Horizon Scanning in Oncology

Bevacizumab (Avastin®) as maintenance therapy after first progression on bevacizumab for patients with advanced colorectal carcinoma

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 46
ISSN online 2076-5940

Horizon Scanning in Oncology

Bevacizumab (Avastin®) as maintenance therapy after first progression on bevacizumab for patients with advanced colorectal carcinoma

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, July 2014

Institute for Health Technology Assessment Ludwig Boltzmann Gesellschaft

Author: Dr. med. Eleen Rothschedl
Project leader: Dr. med. Anna Nachtnebel, MSc
External review: Dr. med. Christian Pox, Medizinische Universitätsklinik Bochum Innere Medizin, Gastroenterologie

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessment.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at:

DSD: Horizon Scanning in Oncology No.46
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abbreviations

5-FU	5-fluorouracil
BBP	Bevacizumab beyond progression
CapeIRI	Capecitabine plus irinotecan
CapeOx	Capecitabine plus oxaliplatin
CI	Confidence interval
CRC	Colorectal Cancer
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FOLFIRI	Fluorouracil plus leucovorin plus irinotecan
FOLFOX	Fluorouracil plus leucovorin plus oxaliplatin
FOLFOXIRI	Fluorouracil plus leucovorin plus oxaliplatin plus irinotecan
HR	Hazard ratio
IFL	Irinotecan plus leucovorin plus fluorouracil
IROX	Irinotecan plus oxaliplatin
ITT	Intention-to-treat
kg	Kilogramme
KRAS	Kirsten rat sarcoma
LV	Leucovorin
mCRC	Metastatic colorectal cancer
mg	Milligramme
ml	Millilitre
NRAS	Neuroblastoma RAS viral oncogene homolog
OS	Overall survival
PFS	Progression-free survial
PFS1	PFS from randomisation to first progression
PFS2	PFS from randomisation to second progression
RECIST	Response Evaluation Criteria in Solid Tumours
SEER	Surveillance, Epidemiology and End Results
TTP	Time to progression
TT2PD	Time from randomisation to disease progression upon any treatment given after PFS1
VEGF	Vascular endothelial growth factor
XELIRI	Capecitabine plus irinotecan
XELOX	Capecitabine plus oxaliplatin

1 Drug description

Generic/Brand name/ATC code:

Bevacizumab/Avastin®/L01XC07

Developer/Company:

Roche Registration Ltd.

Description:

bevacizumab inhibits growth and maintenance of tumour blood vessels

Bevacizumab (Avastin®) is a recombinant monoclonal antibody that binds to vascular endothelial growth factor (VEGF). By inhibiting VEGF receptor binding, bevacizumab prevents the growth and maintenance of tumour blood vessels [1].

intravenous administration

Bevacizumab is used for the treatment of different types of cancer and in various combinations with other drugs. In patients with metastatic colorectal cancer (mCRC) who have progressed on a first-line Avastin®-containing regimen, the drug is administered at a dosage of 5 mg/kg every two weeks or 7.5 mg/kg every three weeks when used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen. Patients receive Avastin® as an intravenous infusion; treatment should be continued until disease progression or unacceptable toxicity [2].

2 Indication

indicated in patients who have progressed on first-line bevacizumab-containing regimen

Bevacizumab (Avastin®) can be used for patients with mCRC who have progressed on first-line Avastin®-containing regimen. It is administered in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy [2].

3 Current regulatory status

approved by the EMA for all lines of therapy

The EMA granted marketing authorisation for Avastin® in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of adult patients with mCRC in 2005. The indication was extended subsequently and is no longer connected to specific lines of therapy. The indication of this assessment was included in the Summary of Product Characteristics in May 2013.

The EMA approved Avastin® for the following further indications [3]:

- first-line treatment of adult patients with metastatic breast cancer (combination with paclitaxel)
- first-line treatment of adult patients with metastatic breast cancer in combination with capecitabine (when other chemotherapy options including taxanes or anthracyclines are not considered appropriate)

- adult patients with unresectable, advanced, metastatic or recurrent non-small cell lung cancer (in addition to platinum-based chemotherapy)
- first-line treatment of adult patients with advanced and/or metastatic renal cancer (in combination with interferon alfa-2a)
- front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (in combination with carboplatin and paclitaxel)
- adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (in combination with carboplatin or gemcitabine).

indication approved by the FDA

In February 2004, the FDA approved Avastin® for the first-line treatment of patients with mCRC for the use in combination with intravenous 5-fluorouracil-based chemotherapy [4]. On 23 January 2013, the approval for bevacizumab was extended and is currently valid for:

- patients with mCRC, combined with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment
- as second-line treatment in combination with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin based chemotherapy for patients with mCRC who have progressed on a first-line Avastin®-containing regimen [4]
- non-squamous non-small cell lung cancer (in combination with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease)
- glioblastoma in adult patients with progressive disease following prior therapy (used as single agent)
- patients with metastatic renal cell carcinoma in combination with interferon alfa [4].

In November 2011 the FDA removed breast cancer indication from the Avastin® label. The decision was based on a lack of benefit concerning delay in the growth of tumours that would justify the potential risks. Furthermore, there is no evidence that Avastin® treatment lengthens life or improves the quality of life of women with breast cancer [5].

4 Burden of disease

CRC develops in the tissues of the colon and/or rectum.

Advanced CRC can be defined as a disease that

- is metastatic at presentation of a patient
- progresses to become metastatic or
- is locally advanced in a way that its resectability is uncertain [6].

incidence rate in Austria 26.8 per 100,000 per year

Incidence rates of CRC are declining, potentially also caused by increased use of screening tests. These tests allow the early detection and consecutive removal of colorectal polyps before their progress to cancer [7]. In Austria, CRC is the third most common malignancy diagnosed in men and the second most

common malignancy diagnosed in women. In 2011, the incidence rate in Austria for both men and women was 26.8 (per 100,000 people per year), the mortality rate was 11.7 (per 100,000 people per year) [8].

average age at the time of diagnosis: 72 years

At the time of diagnosis, more than 90% of patients with CRC are older than 50 years; the average age at diagnosis is 72 years [9]. The 1-year relative survival rate for patients with CRC is 83%, the 5-year relative survival rate is 65% (relative survival compares survival among cancer patients to that of people not diagnosed with cancer who are of the same age, race and sex). When detected at a localised stage, the 5-year survival for patients with CRC is 90%, it declines to 70% when the tumour has spread to nearby organs or lymph nodes and to 13% in case of distant metastases [9].

more than 95% of CRCs are adenocarcinomas

Histologically, more than 95% of CRCs are adenocarcinomas. Other, less common types are carcinoid tumours, gastrointestinal stromal tumours (GISTs), lymphomas or sarcomas [10].

Risk factors for the development of CRC are:

- increasing age
- hereditary and medical factors such as a personal or family history of CRC and/or polyps, a personal history of chronic inflammatory bowel disease, certain inherited genetic conditions and type 2 diabetes
- modifiable factors: obesity, physical inactivity, a diet high in red or processed meat, alcohol consumption, long-term smoking, very low intake of fruit and vegetables [9].

In contrast, consumption of milk and calcium, and higher blood levels of vitamin D seem to decrease the risk for CRC [9].

Common symptoms of CRC are visible blood in the stool, abdominal pain, otherwise unexplained iron-deficiency anaemia and/or changes in bowel habits. Less common symptoms are abdominal distension, and/or nausea and vomiting. Straining to defecate, rectal pain or small-calibre stools indicate that the tumour is located in the rectum. CRC is a potentially metastatic disease; the most frequently affected sites are the regional lymph nodes, the liver, the lungs and the peritoneum. Approximately 20% of patients have metastases at the time of diagnosis. The preferred staging system for CRC is the TNM classification: primary tumour (T), regional lymph node (N), distant metastasis (M) [11].

5 Current treatment

therapy options for patients with mCRC after progression on first-line therapy

The recommended therapy options for patients with mCRC after progression on first-line therapy depend on previously administered therapies [10]:

Initial treatment	Recommended therapy options after progression of mCRC
FOLFOX- or CapeOx-based regimen	FOLFIRI or irinotecan alone or with cetuximab or panitumumab (KRAS/NRAS wild-type tumour only), bevacizumab or ziv-aflibercept
FOLFIRI-based regimen	FOLFOX or CapeOX alone or with bevacizumab, cetuximab or panitumumab plus irinotecan; or single-agent cetuximab or panitumumab (for patients not appropriate for the combination with irinotecan)
5-FU/LV or capecitabine without oxaliplatin or irinotecan	FOLFOX, CapeOx, FOLFIRI, single-agent irinotecan, or irinotecan plus oxaliplatin (IROX; less common); can be varyingly combined with bevacizumab or ziv-aflibercept
FOLFOXIRI	Cetuximab or panitumumab plus irinotecan or cetuximab or panitumumab alone (patients with wild-type KRAS/NRAS)

Abbreviations: FOLFOX = fluorouracil, leucovorin, oxaliplatin; CapeOx = capecitabine, oxaliplatin; FOLFIRI = fluorouracil, leucovorin, irinotecan; KRAS = Kirsten rat sarcoma; NRAS = neuroblastoma RAS viral oncogene homolog; 5-FU = 5-fluorouracil; LV = leucovorin; FOLFOXIRI = fluorouracil, leucovorin, oxaliplatin, irinotecan

As a part of initial therapy, bevacizumab, panitumumab or cetuximab can be used; analysis within the SEER (Surveillance, Epidemiology and End Results) database showed that the addition of bevacizumab to first-line chemotherapy was associated with a small improvement in OS, whereas the risk for stroke and perforation (but not for cardiac events) was increased [12].

The addition of bevacizumab continuation to second-line treatment options was included in the recommended therapy options in 2013. The VEGF inhibitor may be added to any regimen that does not contain an epidermal growth factor receptor (EGFR) inhibitor or ziv-aflibercept [10].

6 Evidence

2 phase III studies, 4 phase II and 2 observational cohort studies were included

A literature search was conducted in April 2014 in four databases (Medline, Embase, CRD Database and The Cochrane Library). Search terms were “Colorectal Neoplasms”, “Bevacizumab”, “Avastin”, “Altuzan”, “nsc704865”, “Neoplasm Metastasis”. Also, the manufacturer was contacted for any further evidence, and submitted 2 references (both already identified by the systematic literature search) and information about 1 trial (CAIRO3, results not published yet, see 6.1).

Overall, 810 references were identified. Included in this report are:

- 2 phase III studies, assessing continued use of bevacizumab plus standard second-line chemotherapy in patients with mCRC progressing after standard first-line bevacizumab-based treatment [12, 13].
- 4 phase II studies and 2 observational cohort studies, described in 6.2.

6.1 Efficacy and safety – phase III studies

6.1.1 NCT00700102

Table 1: Summary of efficacy

Study title Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase III trial [12].			
Study identifier	NCT00700102, EudraCT Number 2006-004634-32		
Design	Prospective, intergroup, randomised (1:1 ratio), open-label, multicentre (220 centres in 15 countries)		
	Duration	*Enrolment:* 2006-02-01 to 2010-06-09 *Median follow-up:* 11.1 months (bevacizumab plus chemotherapy group), 9.6 months (chemotherapy alone group) *Cut-off dates for analyses:* 2011-05-31	
Hypothesis	Superiority The study was designed to detect a 30% (hazard ratio 0.77) improvement in median overall survival with 90% power, assuming a two-sided 5% type 1 error and median overall survival for chemotherapy alone of 10 months.		
Funding	F. Hoffmann-La Roche		
Treatment groups	Intervention (n=409)	Second-line chemotherapy (infusional or bolus fluorouracil or oral capecitabine plus irinotecan or oxaliplatin) plus Bevacizumab at 2.5 mg/kg per week equivalent (either 5 mg/kg intravenously every two weeks or 7.5 mg/kg every 3 weeks intravenously)	
	Control (n=411)	Second-line chemotherapy (infusional or bolus fluorouracil or oral capecitabine plus irinotecan or oxaliplatin)	
Endpoints and definitions	Overall survival (primary outcome)	OS	Time from randomisation to death from any cause
	Progression-free survival	PFS	Time from randomisation to documented disease progression or death from any cause
	Overall survival from the start of first-line treatment	-	Time from the start of first-line treatment to death from any cause
	Confirmed best overall response	-	Assessed with modified Response Evaluation Criteria in Solid Tumours (RECIST, version 1.0)
	Safety	-	Adverse events, laboratory data
	On-treatment progression-free survival	-	Time from randomisation to documented disease progression or death from any cause only if occurred up to 28 days after the last confirmed dose of study treatment
	Exploratory endpoints	-	Evaluation of OS, PFS and subsequent anticancer treatments according to KRAS mutation status

Results and analysis				
Analysis description	Intention-to-treat analysis Overall survival curves were estimated with the Kaplan-Meier method Primary analysis was done with unstratified log-rank tests Unstratified Cox regression models were used to estimate the HR for OS, unstratified log-rank tests were used to assess differences Unstratified log-rank tests were used for analysis of PFS, PFS on treatment and OS from the start of first-line treatment Cox regression models were used to generate HRs Unstratified Cox regression models were used to generate HRs and corresponding 95% CIs for all secondary endpoints, subgroup analysis and the exploratory analysis by KRAS status Unstratified χ^2 tests were used to assess between-groups differences for best overall response and post-hoc analysis of disease control Analyses were done with SAS (version 8.2)			
Analysis population	Inclusion	❖ Age ≥ 18 years ❖ Histologically confirmed, measurable mCRC ❖ ECOG performance status 0–2 ❖ Tumour disease according to RECIST by investigator up to 4 weeks prior to start of study treatment ❖ Previous treatment with bevacizumab plus standard first-line chemotherapy including a fluoropyrimidine plus either oxaliplatin or irinotecan ❖ Not appropriate for primary metastasectomy		
	Exclusion	❖ Progressive disease for more than 3 months after the last bevacizumab administration ❖ First-line PFS of less than 3 months ❖ Less than 3 months (consecutive) of first-line bevacizumab		
	Characteristics		Intervention	Control
		Sex, % Male/female	65/35	63/37
		Median age, years	63	63
		ECOG performance status, % 0/1/2	44/51/5	43/52/5
		First-line PFS, months ≤9/>9	54/46	56/44
		Liver metastasis only, % No/yes	73/27	71/29
		Number of organs with metastases, % ≤1/>1	36/64	39/61
		Time from last bevacizumab dose, days ≤42/>42	77/23	77/23
		First-line chemotherapy, % Irinotecan-based Oxaliplatin-based	59 41	58 42

Descriptive statistics and estimated variability	Treatment group	*Intervention* (Bevacizumab plus chemotherapy)	*Control* (chemotherapy alone)
	Number of subjects	N=409	N=411
	OS Median (95% CI), months	11.2 (10.4–12.2)	9.8 (8.9–10.7)
	PFS Median (95% CI), months	5.7 (5.2–6.2)	4.1 (3.7–4.4)
	OS from the start of first-line treatment Median (95% CI), months	23.9 (22.2–25.7)	22.5 (21.4–24.5)
	PFS on treatment Median (95% CI), months	5.7 (5.2–6.2)	4.0 (3.7–4.3)
	Number of subjects	N = 404	N = 406
	Tumour response, number (%) Complete response Partial response Stable disease Progressive disease Missing or not assessable	1 (<1) 21 (5) 253 (63) 87 (22) 42 (10)	2 (<1) 14 (3) 204 (50) 142 (35) 44 (11)
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	OS	HR	0.81
		95% CI	0.69–0.94
		P value	0.0062
	PFS	HR	0.68
		95% CI	0.59–0.78
		P value	<0.0001
	OS from the start of first-line treatment	HR	0.90
		95% CI	0.77–1.05
		P value	0.17
	PFS on treatment	HR	0.63
		95% CI	0.53–0.74
		P value	<0.0001
	Confirmed response	HR	NR
		95% CI	NR
		P value	0.31
	Disease control	HR	NR
		95% CI	NR
		P value	<0.0001

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; KRAS = Kirsten rat sarcoma; NCT = National Clinical Trial; NR = not reported; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

Table 2: Most frequent adverse events (occurring in 2% or more of patients, safety population)

Adverse Event (according to NCI-CTC version 3.0)	**Bevacizumab plus chemotherapy (N=401)**	**Chemotherapy alone (N=409)**
Grade 3–5, n (%)		
Neutropenia	65 (16)	52 (13)
Leucopenia	16 (4)	12 (3)
Asthenia	23 (6)	17 (4)
Fatigue	14 (3)	10 (2)
Diarrhoea	40 (10)	34 (8)
Vomiting	14 (3)	13 (3)
Nausea	13 (3)	11 (3)
Decreased appetite	5 (1)	9 (2)
Mucosal inflammation	13 (3)	4 (1)
Abdominal pain	15 (4)	12 (3)
Polyneuropathy	12 (3)	6 (1)
Peripheral neuropathy	5 (1)	10 (2)
Hypokalaemia	9 (2)	8 (2)
Dyspnoea	6 (1)	12 (3)
Pulmonary embolism	10 (2)	8 (2)
Hypertension	7 (2)	5 (1)
Bleeding or haemorrhage	8 (2)	1 (<1)
Venous thromboembolic events	19 (5)	12 (3)
Gastrointestinal perforation	7 (2)	3 (<1)
Subileus	8 (2)	2 (<1)
Other		
Treatment discontinuation due to adverse events:		
Discontinuation of any treatment	63 (16)	36 (9)
Discontinuation of chemotherapy only or chemotherapy plus bevacizumab	53 (13)	NR
Discontinuation of bevacizumab	10 (2)	–
Deaths not related to PD	23 (6)	22 (5)

Abbreviations: NCI = National Cancer Institute; n = number; CTC = Common Toxicity Criteria; NR = not reported; PD = progressive disease

the continued use of bevacizumab plus standard second-line therapy was assessed in 820 patients

This phase III study was conducted to assess the continued use of bevacizumab plus standard second-line therapy in 820 patients with mCRC who have progressed after a standard first-line bevacizumab-containing regimen. Patients were randomly assigned in a 1:1 ratio to two treatment arms: 50% (N=409) of patients received bevacizumab plus chemotherapy and 50% (N=411) received chemotherapy alone. At the investigator's discretion, patients were treated with infusional or bolus fluorouracil or oral capecitabine plus irinotecan or oxaliplatin, with or without bevacizumab at 2.5 mg/kg per week equivalent (either 5 mg/kg intravenously every two weeks or 7.5 mg/kg intravenously every three weeks). The type of second-line chemotherapy de-

pended on the first-line regimen (switch of chemotherapy). At the discretion of the physician several different chemotherapy regimens were applied as second-line therapy (e.g. FOLFIRI, FOLFOX, XELOX). Treatment was continued until progression of disease, patient's refusal to continue or occurrence of unacceptable toxicity.

all patients had prior bevacizumab treatment plus first-line chemotherapy

All patients had previously been treated with bevacizumab plus standard first-line chemotherapy including a fluoropyrimidine plus either oxaliplatin (41% bevacizumab plus chemotherapy group vs. 42% chemotherapy alone group) or irinotecan (59% bevacizumab plus chemotherapy group vs. 58% chemotherapy alone group). Patients in both groups had a median age of 63 years and an ECOG performance status of 0–2. 64% of patients (bevacizumab plus chemotherapy group) and 61% (chemotherapy alone group) had more than one organ with metastases.

median age of patients was 63 years, EGOG performance status was 0–2

Median duration of treatment with bevacizumab was 3.9 months; median overall treatment exposure was 4.2 months in the bevacizumab plus chemotherapy group compared to 3.2 months in the chemotherapy alone group. After study treatment was completed, 69% (bevacizumab plus chemotherapy group) and 68% of patients (chemotherapy alone group) received one or more subsequent anticancer treatments.

The primary endpoint of this trial was OS; secondary endpoints were PFS, OS from the start of first-line treatment, confirmed best overall response and safety, and on-treatment PFS as an additional secondary endpoint. As exploratory endpoints, evaluation of OS, PFS and subsequent anticancer treatments according to the KRAS mutation status were mentioned.

OS extended by 1.4 months and PFS by 1.6 months

Median OS was 11.2 months (95% CI 10.4–12.2) in the bevacizumab plus chemotherapy group compared to 9.8 months (8.9–10.7) in the chemotherapy alone group (HR 0.81, 95% CI 0.69–0.94; p=0.0062). In the bevacizumab plus chemotherapy group, median PFS was 5.7 months (95% CI 5.2–6.2) compared to 4.1 months (95% CI 3.7–4.4) in the chemotherapy group (HR 0.68, 95% CI 0.59–0.78; p<0.0001). A confirmed response, primarily partial responses, in patients with one or more measurable lesions at baseline was achieved by 5% in the bevacizumab plus chemotherapy group and by 4% of patients in the chemotherapy alone group (unstratified χ^2 test p=0.31).

The retrospectively documented median OS from the start of first-line treatment was 23.9 months (95% CI 22.2–25.7) in the bevacizumab plus chemotherapy arm compared to 22.5 months (21.4–24.5) in the chemotherapy alone arm (HR 0.90, 95% CI 0.77–1.05; unstratified log-rank p=0.17). Analysis of the median PFS on treatment showed the following results: 5.7 months (95% CI 5.2–6.2) in the bevacizumab plus chemotherapy group and 4.0 months (95% CI 3.7–4.3) in the chemotherapy alone group (HR 0.63, 95% CI 0.53–0.74; unstratified log-rank p<0.0001).

high rates of adverse events in both treatment arms

Adverse events occurred in 98% (bevacizumab plus chemotherapy group) and 99% (chemotherapy alone group) of patients. 64% of patients in the bevacizumab plus chemotherapy arm and 57% of the chemotherapy alone arm showed grade 3–5 adverse events. The most common grade 3–5 adverse events were neutropenia, diarrhoea and asthenia. In total, 11 grade 5 adverse events (resulting in death) were reported in each group. 4 of those deaths in the bevacizumab plus chemotherapy group and 3 in the chemotherapy alone group were deemed to be treatment-related; they were caused by upper gastrointestinal haemorrhage, cerebrovascular accident, sudden death and neutropenia (bevacizumab plus chemotherapy arm), intestinal perforation, gen-

eral physical health deterioration and acute prerenal failure (chemotherapy alone arm). Serious adverse events were reported in 32% of patients in the bevacizumab plus chemotherapy group and in 33% of patients in the chemotherapy alone group.

16% of patients (bevacizumab plus chemotherapy) and 9% of patients (chemotherapy alone group) discontinued treatment due to the occurrence of adverse events. In the bevacizumab plus chemotherapy arm, 13% of patients discontinued chemotherapy or both chemotherapy and bevacizumab because of adverse events and 2% of patients discontinued bevacizumab treatment due to adverse events. According to the study protocol, a dose reduction of bevacizumab during the study was not allowed.

Additionally, an exploratory analysis evaluating outcomes according to tumour Kirsten rat sarcoma virus oncogene (KRAS) status was conducted. Thereby, no apparent effect of tumour KRAS mutational status on the efficacy of second-line bevacizumab in study patients has been shown, which means that bevacizumab beyond first progression is an option for patients with mCRC, independent of their KRAS-status [14].

6.1.2 NCT00442637

CAIRO3 evaluated the use of maintenance bevacizumab plus capecitabine after induction with bevacizumab plus XELOX

The manufacturer of Avastin® provided information about CAIRO3, a randomised, multicentre, open-label phase III study [13]. Results are not yet fully published, but final results were presented at ASCO 2014. 558 patients with previously untreated mCRC received six cycles of induction therapy with bevacizumab plus XELOX and were then randomised either to arm A (observation, N=279) or to arm B (bevacizumab plus capecitabine, N=279). After first progression of disease, patients of both groups received bevacizumab plus XELOX until second progression. Primary endpoint of the study was PFS2 (= PFS from randomisation to second progression), secondary endpoints were PFS1 (= PFS from randomisation to first progression), OS, TT2PD (= time from randomisation to disease progression upon any treatment given after PFS1), overall response rate and safety. Median follow-up was 48 months; the cut-off date was 2014-01-06.

significant benefit in PFS1 and TT2PD

Median PFS2 was 11.7 months in arm B versus 8.5 months in arm A (HR 0.67, 95% CI, 0.56–0.81, p<0.0001). Analysis showed that median PFS1 significantly improved with maintenance of bevacizumab plus capecitabine (8.5 months) versus observation (4.1 months), resulting in stratified HR 0.43 (95% CI, 0.36–0.52, p<0.0001). After first progression, bevacizumab plus XELOX was reintroduced in 60% of patients in arm A and in 47% in arm B [15]. Median TT2PD was 13.9 months in the maintenance treatment group compared to 11.1 months in the observation group (HR 0.68, 95% CI, 0.57–0.82, p<0.0001). In contrast, there was a non-significant benefit in median OS for ITT (intention-to-treat) population: 21.6 months in the maintenance group, 18.1 months in the observation group (HR 0.89, 95% CI, 0.73–1.07, p=0.22). Furthermore, despite statistically significant differences favouring the observation group, results on quality of life did not show a clinically relevant difference. The authors concluded that quality of life was preserved in patients treated with maintenance (bevacizumab plus capecitabine) therapy.

6.2 Efficacy and safety – further studies

phase II study evaluated the timing of bevacizumab in 41 patients

Assessing the timing (first-line or later use) of bevacizumab in the overall treatment of advanced mCRC was the aim of this phase II study [16]: 41 patients (median age was 61 years) who progressed after first-line therapy of 5-fluorouracil, oxaliplatin-/irinotecan-based regimens with (19 patients) or without bevacizumab (22 patients) were randomised to receive second-line therapy consisting of either chemotherapy plus bevacizumab or chemotherapy alone (FOLFOX or FOLFIRI). Of the 19 patients who had progressed on bevacizumab containing first-line therapy, 7 received second-line therapy with chemotherapy plus bevacizumab. Partial response was 25% (second-line bevacizumab group) and 18.8% (patients with first-line chemotherapy and bevacizumab-based regimen) compared to 11.8% and 5.9% with second-line chemotherapy. TTP (median time to progression) was 3.1 months compared to 2.3 months in patients with first-line chemotherapy and bevacizumab-based regimens respectively. Median survival was 8.2 versus 4 months in both groups. Adverse events were not statistically significant between bevacizumab with or without chemotherapy, but cardiovascular events such as hypertension or bleeding occurred only in the combination group.

SILK study assessed the efficacy and safety of BBP in 39 patients

The SILK study [17], a phase II trial, evaluated the efficacy and safety of bevacizumab beyond progression (BBP) for patients with mCRC who progressed on first-line chemotherapy plus bevacizumab. Therefore, 39 patients received either FOLFIRI plus bevacizumab or FOLFOX plus bevacizumab, depending on the previous first-line regimen. Median age of patients was 62 years, all had confirmed disease progression and had received a combination of bevacizumab and FOLFOX or FOLFIRI as first-line therapy. The overall response rate (primary endpoint) was 16.2%; disease control rate was 76%. Median OS was 417 days, median PFS was 150 days and total survival from initiation of first-line treatment was 988 days. Safety analysis showed that fatigue (23%), hypertension (18%), diarrhoea (10%), vomiting (5%) and anorexia (5%) were the most common non-haematological grade 3 or 4 adverse events, whereas neutropenia (33%), leucopenia (13%), febrile neutropenia (13%) and haemoglobin decrease (8%) were the most common grade 3 or 4 haematological toxic events.

Korean study investigated the efficacy and safety of BBP combined with doublet chemotherapy in 76 patients

Another prospective, open-label, multicentre phase II study conducted in Korea [18] evaluated the efficacy and safety of BBP combined with doublet chemotherapy in patients with mCRC. The study included 76 patients who received second-line continuation of bevacizumab (5 mg/m^2 every two weeks when 5-FU-based regimen was used or 7.5 mg/m^2 every three weeks when combined with capecitabine-based regimen) plus switched doublet chemotherapy consisting of FOLFOX, CapeOx or FOLFIRI. Patients had a median age of 57 years and the ECOG performance status was 0–1. 52.6% of patients had received CapeOx, 22.4% FOLFOX, 17.1% FOLFIRI and 7.9% received CapeIRI (capecitabine plus irinotecan) as first-line chemotherapy (plus bevacizumab). Patients with disease progression after first-line FOLFIRI or CapeIRI (plus bevacizumab) received FOLFOX or CapeOx, those who had first-line FOLFOX or CapeOx (plus bevacizumab) subsequently received FOLFIRI. The treatment was given until the occurrence of disease progression, unacceptable toxicity or patient refusal. After a median follow-up of 12.3 months, median PFS was 6.5 months (95% CI, 5.2–7.8), median OS was 12.8 months (95% CI, 8.8–16.9) and no significant differ-

ences according to combined chemotherapy were established. Regarding the overall response rate of 17.1% (95% CI, 8.6–25.6), the majority of responses were stable disease with complete responses in 2 patients and partial responses in 11 patients. Bevacizumab-related adverse events of grade 3 or 4 were proteinuria (1.3% of patients) and thromboembolism (1.3% of patients).

evaluation of efficacy and safety of BBP in 47 Japanese patients

The aim of a phase II, multicentre, single-arm study [19] was to investigate the efficacy and safety of BBP in Japanese patients with mCRC. Therefore, 47 patients (median age 63 years) initially received bevacizumab (5 mg/kg) plus FOLFOX6 until tumour progression. Subsequently, 31 patients received bevacizumab plus FOLFIRI for second-line therapy. The primary endpoint of the trial, the 2nd PFS (duration from enrolment until progression after second-line therapy), was 18.0 months (95% CI, 13.7–22.3 months). The median OS was 30.8 months (95% CI, 27.7–34.0 months), median survival beyond first progression was 19.6 months (95% CI, 13.5–25.7 months), the response rate was 29.0%, the disease control rate was 64.5% and median PFS from initiation of second-line therapy was 7.3 months (95% CI, 5.0–9.6 months). Haematologic and non-haematologic adverse events grade >3 occurred in 44.4% and 16.7% respectively. Bevacizumab-associated toxicity (>grade 3) occurred in 2.1% of patients receiving first-line therapy (gastrointestinal perforation) and in 3.2% of patients receiving second-line therapy (hypertension).

BRiTE study: large-scale observational cohort study

A frequently cited study is BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) [20], a prospective observational cohort bevacizumab treatment study. 1,953 patients were enrolled; previously untreated patients and patients with first-line treatment with bevacizumab were included. More than half of the patients (55.9%) had received FOLFOX for first-line chemotherapy. The median age of patients at baseline was 63 years, and the majority (>80%) had an ECOG performance status of 0 or 1. At a median follow-up of 19.6 months, 1,445 patients experienced first progression and were then classified into three groups according to the treatment they had received: no treatment, post-disease progression treatment without bevacizumab and post-disease progression treatment with bevacizumab. Post-progression treatment could include any systemic anticancer therapy (cytotoxic and/or biologic agents as well) at the discretion of the physician. Overall, 642 patients received bevacizumab mainly at a dosage of 5 mg/kg every two weeks (90.7%). Of these, 69.2% had received bevacizumab continuously beyond progression or restarted the therapy within 1 month, whereas 30.8% had discontinued bevacizumab before progression or at first progression and restarted more than 1 month after first progression. OS and survival beyond first progression showed better outcomes for patients who had received bevacizumab after first progression (median OS 31.8 months, median survival beyond first progression 19.2 months) in comparison to patients without any further therapy (median OS 12.6 months, survival beyond first progression 3.6 months) or those not receiving bevacizumab (median OS 19.9 months, survival beyond first progression 9.5 months). Results for time to progression were similar across the three groups. When patients were analysed according to the time-lag (i.e. >2 months) of initiation of further therapy after disease progression, patients receiving bevacizumab within 2 months of disease progression had an even greater improvement in OS than those who had not received bevacizumab beyond first progression. The most common adverse event was new or worsened hypertension: 19.0% (no post-disease progression treatment), 19.2%

(post-disease progression treatment without bevacizumab) and 24.6% (bevacizumab beyond first progression) of patients were affected.

ARIES study: investigating the combination of bevacizumab with first- or second-line therapy

Another prospective, multicentre, observational cohort study is ARIES: Avastin® Registry – Investigation of Effectiveness and Safety [21]. Patients receiving bevacizumab in combination with either first- or second-line chemotherapy were enrolled. 482 patients were enrolled in the second-line setting. Median age was 62 years and only 8.6% had ECOG PS ≥2. Chemotherapy in the second-line setting was at the discretion of the physician, but the most commonly administered regimens were FOLFOX and FOLFIRI. 210 patients had received bevacizumab as first-line therapy, whereas 272 were bevacizumab-naïve. At a median follow-up of 16.9 months, PFS was 7.6 for bevacizumab-exposed patients in comparison to 8.1 months for bevacizumab-naïve patients. For OS, measured from the beginning of the second-line therapy, the corresponding numbers were 19.8 months and 17.2 months. Adverse events occurred in 16.4% of patients, of which 6.8% were serious. Adverse events were comparable between bevacizumab-naïve and exposed patients, with the exception of 4 deaths (1.5%) due to adverse events in the bevacizumab-exposed group in comparison to no deaths in the naïve group.

7 Estimated costs

monthly costs for bevacizumab maintenance treatment: approx. € 2,843.8

The dosage schedule for Avastin® maintenance therapy in patients with mCRC who have progressed after first-line Avastin®-containing therapy is 5 mg/kg every two weeks or 7.5 mg/kg every three weeks (intravenously) when used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based regimen [4]. Bevacizumab (Avastin®) is available in vials of 4 ml (25 mg/ml) at € 414.05 and vials of 16 ml (25 mg/ml) at € 1,421.9 [22].

Assuming a body weight of 70 kg and median treatment duration of four months (median treatment duration in ML18147 trial was 3.9 months [12]), total costs for bevacizumab maintenance treatment are approximately € 11,375.2 (monthly costs: € 2,843.8). Additionally, costs for first-line bevacizumab, chemotherapeutical regimens and the management of adverse events incur.

8 Ongoing research

various ongoing phase III and phase IV trials

In May 2014, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following trials were identified:

- NCT00973609 (EudraCT Number 2008-007797439): A randomised, three-arm phase III study evaluating the efficacy of maintenance and reinduction treatment or no treatment and watchful waiting in patients with inoperable or irresectable and non-progressive metastatic CRC after first-line induction treatment for 24 weeks with fluoropyrimidine-, oxaliplatin- and bevacizumab-based chemotherapy. The estimated study completion date is December 2015.

- NCT00544700: This phase III trial aims to evaluate the efficacy of bevacizumab as maintenance therapy in patients with CRC after first-line therapy. Comparators are bevacizumab maintenance therapy versus no anti-tumour treatment until progression. The estimated study completion date is December 2017.
- NCT01588990: An open-label, prospective, single-arm, phase IV study evaluating the markers of inflammation and PFS in patients with previously untreated mCRC. The study is conducted in two phases, phase A treatment (XELOX plus bevacizumab or mFOLFOX6 plus bevacizumab) until first disease progression and phase B treatment (FOLFIRI plus bevacizumab) until second disease progression. The estimated study completion date is August 2016.
- NCT01912443: An observational study that aims to assess the safety profile of bevacizumab in combination with chemotherapy in patients with mCRC (unlimited line of treatment). Estimated study completion date is August 2017.
- NCT00952029: A randomised phase III trial evaluating the efficacy of FOLFIRI plus bevacizumab followed by combination chemotherapy with or without bevacizumab in patients with mCRC. Estimated study completion date is July 2016.
- NCT01996306: A multinational, randomised phase III trial assessing the effect of XELIRI with or without bevacizumab compared with FOLFIRI with or without bevacizumab as second-line therapy in patients with mCRC. Estimated study completion date is January 2017.
- NCT00720512: (EudraCT Number 2007-002886-11): An open-label, multicentre, randomised phase III study of second-line chemotherapy with or without bevacizumab in patients with mCRC after first-line chemotherapy with bevacizumab. Study completion date was March 2014; there are no results available yet.
- NCT01878422: (EudraCT Number 2007-004539-44): A randomised, prospective, multicentre study (phase III) assessing the role of new target molecules with chemotherapy in first- and second-line treatment of mCRC. Patients receive chemotherapy with or without bevacizumab as first-line therapy followed by chemotherapy alone or chemotherapy plus bevacizumab with or without cetuximab as second-line therapy. Primary completion date is March 2014

There are several trials ongoing, evaluating the use of bevacizumab for various indications and different diseases.

9 Commentary

approved by the EMA and the FDA

In 2013, the FDA approved second-line therapy with bevacizumab (Avastin®) for patients with mCRC who have progressed on a first-line bevacizumab-containing regimen, for the use in combination with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin based chemotherapy [4]. The EMA had initially approved bevacizumab in combination with fluoropyrimide-based chemotherapy for the first-line therapy of mCRC, but specifically incorporated the results of the ML18147 trial in May 2013.

Based on the positive results of 2 large observational studies, the BRiTE and the ARIES studies, continued use of bevacizumab beyond first progression

became of interest as a treatment option for mCRC patients [20, 21]. In line with this development, a pivotal ML18147 trial was published in 2013 [12] and first results of a second phase III trial (CAIRO3) have recently been published as an abstract [13]. Several phase II studies provide further data in support of this hypothesis.

The ML18147 trial [12], a prospective, randomised, open-label phase III study, evaluated the continued use of bevacizumab plus standard second-line chemotherapy in patients with mCRC who had progressed after standard first-line bevacizumab-based treatment. 820 patients were randomly assigned to two treatment arms. They received either chemotherapy plus bevacizumab (N=409) or chemotherapy alone (N=411). Median duration of treatment with bevacizumab was 3.9 months. All patients were previously treated with bevacizumab plus standard first-line chemotherapy, including fluoropyrimidine plus either oxaliplatin or irinotecan.

ML18147 trial: OS increased by 1.4 months

Analyses showed a gain in median OS of 1.4 months for the bevacizumab plus chemotherapy group compared to the chemotherapy alone group. For median PFS a risk reduction of 32% was observed, also favouring the combination regimen. Median OS from the start of first-line treatment was prolonged by 1.4 months in the bevacizumab plus chemotherapy arm compared to the chemotherapy alone arm.

High rates of adverse events were observed in both treatment arms: 98% (bevacizumab plus chemotherapy group) and 99% of patients (chemotherapy alone group) had adverse events. Grade 3–5 adverse events occurred in 64% (bevacizumab plus chemotherapy) and 57% (chemotherapy alone) of patients. From overall 11 grade 5 adverse events resulting in death, 4 deaths in the bevacizumab plus chemotherapy group and 3 in the chemotherapy alone group were deemed to be treatment-related. Serious adverse events were similar in the two groups, which confirms the safety observations made in the BRiTE study [20], where only a higher incidence of new or worsened hypertension was observed; a fact that the authors attributed to the prolonged treatment exposure to bevacizumab.

Preliminary published results from the CAIRO3 study demonstrate that administering maintenance treatment with capecitabine plus bevacizumab after induction therapy with bevacizumab, capecitabine and oxaliplatin significantly prolonged time to disease progression in comparison to observation only by 4.4 months [13]. The time from randomisation to progression after the reintroduction of XELOX was extended by 3.2 months. OS did not reach a statistically significant difference.

Even though these results indicate that maintenance therapy with bevacizumab therapy adds some benefit after first disease progression, several questions remain unanswered.

median age of 63 years and good performance status of study population: applicability of results is questionable

Firstly, median age of patients in the ML18147 trial in both treatment arms was 63 years and the majority of patients (95% in each group) had a good performance status (ECOG 0–1). Considering these facts, the applicability of study results to a clinical setting is questionable, since affected patients often are at a higher age (the average age at diagnosis of patients with mCRC is 72 years) [22]. However, a phase II study indicates that XELOX combined with bevacizumab is effective and its tolerability profile is manageable when administered to elderly people (median age of study population was 74 years) [23].

Secondly, there is no single standard first-line therapy for the treatment of mCRC. Commonly used regimens are chemotherapy doublets using irinotecan (FOLFIRI) or oxaliplatin (e.g. FOLFOX, XELOX) as backbone. Even though recommendations concerning first-line therapy mention that bevacizumab can be added to commonly used first-line therapies, evidence for an additional benefit is scarce and improvements are limited [10, 24, 25]. A more pronounced benefit was derived when bevacizumab was added to "weaker" chemotherapy regimens not routinely used in the first-line setting of patients appropriate for intensive therapy such as FU/LV or bolus IFL (irinotecan plus leucovorin plus fluorouracil) [25, 26]. Therefore, incorporating bevacizumab first-line therapy, followed by bevacizumab maintenance therapy as the standard approach for the treatment of all mCRC patients remains questionable.

no single standard first-line therapy for mCRC treatment

It should also be mentioned that the ML18147 trial excluded patients who had a first-line PFS of less than 3 months or those who did not receive the drug for more than 3 consecutive months. Therefore patients more likely to benefit from bevacizumab and those more likely to tolerate bevacizumab were included in this trial [27]. Furthermore, there is no clear distinction between second-line therapy and maintenance therapy with bevacizumab, a fact reflected in the inclusion criteria for the studies available. Patients were included up to less than 1–3 months after the last bevacizumab administration [12, 18, 20], they received bevacizumab continuously beyond progression [20], or no detailed information was provided for the time to initiation of second-line treatment [13, 19, 21]. Since analyses showed that cumulative exposure to bevacizumab after progression of disease is associated with increased post-progression survival in patients with mCRC [28, 29] and subgroup analyses indicate improved outcomes for patients receiving bevacizumab within up to 2 months after first progression or the last bevacizumab administration, a clear definition of treatment lines (as described by Abrams et al. [29]) needs to be determined, most notably a precise distinction between maintenance therapy and second-line therapy.

inclusion of patients more likely to benefit from bevacizumab in ML18147 trial

In addition to high costs associated with prolonged bevacizumab therapy, alternative treatment options including EGFR inhibitors (e.g. cetuximab and panitumumab) or VEGF inhibitors (e.g. aflibercept or regorafenib) may yield better outcomes. Thus the application of different VEGF inhibitors or EGFR inhibitors for maintenance treatment should be taken into consideration. For example, even though exploratory subgroup analyses from ML18147 did not show a difference in treatment effect in correlation with KRAS mutational status, preliminary results indicate better outcomes for KRAS wild-type mCRC for cetuximab (anti-EGFR) than for bevacizumab [30]. Positive results for continued VEGF inhibition were also presented for regorafenib, another VEGF inhibitor, in the CORRECT trial [31]. Findings about nintedanib, a small molecule angiokinase inhibitor with the ability to overcome different resistance mechanisms, might also be of interest [32].

use of EGFR or VEGF inhibitors should be considered

Besides the optimal timing and duration of bevacizumab therapy, another issue concerns the optimal dosage of bevacizumab – with all factors impacting on the costs. In this respect, the results of the EAGLE study [33] will be of peculiar interest: the multicentre, randomised phase III study aims to assess the efficacy of the appropriate dose of bevacizumab (5 mg/kg or 10 mg/kg) with FOLFIRI in patients with advanced or metastatic CRC who have failed prior bevacizumab plus oxaliplatin-based chemotherapy.

EAGLE study (ongoing) evaluates appropriate dose of bevacizumab

side effects of long-term therapy are unknown

In addition to the financial impact of prolonged bevacizumab therapy, side effects associated with long-term therapy are unknown. Foremost cardiovascular adverse events have been reported [26] and the BRiTE study [22] also mentions the occurrence of hypertension as a possible side effect of prolonged bevacizumab administration.

a feasible treatment option despite modest clinical benefits and high treatment costs

In conclusion, patients with mCRC who experienced disease progression after first-line treatment have a poor prognosis and the use of bevacizumab in maintenance therapy adds to the armamentarium of available treatment options. However, modest clinical benefits and high treatment costs have to be weighed against each other. Future research is required to evaluate optimal treatment line(s), dosage and further treatment combinations, as are investigations into EGFR and various VEGF inhibitors for this indication.

References

[1] National Cancer Institute. NCI Thesaurus: Bevacizumab. 2014 [cited 2014-05-09; Available from: http://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI%20Thesaurus&code=C2039

[2] U.S. Food and Drug Administration. Drugs@FDA. Label information. 2014 [cited 2014-05-09; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125085s285lbl.pdf

[3] EMA. Avastin.Product information. 2014 [cited 2014-05-09; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf

[4] U.S. Food and Drug Administration. Drugs@FDA. Approval Letter. 2004 [cited 2014-05-13; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/STN-125085_Avastin_Approv.pdf

[5] U.S. Food and Drug Administration. Commissioner Statement: Avastin. 2011 [cited 2014-05-14; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279485.htm

[6] ASCRS. American Society of Colon and Rectal Surgeons. Advanced colon and rectal cancer. [cited 2014-05-19; Available from: http://www.fascrs.org/physicians/education/core_subjects/2007/advanced_colon_rectal_cancer/

[7] American Cancer Society. Cancer Facts & Figures 2014. 2014 [cited 2014-05-19; Available from: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

[8] Statistik Austria. Dickdarm und Enddarm - Krebsinzidenz und Krebsmortalität. 2014 [cited 2014-05-19; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/dickdarm_enddarm/index.html

[9] National Cancer Institute. Cancer of the Colon and Rectum. 2014 [cited 2014-05-20; Available from: http://www.cancer.gov/cancertopics/wyntk/colon-and-rectal/page4

[10] National Comprehensive Cancer Network. NCCN Guidelines Version 3.2014. 2014 [cited 2014-05-20; Available from: http://www.nccn.org/

[11] UpToDate. Clinical presentation, diagnosis, and staging of colorectal cancer. 2014 [cited 2014-05-20; Available from: http://www.uptodate.com/contents/clinical-presentation-diagnosis-and-staging-of-colorectal-cancer?source=machineLearning&search=colorectalplus cancer&selectedTitle=1~150&sectionRank=2&anchor=H625914#H12

[12] Bennouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncology. 2013 Jan;14(1):29-37.

[13] Koopman M, Simkens L, May AM, Mol L. Final results and pre-planned subgroup analyses: Phase III CAIRO3 (maintenance Avastin plus Xeloda vs observation after induction Avastin plus CT in mCRC). *Oral Abstract presented at: 2014 Gastrointestinal Cancer Symposium* San Francisco, CA 2014.

[14] Kubicka Prof S, Greil R, Andre T, Bennouna J, Sastre J, Van Cutsem E, et al. Bevacizumab plus chemotherapy continued beyond first progression in patients withmetastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings. Annals of Oncology. 2013;24(9):2342-9.

[15] Koopman M, Simkens L, May AM, Mol L. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine plus bevacizumab versus observation after induction treatment with chemotherapy plus bevacizumab in metastatic colorectal cancer (mCRC). JCO. 2014;32(3s):abstract LBA388.

[16] Galal KM, Zaghlol K, Fawzy EE, Mansour S, Salam MA, Mohamed EM. Does maintenance of Bevacizumab after treatment failure have a role in metastatic colon cancer? Chinese-German Journal of Clinical Oncology. 2009;8(1):P24-P32.

[17] Tsutsumi S, Ishibashi K, Uchida N, Ojima H, Hosouchi Y, Yashuda N, et al. Phase II trial of chemotherapy plus bevacizumab as second-line therapy for patients with metastatic colorectal cancer that progressed on bevacizumab with chemotherapy: the Gunma Clinical Oncology Group (GCOG) trial 001 SILK study. Oncology. 2012;83(3):151-7.

[18] Hong YS, Lee J, Kim K-p, Lee J-L, Park YS, Park JO, et al. Multicenter phase II study of second-line bevacizumab plus doublet combination chemotherapy in patients with metastatic colorectal cancer progressed after upfront bevacizumab plus doublet combination chemotherapy. Investigational New Drugs. 2013 Feb;31(1):183-91.

[19] Nakayama G, Uehara K, Ishigure K, Yokoyama H, Ishiyama A, Eguchi T, et al. The efficacy and safety of bevacizumab beyond first progression in patients treated with first-line mFOLFOX6 followed by second-line FOLFIRI in advanced colorectal cancer: a multicenter, single-arm, phase II trial (CCOG-0801). Cancer Chemotherapy & Pharmacology. 2012 Oct;70(4):575-81.

[20] Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). Journal of Clinical Oncology. 2008 Nov 20;26(33):5326-34.

[21] Hurwitz HI, Bekaii-Saab TS, Bendell JC, Cohn AL, Kozloff M, Roach N, et al. Safety and Effectiveness of Bevacizumab Treatment for Metastatic Colorectal Cancer: Final Results from the Avastin(registered trademark) Registry - Investigation of Effectiveness and Safety (ARIES) Observational Cohort Study. Clinical Oncology. 2014.

[22] Warenverzeichnis Apothekerverlag Online. 2014 [cited 2014-05-23; Available from: http://warenverzeichnis.apoverlag.at/

[23] Rosati G, Avallone A, Aprile G, Butera A, Reggiardo G, Bilancia D. XELOX and bevacizumab followed by single-agent bevacizumab as maintenance therapy as first-line treatment in elderly patients with advanced colorectal cancer: the boxe study. Cancer Chemotherapy & Pharmacology. 2013 Jan;71(1):257-64.

[24] Leitlinienprogramm Onkologie. S3-Leitlinie Kolorektales Karzinom, Langversion 1.0. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF 2013.

[25] Clark JW, A G. Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations. 2014 [cited 27 June 2014]; Available from: http://www.uptodate.com

[26] Salazar R, Grasselli J, Santos C, Tabernero J. Tenth anniversary of bevacizumab in colorectal cancer: Has it fulfilled its promise? Future Oncology. 2014;10(2):149-52.

[27] Saif MW. Antiangiogenesis therapy in second line metastatic colorectal cancer: Similar but different. Expert Opinion on Biological Therapy. 2013;13(11):1489-93.

[28] Flick ED, Barr CE, Fish SM, Leon LF, Mun Y, Dalal D. Dose-response relationship between post-progression bevacizumab exposure and survival among metastatic colorectal cancer patients. Pharmacoepidemiology and Drug Safety. 2012;21:244-5.

[29] Grothey A, Bekaii-Saab TS, Hurwitz H, Kozloff M, Roach N, Mun Y, et al. Cumulative exposure to bevacizumab (BV) after progression correlates with increased survival in patients (pts) with metastatic colorectal cancer (mCRC): A time-dependent analysis of the aries observational cohort study. European Journal of Cancer. 2011;47:S395.

[30] Heinemann V, Fischer Von Weikersthal L, Decker T, Kiani A, Verhling-Kaiser U, Al Batran S, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: The FIRE- 3 trial (AIO KRK 0307). Onkologie. 2013;36:105.

[31] Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

[32] Mésange P PV, Sabbah M, Escargueil AE, de Gramont A, Larsen AK,. Intrinsic bevacizumab resistance is associated with prolonged activation of autocrine VEGF signaling and hypoxia tolerance in colorectal cancer cells and can be overcome by nintedanib, a small molecule angiokinase inhibitor. Onkotarget [cited 2014]; Available from: http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=1671

[33] Mishima H, Oba K, Sakamoto J, Muro K, Yoshino T, Hyodo I, et al. FOLFIRI plus bevacizumab 5 mg/kg versus 10 mg/kg as second-line therapy in patients with metastatic colorectal cancer who have failed first-line bevacizumab plus oxaliplatin-based therapy: a randomized phase III study (EAGLE Study). Japanese Journal of Clinical Oncology. 2012 Feb;42(2):134-8.