml)	73	85
$C_{ss,max}$ (μg/ml)	270	215
AUC_{ss} (μg day/ml per cycle)	2,529	1,697
AUC_{ss} (μg day/ml/week)	843	848

Procedures

Drug formulation and administration

Capecitabine (Xeloda®) was supplied as film-coated tablets of 150 and 500 mg. The appropriate daily dose of capecitabine was identified by determining the patients' BSA at baseline and the maximal dose to be administered corresponded with a BSA of 2.23 m^2. Oxaliplatin (Eloxatin®) was supplied in vials containing 50 or 100 mg of oxaliplatin as sterile, preservative-free lyophilized powder for reconstitution. The maximal dose to be administered corresponded with a BSA of 2.23 m^2. All patients participating in this study received one or more of a 5-HT3 antagonist (granisetron, ondansetron, tropisetron, and/or dolasetron), prochlorperazine, and the corticosteroid dexamethasone as premedication.

BV was to be administered initially over 90 (±15) min. If the first infusion was tolerated without infusion-associated AEs (fever and/or chills), the second infusion could be delivered over 60 ± 10 min. If the 60-min infusion was well tolerated, all subsequent infusions could be delivered over 30 (±10) min. The maximal dose to be administered corresponded to a body weight of 135 kg.

5-FU and LV were obtained locally by prescription and administered as previously described [9].

Dose modification

A single dose modification of any medication (except for BV) was permitted for safety reasons, and the following levels were considered acceptable:

- Capecitabine could be reduced to 75% of the original dose,
- Oxaliplatin could be reduced to 100 mg/m^2 for Arm A, and 65 mg/m^2 for Arm B, and
- 5-FU could be reduced to 300 mg/m^2 for the bolus administration and 500 mg/m^2 for the infusion administration.

Any dose reduction for safety that required the dose to be reduced lower than these acceptable levels resulted in the patient becoming non-evaluable for PK assessments. In this situation, PK sampling was to be stopped, or not initiated if the patient had not reached the PK cycle.

PK sample collection for bevacizumab

According to BV pharmacokinetics characterized in eight clinical trials and a population PK analysis, it was estimated that after multiple dosing, steady-state was reached at ~100 days. Therefore, venous blood samples were collected on day 1 of cycle 5 (at the earliest) for XELOX + BV treatment and day 1 of cycle 7 (at the earliest) of FOLFOX-4 + BV treatment to assess the steady-state PK of BV. A 5-ml sample was drawn predose (before starting BV infusion), immediately after stopping the infusion of BV, 2, 8, 24, 48, 72, 120, 168, and 336 (prior to the commencement of the next BV infusion) hours post the beginning of the BV infusion. In Arm A, the 504-h sample (3 weeks post-dose) was to be taken on Day 1 of the next cycle, immediately prior to the commencement of the BV infusion.

Serum samples were analyzed for BV using validated ELISA method at Xendo Drug Development B.V. (Leiden, The Netherlands).

Study parameters

Pharmacokinetic parameters for BV

The primary parameter for the study was the weekly steady-state exposure of BV, $AUC_{ss(per\ week)}$. The secondary parameters of the study were as follows: $AUC_{ss(0\text{-}tau)}$, $AUC_{(0\text{-}last)}$, $C_{ss,min}$, $C_{ss,max}$, CL, V_{ss}, and $t_{1/2}$. The PK parameters of BV at steady-state were estimated for each patient from the concentration–time data obtained during the PK cycle using standard non-compartmental methods.

Safety parameters

Safety parameters included exposure to trial treatment, adverse events, serious adverse events, deaths, dose modifications, premature withdrawals from treatment, laboratory abnormalities, vital signs, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance status.

Statistical PK primary analysis

Only patients who had experienced no more than one dose reduction of any medication (except for BV) during cycles prior to and including the PK cycles were evaluable for PK analysis.

Statistically, the assessment was based on a parallel group comparison between XELOX + BV treatment and FOLFOX-4 + BV treatment of $AUC_{ss(per\ week)}$ of BV determined during the corresponding PK cycles. For calculation convenience, AUCtaun (normalized to AUCtau/day) was used in ANOVA analysis. The statistical model used for the analysis was

$$\ln Y_{ij} = \mu + \tau_j + \varepsilon_{ij}$$

wherein Y_{ij} was the PK parameter of interest, μ denoted the general mean, τ_j was the fixed effects comparing the results obtained during the PK cycle on XELOX + BV treatment ($j = 1$) to those obtained during the PK cycle on FOLFOX-4 + BV treatment ($j = 2$), and ε_{ij} was normally distributed random errors with means zero and standard deviation σ_ε. The results are reported as the geometric mean ratio (XELOX + BV treatment versus FOLFOX-4 + BV treatment) and the associated 90% confidence interval. No adjustments for multiple testing were done.

Results

Disposition of patients

A total of 64 patients from seven international sites were enrolled into this study. Patients were randomized to receive either XELOX + BV (Arm A; 32 patients) or FOLFOX-4 + BV (Arm B; 32 patients). All 64 patients enrolled in this study were included in the safety analysis population.

A similar number of XELOX + BV- and FOLFOX-4 + BV-treated patients were withdrawn from study treatment before 48 weeks (27 [84%] and 24 [75%] patients, respectively). The majority of patients in each arm were withdrawn for non-safety reasons, primarily due to insufficient therapeutic response; six patients in each arm were withdrawn for safety reasons (AEs). Due to either early withdrawal or more than one dose modification prior to planned PK assessment, only 42 patients participated, of whom, 37 with complete data were eligible and thus included in the PK analysis.

Demographic data and baseline characteristics

Patient demographic data were comparable across the two treatment arms (Table 2). A similar number of men and women were enrolled into each arm (19 men and 13 women in Arm A and 15 men and 17 women in Arm B), and the majority of patients were Caucasian (81% in Arm A, 100% in Arm B). The median age was 53 years in Arm A and 60 years in Arm B, and all patients had baseline ECOG scores of 0 or 1.

The treatment arms were generally well balanced with respect to history of CRC. All patients participating in this study had locally advanced or mCRC at first diagnosis. Most patients had colon cancer (78% in Arm A, 63% in Arm B) and tumors that were moderately differentiated

Table 2 Summary of baseline demographic characteristics

	Arm A XELOX + Avastin $N = 32$	Arm B FOLFOX + Avastin $N = 32$
Sex		
Female	13 (41%)	17 (53%)
Male	19 (59%)	15 (47%)
n	32	32
Race		
White	26 (81%)	32 (100%)
Asian or Pacific Islander	5 (16%)	–
Greek	1 (3%)	–
n	32	32
Age in years		
Mean	55.6	57.9
SD	12.56	10.84
SEM	2.22	1.92
Median	53.0	60.0
Min–max	31–80	22–74
n	32	32
Weight in kg		
Mean	78.00	73.45
SD	19.303	13.084
SEM	3.467	2.313
Median	83.80	72.40
Min–max	45.0–122.5	54.0–105.3
n	31	32
Height in cm		
Mean	168.7	166.6
SD	11.47	7.89
SEM	2.03	1.40
Median	168.0	166.0
Min–max	150–193	148–183
n	32	32
Body surface area in sqm		
Mean	1.87	1.82
SD	0.271	0.157
SEM	0.049	0.028
Median	1.90	1.80
Min–max	1.4–2.4	1.5–2.1
n	31	32
ECOG performance status		
0	23 (72%)	21 (66%)
1	9 (28%)	11 (34%)
n	32	32

n represents number of patients contributing to summary statistics

Percentages are based on *n* (number of valid values). Percentages not calculated if $n < 10$

(59% in each treatment arm). Nearly all patients were enrolled to receive study drug for their first occurrence of mCRC (100% in Arm A, 90% in Arm B).

Previous and concurrent diseases, symptoms, and treatment

The most frequently reported types of concurrent symptoms or non-malignant diseases were abdominal pain (25% in each arm), constipation (16% in Arm A, 25% in Arm B), hypertension (16% in Arm A, 22% in Arm B), insomnia (19% in each arm), and fatigue (9% in Arm A, 22% in Arm B).

The profile of previous and concomitant treatments was generally similar between the two treatment arms, and no clinically significant differences were observed.

All patients received at least one concomitant treatment, excluding anticoagulant treatments. The most commonly used treatments were 5-HT3 antagonists (59% in Arm A, 56% in Arm B), primarily granisetron (59% in Arm A, 41% in Arm B), the phenothiazine prochlorperazine (66% in Arm A, 50% in Arm B), and the corticosteroid dexamethasone (59% in Arm A, 53% in Arm B). Five patients (16%) in Arm A and 2 patients (6%) in Arm B received anticoagulant treatment.

BV pharmacokinetic results

Mean steady-state serum concentrations versus time curves of BV in Arm A and Arm B are shown in Fig. 1.

The mean values of BV PK parameters ($AUC_{ss(per\ week)}$, $AUC_{ss(0\text{-}tau)}$, $AUC_{0\text{-}last}$, $C_{ss,max}$, $C_{ss,min}$, CL, V_{ss}, and $t_{½}$) from BV concentrations, and their coefficients of variation,

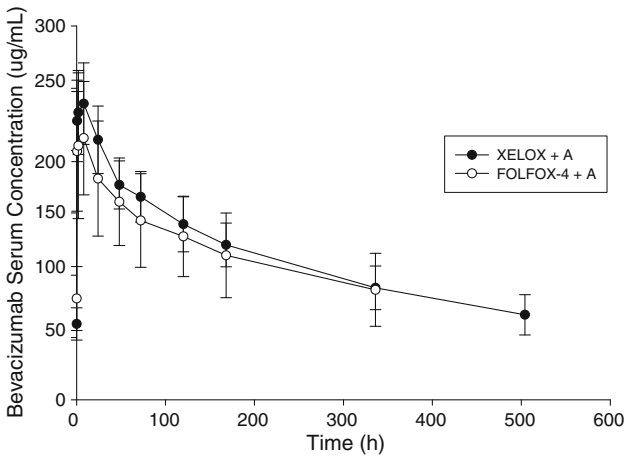

Fig. 1 Mean (±SD) steady-state BV serum concentration versus time profile of dosing regimens XELOX + BV ($N = 19$) and FOLFOX-4 + BV ($N = 18$). *A* Avastin (bev)

Table 3 BV pharmacokinetic parameters (arithmetic mean) of XELOX + BV and FOLFOX-4 + BV

Parameter	Arm A XELOX + BV[a] (CV%) $N = 19$	Arm B FOLFOX-4 + BV[b] (CV%) $N = 18$
$AUC_{ss(per\ week)}$ (day·µg/ml)	819 (15)	880 (27)
$AUC_{ss(0\text{-}tau)}$ (day·µg/ml)	2,457 (15)	1,759 (27)
$AUC_{0\text{-}last}$ (day·µg/ml)	2,457 (15)	1,710 (30)
$C_{ss,max}$ (µg/ml)[c]	242 (13)	216 (25)
$C_{ss,min}$ (µg/ml)	59.6 (24)	80.0 (32)
CL (l/day)	0.236 (21)	0.226 (25)
V_{ss} (l)	4.93 (29)	4.91 (32)
$t½$ (day)	15.88 (1)	16.42 (1.29)
t_{max} (h)	6.4 (median 5.17; range 0.5–24.1)	5.0 (median 5.36; range 0.5–9.1)

[a] XELOX + BV (7.5 mg/kg) q3w

[b] FOLFOX-4 + BV (5.0 mg/kg) q2w

[c] $N = 18$ for calculation of $C_{ss,max}$ for the XELOX + BV arm due to an outlier

as well as the mean values for t_{max} with medians and ranges in Arm A and Arm B, are presented in Table 3.

V_{ss} did not differ between the two arms: mean V_{ss} was 4.93 l in the XELOX + BV arm and 4.91 l in the FOLFOX-4 + BV arm. CL was similar for both arms: for the XELOX + BV and FOLFOX-4 + BV arms, mean CL was 0.236 l/day and 0.226 l/day, respectively. BV $t_{½}$ during the PK cycle was also similar for both arms at approximately 16 days; $t_{max,}$ at steady-state, was comparable with medians of 5.17 h for the XELOX + BV arm and 5.36 h for the FOLFOX-4 + BV arm.

As expected, due to a higher dose of BV given in the XELOX + BV arm (7.5 mg/kg), $C_{ss,max}$ was higher in this arm with an estimated 14% increase compared to the FOLFOX-4 + BV arm (5 mg/kg). Similarly, due to the increase in dosing interval with the XELOX + BV arm (q3w), $C_{ss,min}$ was slightly lower with a decrease of 24% compared to the FOLFOX-4 + BV arm (q2w). The inter-patient variability for both arms was moderate (13 and 25% for $C_{ss,max}$ and 24 and 32% for $C_{ss,min}$; Table 3) and was generally lower for XELOX + BV.

One-way ANOVA was used to compare the primary PK variable after log transformation. Estimated least squares means, together with estimates for the coefficients of variation per treatment arm, are presented in Table 4. In the model, different residual (between patient) variabilities were allowed for the two treatments as this leads to a statistically significant improvement ($P < 0.05$, likelihood ratio test for $AUC_{ss(per\ week)}$) as compared to the homoscedastic model.

The estimated geometric mean ratio (XELOX + BV versus FOLFOX-4 + BV) of AUC taun is 0.951 with the associated 90% confidence interval of 0.848–1.067. Thus, the primary parameter, $AUC_{ss(per\ week)}$, of BV was statistically similar between the two dosing regimens with the 90% confidence interval in the commonly used no-effect boundaries of 0.8 and 1.25.

In light of the recent data from Lu et al. [13] on the influence of gender and weight on clearance of bevacizumab, we examined the two groups. There was no significant difference in the proportion of women or the mean weight between the two groups and no statistically significant interaction between treatment and either gender or weight [data not shown].

Safety results

In general, the incidences and types of AEs were similar between the two treatment arms, and no clinically significant differences were observed.

Discussion

This was an open-label, multi-center, randomized study in patients with mCRC. The two arms in this study consisted of two different dosing regimens of BV, 7.5 mg/kg q3w and 5.0 mg/kg q2w, given in combination with XELOX and FOLFOX-4, respectively. The primary objective of this study was to examine and compare the pharmacokinetics of

Table 4 Estimated least squares means for primary pharmacokinetic parameters by treatment arm

Pharmacokinetic parameter	Treatment	Least squares mean	Confidence interval			Confidence residual limit CV (in %)
			Lower limit	Upper limit	Level (%)	
AUC_TAUN/day	FOLFOX + Avastin	122	110	135	90	26
	XELOX + Avastin	116	110	122	90	14

AUC_TAUN is the normalized AUC_TAU at steady-state normalized by 14 days for FOLFOX + Avastin and by 21 days for XELOX + Avastin

BV at steady-state under these two dosing regimens. A total of 64 patients were enrolled into this study, of which 37 patients were eligible and deemed evaluable for PK analysis. The $AUC_{ss(per\ week)}$ was compared between the PK cycle of XELOX + BV treatment and the PK cycle of FOLFOX-4 + BV treatment.

Statistically, the assessment was based on a parallel group comparison between XELOX + BV treatment and FOLFOX-4 + BV treatment of $AUC_{ss(per\ week)}$ of BV determined during the PK cycle on XELOX + BV treatment and the PK cycle on FOLFOX-4 + BV treatment. The primary parameter, BV $AUC_{ss(per\ week)}$, was very similar between both arms with the geometric mean ratio being very close to 1. This similarity was expected in that the same BV dose intensity of 2.5 mg/kg was maintained per week for both arms.

Following i.v. administration in the PK cycle, BV had low clearance and a low volume of distribution consistent with limited extra-vascular distribution. CL and V_{ss} were very similar for both arms; $t_{½}$ and t_{max} for BV were also similar for both arms. Also as expected, slight differences were observed for BV $C_{ss,max}$ and $C_{ss,min}$ between the two arms due to the different doses of BV; 7.5 mg/kg for the XELOX + BV arm compared to a lower dose of 5.0 mg/kg for the FOLFOX-4 + BV arm. These slight differences are not considered to be clinically relevant.

Treatment with BV in combination with XELOX and FOLFOX-4 was generally well tolerated with no new unexpected safety signals. All 64 patients participating in the study experienced at least one AE. The most common types of AEs reported were nervous system disorders (peripheral sensory neuropathy, peripheral neuropathy, and headache), gastrointestinal disorders (diarrhea, nausea), and general disorders and administration site conditions (fatigue). No deaths were reported in this study. Nine patients in the XELOX arm and 15 patients in the FOLFOX-4 arm experienced at least one SAE, of which GI disorders were the most common. SAEs led to dose modification and premature withdrawal in seven and two patients, respectively, in the XELOX arm and nine and five patients, respectively, in the FOLFOX-4 arm. Six patients in each treatment arm were prematurely withdrawn from the study due to AEs. Laboratory test results were unremarkable, and there were no clinically significant changes in vital signs.

The results of this study demonstrate that due to the slow clearance and long terminal half-life, dosing BV either 7.5 mg/kg q3w or 5.0 mg/kg q2w does not have a clinically relevant effect on the pharmacokinetic profile of BV. Overall, the pharmacokinetic parameters of BV were very similar between both dosing regimens. This, together with a lack of significant safety concerns, provides further support for the use of both treatment regimens for patients with mCRC.

Conclusion

The pharmacokinetics of BV were very similar between the two regimens: BV given 7.5 mg/kg q3w in combination with XELOX or 5.0 mg/kg q2w with FOLFOX-4 in patients with mCRC.

Conflict of interest Dr. Major has Novartis and Amgen consultancy/advisory role. None for others.

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