ABSTRACT

Background. After approval of bevacizumab in Germany in 2005 for the treatment of unresectable advanced or refractory colorectal cancer (CRC), this observational cohort study was initiated to assess the efficacy and safety of bevacizumab with various chemotherapy regimen in patients with metastatic CRC (mCRC).

Material and methods. To facilitate enrolment of a typical mCRC population, eligibility criteria were minimised. Choice of chemotherapy regimen was at the physicians’ discretion, but influenced by current registration status. Predefined endpoints were treatment characteristics, response rate, progression-free survival (PFS), overall survival (OS) and adverse events assessed as potentially related to bevacizumab treatment. Patients were followed for up to four years.

Results. In total 1777 eligible patients were enrolled at 261 sites from January 2005 to June 2008. Median age: 64 years (range 19–100); male 62%; ECOG performance status 0–1/2 89%/11%. Chemotherapy choice was fluoropyrimidine (FU) 12%, FU/oxaliplatin 18%, FU/irinotecan 64%, no chemotherapy concurrent to bevacizumab 2% and other 4%. Best investigator-assessed response rate was 60% (complete response 10%, partial response 51%). Median PFS was 10.2 months and median OS was 24.8 months.

Conclusions. The efficacy and safety profile of bevacizumab in this population of mCRC patients with different chemotherapy regimens is consistent with that observed in other patient registries/non-randomised trials and also corresponds well with data from similar treatment arms of phase III trials.

The humanised monoclonal vascular endothelial growth factor (VEGF) antibody bevacizumab has been shown to improve efficacy of first and second line chemotherapy in patients with metastatic colorectal cancer (mCRC) [1–5]. Evaluation of the adverse events associated with bevacizumab found the majority to be mild to moderate in severity and manageable using standard therapies [2–4]. However, several mechanism-based adverse events (AE) have been reported with bevacizumab including, hypertension, gastrointestinal perforation, wound-healing complications, bleeding, proteinuria and arterial thromboembolic events [1,3,6]. These efficacy and tolerability findings are supported by obser-
vational cohort studies and patient registries performed in broad patient populations [7–9].

Following the approval of bevacizumab in Germany in 2005 for the treatment of unresectable advanced or refractory CRC, an observational cohort study was initiated to assess the efficacy and safety of bevacizumab with various first-line chemotherapy regimens.

In pivotal phase III studies in both first- and second-line treatment of mCRC, study protocols permitted bevacizumab to be continued until disease progression even if the corresponding chemotherapy was modified or discontinued; improved clinical outcomes in these studies reflected the large proportion of patients receiving bevacizumab treatment until disease progression [3,5,10]. At present, little is known about how induction and maintenance regimens are employed outside of clinical trials and how their use affects PFS and OS in a broad patient population. Therefore, in addition to assessing the efficacy and safety of bevacizumab as part of first-line chemotherapy for mCRC, an exploratory post-hoc subgroup analysis evaluated the induction and maintenance treatments used and their effects on PFS and OS in this observational cohort study.

Material and methods

Observational cohort design

To facilitate enrolment of a typical mCRC population, eligibility criteria were minimised to age ≥ 18 years, histologically confirmed CRC without prior palliative treatment and eligibility for bevacizumab treatment based on the summary of product characteristics. All patients scheduled to undergo first-line treatment with bevacizumab were included. The choice of chemotherapy regimen was at the physicians’ discretion, but was influenced by current registration status (i.e. 5-FU or capecitabine alone or in combination with oxaliplatin or irinotecan). The target was to recruit 1600 patients. Detailed information on baseline data, antineoplastic treatment, tumour development and safety were collected up to termination of bevacizumab therapy, or for a period of 12 months, in most cases. Thereafter, long-term assessment data on key parameters were retrieved repeatedly by additional fax forms for up to four years after initiation of treatment.

Treatment

Patients received bevacizumab 5–10 mg/kg every two weeks or 7.5–15 mg/kg every three weeks in combination with chemotherapy; patients were able to receive bevacizumab monotherapy.

Endpoints

Predefined efficacy endpoints were treatment characteristics, investigator assessed response rate according to adapted RECIST version 1 (defined as best response, without requirement of confirmation) [11], PFS (time from start of first-line therapy to investigator-assessed progression or death, whichever occurred first), and OS (time from start of first bevacizumab administration to death). Adverse drug reactions potentially related to antibody treatment were recorded (by use of open questions) and assessed, especially those of interest for bevacizumab, such as hypertension, proteinuria, gastrointestinal perforation, haemorrhage, and arterial and venous thromboembolic events. A serious adverse drug reaction was defined as any event that resulted in death, was incapacitating, or required inpatient hospitalisation/prolongation of existing hospitalisation for treatment.

Data analysis

Database lock point was November 2011. The analysis included patients receiving at least one dose of bevacizumab. PFS and OS were recorded based on the investigators’ evaluation (with the assessment schedule at investigators’ discretion) and analysed using Kaplan-Meier estimates, including median time to event. The rate of adverse reactions (all types and those of special interest for bevacizumab) were presented descriptively and summarised by study treatment.

Exploratory post-hoc subgroup analyses were performed to evaluate the effects of different induction and de-escalating maintenance regimens on PFS. In the absence of predefined definitions, ‘induction therapy’ was defined as treatment with combination chemotherapy plus bevacizumab before withdrawing at least one chemotherapeutic agent; and ‘maintenance therapy’ was defined as treatment with a de-escalated regimen until progression or bevacizumab termination for other reasons. Induction therapy with oxaliplatin compared with irinotecan and maintenance with single-agent bevacizumab compared with fluoropyrimidine combined with bevacizumab were evaluated in terms of median treatment duration and survival.

Results

Patients and treatment

Between January 2005 and June 2008, 1777 eligible patients were enrolled at 261 sites in Germany. Baseline characteristics of the overall patient population are shown in Table I. Bevacizumab therapy was
started within six months of diagnosis of the primary tumour in 62% of the patient population. Overall, 35% of patients had received prior chemotherapy in the adjuvant or neoadjuvant setting; 73% of these patients received first-line chemotherapy and bevacizumab (in this observational cohort) within two years of prior adjuvant/neoadjuvant therapy. Overall, 64% of patients received bevacizumab in combination with an irinotecan-containing regimen, 18% of patients received the drug in combination with an oxaliplatin-containing regimen, 2% received it as monotherapy, and 4% received it as part of some other regimen. Median documented treatment duration with bevacizumab was 7.0 months (range 0–37); 20% of patients received bevacizumab for >12 months. However, these figures could be underestimated as a result of the limitation of the primary documentation file to a 12-month observational period.

In total, 1503 patients (82% of total) received bevacizumab plus a standard chemotherapy doublet (i.e. FU + oxaliplatin or irinotecan). After ‘induction’ with bevacizumab plus FU/oxaliplatin or bevacizumab plus FU/irinotecan, 274 patients (15%) received de-escalated ‘maintenance’ treatment with either bevacizumab + FU (n = 193; 11%) or bevacizumab alone (n = 81; 5%). The baseline characteristics of these patient groups were similar to the overall population (Supplementary Table I, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.961649).

### Table I. Demographics and baseline characteristics (n = 1777).

| Characteristic                              | Value                  |
|---------------------------------------------|------------------------|
| Male/female, n (%)                          | 1108/669 (62/38)       |
| Median age, years (range)                   | 64 (19–100)            |
| ≥70 years, %                                | 27                     |
| ≥75 years, %                                | 12                     |
| Primary tumour in situ, n (%)               | 125 (7)                |
| Metastatic site,* n (%)                     |                        |
| Liver                                       | 1267 (71)              |
| Lung                                        | 490 (28)               |
| Bone                                        | 57 (3)                 |
| Other                                       | 457 (26)               |
| Number of metastatic sites, n (%)           |                        |
| 1                                           | 1145 (68)              |
| >1                                          | 529 (32)               |
| ECOG performance status, n (%)              |                        |
| 0–1                                         | 1554 (89)              |
| ≥2                                          | 191 (11)               |
| (Neo)adjuvant chemotherapy, n (%)           | 776 (44)               |
| Leucocytes, n (%)                           |                        |
| <8                                          | 1083 (63)              |
| ≥8                                          | 636 (37)               |

*One patient could have more than one metastatic site.

### Table II. Overall response rate (ORR) using RECIST (version 1) by chemotherapy regimen used with bevacizumab (n = 1777).

| Response, % | 5-FU or capecitabine (n = 209) | Oxaliplatin (n = 327) | Irinotecan (n = 1142) | Other (n = 99) | Total (n = 1777) |
|-------------|---------------------------------|-----------------------|-----------------------|----------------|------------------|
| ORR         | 54                              | 65                    | 61                    | 52             | 60               |
| Complete response | 8                              | 10                    | 10                    | 11             | 10               |
| Partial response      | 46                              | 55                    | 51                    | 41             | 51               |
| Stable disease       | 33                              | 26                    | 27                    | 33             | 28               |
| Progressive disease  | 9                               | 3                     | 8                     | 5              | 7                |
| Not evaluable        | 3                               | 6                     | 5                     | 9              | 5                |

### Treatment duration and efficacy

For the intent-to-treat population, the median treatment duration was seven months (range 0–37). In these patients, the investigator-assessed best objective response rate (unconfirmed) was 60% (complete response 10%, partial response 51%) (Table II). The response rate for FU/oxaliplatin/bevacizumab was 65%, for FU/irinotecan/bevacizumab was 61% and for FU/bevacizumab was 54% (Table II).

The median duration of treatment was 9.7 months in those patients receiving oxaliplatin-based de-escalation strategy (median treatment duration for the induction and maintenance phases of 4.1 and 4.9 months, respectively), 10.6 months in those receiving irinotecan-based de-escalation strategy (induction and maintenance phases of 5.6 and 3.7 months, respectively), 10.6 months in those receiving de-escalation to FU and bevacizumab (induction and maintenance phases of 5.1 and 4.8 months, respectively) and 8.9 months in those receiving maintenance with single-agent bevacizumab (induction and maintenance phases of 5.5 and 3.3 months, respectively).

The overall median PFS in the whole patient population was 10.2 months, based on 1390 observed events. Median PFS was almost identical following bevacizumab/irinotecan- or bevacizumab/oxaliplatin-based chemotherapy (10.4 and 10.6 months, respectively) and slightly longer than that seen with bevacizumab/FU (9.2 months). Median PFS in those receiving oxaliplatin-based de-escalation strategy was 11.9 months and similar to those receiving irinotecan-based de-escalation strategy (12.7 months) (Figure 1). Median PFS after induction followed by single-agent bevacizumab was 10.8 months compared with...
13.7 months in patients after induction followed by FU/bevacizumab maintenance therapy (Figure 2).

Median OS for the whole patient population was 24.8 months. Median OS in patients receiving oxaliplatin-based chemotherapy regimen amounted to 27.3 months, which is slightly more than that observed with irinotecan-based and FU-based treatment regimens (24.8 months and 25.5 months, respectively; Figure 3). Median OS in those receiving oxaliplatin-based de-escalation strategy was 29.4 months and in those receiving irinotecan-based de-escalation strategy was 28.5 months (Figure 4). After induction followed by single-agent bevacizumab patients survived for a median of 25.1 months compared with 29.5 months in patients after induction followed by FU/bevacizumab maintenance therapy (Figure 5).

Tolerability

In total, 261 adverse reactions considered to be bevacizumab-related were reported in 187 patients; the most common ones being diarrhoea (n = 46, 2.6%), nausea (n = 33, 1.9%), hypertension (n = 23, 1.3%), and bleeding (n = 21, 1.2%). Of the 261 bevacizumab-related adverse reactions, 57 (22%) were considered serious (reported by 50 patients): venous thromboembolism (n = 13, 0.7%), bleeding (n = 20, 1.1%), pulmonary embolism (n = 8, 0.5%), arterial thromboembolism (n = 7, 0.4%) and gastrointestinal perforation (n = 2, 0.1%). Sixty-day mortality was 10/1777 (0.6%); in six patients this was a result of the tumour while for four patients this was from other causes. This result should be interpreted with caution based on the non-interventional study design.

Discussion

The median PFS of 10.2 months reported in this observational cohort of German patients with mCRC is consistent with the PFS reported in randomised trials in the range of 9.4–10.6 months [3,4,12,13,
and observational cohorts in the range of 9.5–11 months [7–9,14–17].

PFS by chemotherapy regimen was similar for oxaliplatin- and irinotecan-based treatment regimens. For patients receiving 5-FU/FA or capecitabine in combination with bevacizumab, the median PFS of 9.2 months observed is in line with the results achieved in randomised trials [18]. Recently, in patients ≥70 years of age and not suitable for treatment with chemotherapy doublets, the AVEX trial reported a clinically significant benefit of adding bevacizumab to low doses of capecitabine (1000 mg/m² twice daily) in terms of PFS and OS [19]. These results reinforce the concept that in patients without a ‘need for response’, single-agent FU in combination with bevacizumab is a feasible and low toxic treatment option without major differences to triple-agent regimens in terms of PFS.

The median OS of more than two years is slightly higher than previously reported [3,4,8,9]. There are several possible reasons for this, such as the overall increase in OS during the last decades based on the availability of more agents and the increased use of local ablative procedures, the discontinuation of at least one chemotherapy agent after an initial ‘induction’ period and continuation with a de-escalated ‘maintenance’ regimen in about 15% of patients, and the high access rate to active second- and further-line treatment in Germany, in contrast to many of the countries taking part in the BEAT trial.

Evaluation of OS by chemotherapy regimen showed that the median OS in patients receiving oxaliplatin-based chemotherapy regimen was slightly longer compared to patients receiving irinotecan-based regimens. In contrast, slight numerical albeit not clinically relevant differences were noted in the ARIES study, between FOLFOX plus bevacizumab (23.7 months) and FOLFIRI plus bevacizumab (25.5 months) and in the randomised phase II AIO 0604 study between oxaliplatin (24.4 months) and irinotecan (25.5 months) based treatment both
disease progression, although interpretation of these results is likely affected by selection bias. Particularly patients entering a maintenance strategy were positively selected by responding to first line treatment and being able to tolerate further treatment, which is partly reflected by the long median treatment durations achieved in patients with de-escalation/maintenance strategies. Interestingly, only in 15% of unselected mCRC patients a maintenance strategy was administered.

The CAIRO3 study by the Dutch Colorectal Cancer Group investigated the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation in mCRC patients not progressing during induction treatment with six cycles of capecitabine plus oxaliplatin (CAPOX) plus bevacizumab [10]. Median PFS of maintenance phase in the observation arm was 4.1 versus 8.5 months in the maintenance treatment arm (hazard ratio 0.44; \( p < 0.0001 \)). Upon disease progression, CAPOX plus bevacizumab chemotherapy was re-introduced and PFS (from randomisation/start of maintenance) following re-introduction was 10.5 versus 11.8 months in the observation and maintenance arms (hazard ratio 0.81; \( p = 0.028 \)). The median time to second progression in the observation and maintenance arms was 15.0 versus 19.8 months (hazard ratio 0.87; \( p = 0.156 \); adjusted hazard ratio 0.80; \( p = 0.035 \)) suggesting a potential benefit on OS [10]. Similar to our findings with an increased PFS and OS in favour of the more intensive, combined maintenance the results of CAIRO3 study on bevacizumab and FU maintenance compare favourably to the Swiss SAKK 41/06 trial with single agent bevacizumab maintenance [22].

Based on the 1777 evaluable patients in this observational study, the reported overall objective response rate was 60%, which is higher than previously reported in randomised trials or observation cohorts [3,4,21]. Possible explanations for the higher response rate observed in the present study could be the assessment of the investigators only and that confirmation of remission according to RECIST guidelines might not have been taken into account.

One important function of observational cohort studies is to gather more data on the real-world incidence and time to onset of treatment-related AEs in general clinical practice, and to monitor for the occurrence of any new safety signals. Previous studies have been able to characterise the incidence and severity of bevacizumab-associated AEs, including hypertension, bleeding and wound-healing complications, and arterial thromboembolic events. The rate of adverse events of interest for bevacizumab was low in this study in German patients and generally less than those reported in the BEAT and BRiTE studies [8,9]. No new safety signals were detected.

In an attempt to manage intolerable adverse events and continue treatment, de-escalation strategies allowed the removal of irinotecan, oxaliplatin and/or FU, depending upon the occurrence of adverse event(s). In this observational study irinotecan was predominantly used (due to the registration status at its onset) whereas in many of the others reported registries oxaliplatin was the predominant cytotoxic agent. A trend towards prolonged induction treatment and better PFS was observed with irinotecan- versus oxaliplatin-based treatment. Both de-escalation/maintenance (i.e. bevacizumab/FU or single-agent bevacizumab) appear to have resulted in a long PFS and a high number of patients being treated until

combined with capecitabine and bevacizumab [14,20].

Figure 5. OS by maintenance therapy.
KRK 0207 trial were presented; comparing FU/bevacizumab, single-agent bevacizumab or no maintenance therapy following induction therapy with bevacizumab + FU/oxaliplatin in patients with previously untreated mCRC [23]. Compared with maintenance with FU/bevacizumab, maintenance with single agent bevacizumab was non-inferior in terms of PFS (from randomisation/start of maintenance) following re-introduction, whereas non-inferiority could not be excluded compared with no maintenance. PFS of the maintenance phase numerically favoured the maintenance arm with FU and bevacizumab with 6.2 months, compared to single agent bevacizumab with 4.8 months (p = 0.13).

Although observational studies are not as informative as randomised trials, these large trials allow for longitudinal analyses of effectiveness and safety in large and diverse patient populations. The reasons are complex, and likely stem from the non-randomised, non-interventional design. Furthermore, some more limitations must be considered, particularly the bias when selecting patients for specific treatment, maintenance strategies and the methodology of progression assessment and, even more, response. With regard to investigator bias, minimal patient selection criteria were used and all patients scheduled to be treated with bevacizumab in the post-approval period were included in the study; as a result, the population is more likely to be representative of the mCRC patient population eligible for palliative chemotherapy in combination with bevacizumab in Germany rather than studies that are limited to patients with good performance status or the absence of selected comorbidities. Therefore, this observational study provides valuable information regarding the use of bevacizumab under the conditions and specifications of the German healthcare system, which is in line with the ‘global’ findings.

In conclusion, the efficacy and safety profile of bevacizumab plus chemotherapy as first-line therapy in German patients with mCRC patients is consistent with that observed in patient registries/non-randomised trials.

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A. Stein et al.

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Supplementary material available online

Supplementary Table I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.961649