Annals of Oncology 26: 709–714, 2015
doi:10.1093/annonc/mdv011
Published online 20 January 2015

Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06)

D. Koeberle[1*,†], D. C. Betticher[2], R. von Moos[3], D. Dietrich[4], P. Brauchli[4], D. Baertschi[4], K. Matter[5], R. Winterhalder[6], M. Borner[7], S. Anchisi[8], P. Moosmann[9], A. Kollar[10], P. Saletti[11], A. Roth[12], M. Frueh[13], M. Kueng[2], R. A. Popescu[14], S. Schacher[15], V. Hess[16] & R. Herrmann[16]

[1]Department of Oncology, Kantonsspital St Gallen, St Gallen; [2]Department of Oncology, Hôpital Fribourgeois, Fribourg; [3]Department of Oncology, Kantonsspital Chur, Chur; [4]SAKK Coordinating Centre, Bern; [5]Institute of Pharmaceutical Medicine/ECPM, Basel; [6]Department of Oncology, Kantonsspital Luzern, Luzern; [7]Department of Oncology, Spitalzentrum Biel, Biel; [8]Department of Oncology, Hôpital de Sion, Sion; [9]Department of Oncology, Kantonsspital Aarau, Aarau; [10]Department of Oncology, Inselspital Bern, Bern; [11]Department of Oncology, IOSI, Bellinzona; [12]Department of Oncology, HCUG, Geneva; [13]Department of Oncology, Kantonsspital St Gallen, St Gallen; [14]Department of Oncology, Hirslanden Klinik Aarau, Aarau; [15]Department of Oncology, Kantonsspital Winterthur, Winterthur; [16]Department of Oncology, Universitätsspital Basel, Basel, Switzerland

Received 21 September 2014; revised 19 November 2014, 20 December 2014 and 29 December 2014; accepted 30 December 2014

Background: Chemotherapy plus bevacizumab is a standard option for first-line treatment in metastatic colorectal cancer (mCRC) patients. We assessed whether no continuation is non-inferior to continuation of bevacizumab after completing first-line chemotherapy.

Patients and methods: In an open-label, phase III multicentre trial, patients with mCRC without disease progression after 4–6 months of standard first-line chemotherapy plus bevacizumab were randomly assigned to continuing bevacizumab at a standard dose or no treatment. CT scans were done every 6 weeks until disease progression. The primary end point was time to progression (TTP). A non-inferiority limit for hazard ratio (HR) of 0.727 was chosen to detect a difference in TTP of 6 weeks or less, with a one-sided significance level of 10% and a statistical power of 85%.

Results: The intention-to-treat population comprised 262 patients: median follow-up was 36.7 months. The median TTP was 4.1 [95% confidence interval (CI) 3.1–5.4] months for bevacizumab continuation versus 2.9 (95% CI 2.8–3.8) months for no continuation; HR 0.74 (95% CI 0.58–0.96). Non-inferiority could not be demonstrated. The median overall survival was 25.4 months for bevacizumab continuation versus 23.8 months (HR 0.83; 95% CI 0.63–1.1; $P = 0.2$) for no continuation. Severe adverse events were uncommon in the bevacizumab continuation arm. Costs for bevacizumab continuation were estimated to be ~30 000 USD per patient.

Conclusions: Non-inferiority could not be demonstrated for treatment holidays versus continuing bevacizumab monotheray, after 4–6 months of standard first-line chemotherapy plus bevacizumab. Based on no impact on overall survival and increased treatment costs, bevacizumab as a single agent is of no meaningful therapeutic value. More efficient treatment approaches are needed to maintain control of stabilized disease following induction therapy.

Clinical trial registration:: ClinicalTrials.gov, number NCT00544700.

Key words: metastatic colorectal cancer, bevacizumab, maintenance therapy

introduction

Uninterrupted chemotherapy is still considered by some oncologists to be the standard of care in the treatment of metastatic colorectal cancer (mCRC). Recent data from a meta-analysis

*Correspondence to: Prof. Dieter Koeberle, Department of Internal Medicine, Division of Oncology/Hematology, St Claraspital, CH-4016 Basel, Switzerland. Tel: +41-61-6858470; Fax: +41-61-6858347; E-mail: dieter.koeberle@claraspital.ch

†Present address: Department of Oncology, St Claraspital, Basel, Switzerland.

investigating the optimum duration of polychemotherapy regimens in the first-line setting indicate, however, that overall survival (OS) is not significantly different for intermittent versus continuous treatment [1].

Bevacizumab, a monoclonal antibody that inhibits the binding of vascular endothelial growth factor to its receptors, improves the outcome in patients with mCRC when added to first- or second-line chemotherapy, as demonstrated in several studies [2–6]. In these trials, it was intended to continue chemotherapy and bevacizumab until intolerable toxicity or disease progression. The MACRO trial investigated the effectiveness of maintenance treatment with single-agent bevacizumab after six cycles of induction chemotherapy with XELOX + bevacizumab, versus uninterrupted treatment with XELOX + bevacizumab [7]. This study was designed to investigate the question of chemotherapy duration, in an attempt to maintain treatment efficacy and minimize side-effects, in the context of uninterrupted bevacizumab treatment in both arms. Although the prespecified statistical criteria for non-inferiority of shorter chemotherapy were not met, there were no statistically significant differences in response rates (RR), nor in the median progression-free survival (PFS) or OS. Until now, there are no data available on the optimal duration for bevacizumab in the first-line treatment. Our trial was designed to assess the efficacy of continuing treatment with single-agent bevacizumab, compared with no continuation, in patients achieving disease control with induction therapy consisting of chemotherapy plus bevacizumab.

patients and methods

eligibility criteria

Eligible patients were aged ≥18 years with pathologically confirmed metastatic colorectal cancer, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and had stable disease (SD), partial response (PR) or complete response (CR) after the end of first-line induction treatment. Induction treatment comprised a standard chemotherapy with a fluoropyrimidine agent, alone or in combination with irinotecan or oxaliplatin, plus a standard dose of bevacizumab, for 16–24 weeks. Serum creatinine <177 μmol/l and proteinuria <2+ were required. The last bevacizumab dose had to be given within 4 weeks before randomization. Key exclusion criteria included anticipation of the need for major surgery, e.g. resection or ablation of metastases, concurrent treatment with experimental drugs, clinical symptoms or history of central nervous system metastases and any serious underlying medical condition that could impair the ability of the patient to participate in the trial.

study design and treatment

SAKK 41/06 was a prospective, randomized, open-label, phase III trial conducted at 26 sites in Switzerland. Institutional review boards at participating centres and health authorities approved the protocol. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. Randomization was stratified according to best response during induction treatment (CR, PR or SD), duration of induction treatment (16–20 versus 21–24 weeks), type of chemotherapy (irinotecan combination versus oxaliplatin combination versus fluoropyrimidine only), disease burden (one organ versus multiple organs with metastasis) and centre.

randomization and masking

Patients were randomly assigned in a 1:1 ratio to receive treatment with either bevacizumab 7.5 mg/kg intravenously every 3 weeks or no anti-tumour treatment in this open-label study. During the continuation treatment period, bevacizumab was to be withdrawn definitively in the case of symptomatic deterioration, unacceptable toxicity, or major surgery, or if bevacizumab treatment was delayed for more than 4 weeks, calculated from the time of scheduled treatment. Patients in both arms were transferred to the follow-up phase after diagnosis of PD or start of second-line treatment.

assessments

A medical history, physical examination, routine blood and urine analysis, and a pregnancy test for women aged <50 years, were carried out within 2 weeks of study entry. Tumour measurements (CT or MRI scans) were taken within 21 days before start of the study and were repeated every 6 weeks during the first 30 weeks and every 9 weeks thereafter. Scheduled clinical visits were carried out every 3 weeks in both arms. Patients who discontinued treatment before PD were assessed for tumour status until progression. After PD had been documented, patients were followed up for survival data and for subsequent cancer treatments.

Predefined toxicity related to bevacizumab (gastrointestinal perforation, bleeding/haemorrhage, hypertension, proteinuria and venous/arterial thromboembolism) was assessed every 3 weeks and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0).

statistics

The primary end point was time to progression (TTP), which was defined as the interval from the date of random assignment until PD or death due to tumour. Secondary end points included OS, PFS (defined as the time from start of first-line treatment until PD or death), time to second-line treatment (defined as the time from randomization until start of a new line of cancer treatment), adverse events and treatment costs.

Assuming a median TTP of at least 16 weeks for patients without bevacizumab continuation and a maximum of 22 weeks for patients with bevacizumab continuation, as well as a prespecified non-inferiority limit for the hazard ratio (HR) of 0.727 (16/22 weeks), 219 events were required for a one-sided significance level of 10% and a statistical power of 85% to detect an HR of 1, including one interim analysis to stop in the case of non-inferiority or to rule out futility. Non-inferiority was determined based on the O'Brien and Fleming boundary shape calculated by East 5.4. (Cytel Inc., Cambridge, MA). Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The univariate Cox regression models were carried out to explore the effect of bevacizumab on TTP in various patient subgroups. This study was registered with ClinicalTrials.gov, number NCT00544700. Statistical analyses were carried out with SAS 9.2 (SAS Institute Inc., Cary, NC) and S-Plus 8.1 (TIBCO Software, Palo Alto, CA).

cost analysis

The cost analysis included costs for bevacizumab acquisition, drug administration, control visits to oncologist every 3 weeks, in-patient care, and X-ray/CT/MRI scans during the trial phase (supplementary Table S1, available at *Annals of Oncology* online). Costs for laboratory tests, outpatient treatment of adverse events and other outpatient care were not included in the cost analysis. Overall, treatment costs per patient, as well as treatment cost per month for the time until progression, were calculated. As costs for control visits and hospital stay may vary substantially, but the exact variation is unknown, we also conducted a sensitivity analysis estimating costs using low and high (±30% of base case costs) unit costs for these two parameters. Differences in overall costs per patient, as well as costs per month (until progression) per patient, between treatment arms were explored using the Wilcoxon rank-sum test. Multivariate gender- and age-adjusted comparison was also conducted using a generalized linear model (gamma distribution, log link).

results

patient characteristics and treatment administration

Between October 2007 and May 2012, 265 patients were included at 26 sites in Switzerland and 262 were randomly assigned to bevacizumab continuation ($n = 131$) or no bevacizumab continuation ($n = 131$) (supplementary Figure S1, available at *Annals of Oncology* online). Three patients with PD after the end of first-line chemotherapy were excluded. Baseline demographic and clinical characteristics were balanced between the treatment arms (Table 1).

Two patients randomly assigned to the bevacizumab continuation arm did not receive any study treatment: one patient died without treatment and one patient refused treatment. These patients were included in the intention-to-treat analysis. The per-protocol analysis excluding these two patients yields virtually the same results.

Patients in the bevacizumab continuation arm received a median of six cycles (range 1–49 cycles). The median bevacizumab dose was 7.5 mg/kg.

efficacy

The median follow-up time using the reversed Kaplan–Meier method was 36.7 months (range in surviving patients 4.7–60.6 months). The median TTP in the bevacizumab continuation arm was 4.1 [95% confidence interval (CI) 3.1–5.4] versus 2.9 (95% CI 2.8–3.8) months in the no bevacizumab continuation arm (HR 0.74; 95% CI 0.58–0.96) (Figure 1). The observed HR lies close to the non-inferiority margin of 0.727, and non-inferiority could not be demonstrated ($p_{NI} = 0.44$). Prespecified subgroup analyses were generally consistent with the primary findings (Figure 2).

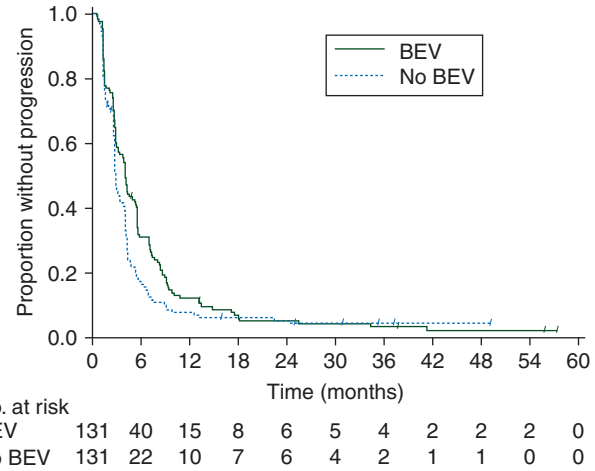

Figure 1. Kaplan–Meier curves for time to progression from randomization. BEV, bevacizumab.

Table 1. Baseline patient demographics and clinical characteristics

	Bevacizumab continuation ($n = 131$)		No bevacizumab continuation ($n = 131$)	
	No.	%	No.	%
Median age (range)	63 (40–83)		65 (23–85)	
Sex				
Male	93	71	96	73
Female	38	29	35	27
ECOG performance status score				
0	97	74	91	69
1	34	26	40	31
Adjuvant chemotherapy	37	28	37	28
Clinically significant comorbidities	76	58	65	50
Response to first-line treatment				
CR/PR	81	62	77	59
SD	50	38	54	41
Duration of first-line treatment				
16–20 weeks	84	64	91	69
21–24 weeks	47	36	40	31
First-line chemotherapy regimen				
Irinotecan + fluoropyrimidine	41	31	42	32
Oxaliplatin + fluoropyrimidine	81	62	82	63
Fluoropyrimidine alone	9	7	7	5
Metastatic spread				
1 organ	49	37	46	35
>1 organ	82	63	85	65

CR, complete response; PR, partial response; SD, stable disease.

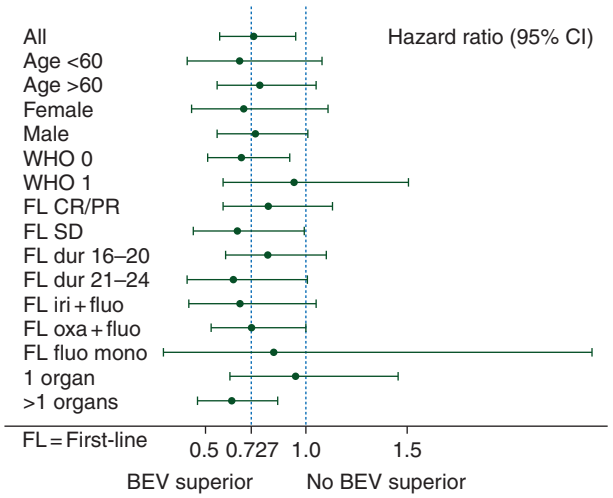

Figure 2. Hazard ratios and 95% confidence intervals for time to progression by patient subgroup. BEV, bevacizumab.

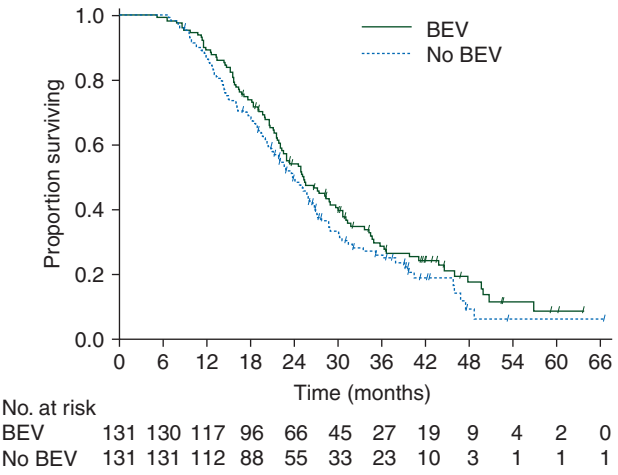

Figure 3. Kaplan–Meier curves for overall survival from start of first-line therapy. BEV, bevacizumab.

There was no statistically significant difference in the median OS: 25.4 (95% CI 22.2–28.9) months in the bevacizumab continuation arm versus 23.8 (95% CI 21–26.8) months in the no bevacizumab continuation arm (HR 0.83; 95% CI 0.63–1.1; $P = 0.19$) (Figure 3). At the time of the analysis, 99 patients (76%) with bevacizumab continuation and 98 (75%) without continuation had died. The median PFS, as measured from the start of first-line treatment, was 9.5 months in the bevacizumab continuation arm (95% CI 8.6–10.2 months) versus 8.5 (95% CI 8–8.9) months in the no bevacizumab continuation arm (HR 0.75; 95% CI 0.59–0.97; $P = 0.025$) (supplementary Figure S2, available at *Annals of Oncology* online).

In a *post hoc* analysis, the types of PD were grouped into three categories: new tumour lesions, progression of existing lesions or a mixture of both. The proportion of patients with PD based on new lesions (28% versus 27%) and PD based on existing lesions (40% versus 37%) were similar for the bevacizumab continuation arm and the no continuation arm.

Table 2. Pre-specified adverse events associated with bevacizumab (CTCAE 3.0)

Patients (%)	Bevacizumab continuation ($n = 131$)			No bevacizumab continuation ($n = 131$)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Haemorrhage	5	—	—	1	—	—
Hypertension	15	6	—	3	1	—
Proteinuria	15	—	—	1	—	—
Thrombosis	—	2	—	—	—	—
GI perforation	—	—	—	—	—	—

The times between randomization and start of second-line treatment were not statistically different (HR 0.82, 95% CI 0.64–1.06 months; $P = 0.14$) between the bevacizumab continuation arm (median 5.9 months, 95% CI 4.8–7.5 months) and the no bevacizumab continuation arm (median 4.8 months, 95% CI 4.1–5.5 months) (supplementary Figure S3, available at *Annals of Oncology* online). After PD, 114 (87%) of patients in the bevacizumab continuation arm and 115 (88%) in the no bevacizumab continuation arm were given one or more subsequent anticancer treatments. Thirty-five patients (27%) in the bevacizumab continuation arm and 53 patients (40%) in the no bevacizumab continuation arm received further bevacizumab treatment.

safety

During the trial period, most adverse events (AEs) were grade 1 or 2, whereas eight patients (6%) in the bevacizumab continuation arm versus one patient (1%) in the no maintenance arm experienced a grade ≥3 AE (Table 2). The most common grade ≥3 AE was hypertension (6 versus 1 patients). There were no drug-related deaths during the trial phase.

cost analysis

The mean cost per patient in the bevacizumab continuation arm was 37 596 USD (range 4794–229 038 USD) versus 8180 USD (range 330–83 465 USD) in the no bevacizumab arm ($P < 0.001$; univariate Wilcoxon rank-sum test). Gender- and age-adjusted cost per patient in the bevacizumab continuation arm was 36 620 USD (95% CI 30 840–43 484) compared with 7882 USD (95% CI 6636–9363) in the no bevacizumab arm ($P < 0.001$; supplementary Table S2, available at *Annals of Oncology* online).

Neither age nor gender had a significant effect on costs. Costs per month until progression were also significantly different between treatment arms [bevacizumab continuation arm 5883 USD/month (range 178–15 882), versus no bevacizumab arm 2063 USD/month (range 73–20 493; supplementary Table S2, available at *Annals of Oncology* online)]. In the multivariable gender- and age-adjusted model, age but not gender had a significant effect on costs/month, showing a decrease in costs with increasing age. Using low or high cost estimations in the cost calculations for control visits to oncologist and hospitalizations confirmed the results for the base case analyses.

discussion

Bevacizumab is an important addition to the range of chemotherapy drugs that are currently used for the treatment of mCRC. The magnitude of benefit derived from bevacizumab in first-line treatment of mCRC appears to some degree to depend on the backbone chemotherapy regimen used [8], although the monoclonal antibody is most often combined with classical chemotherapy regimens like FOLFOX or FOLFIRI.

Until recently, bevacizumab infusions were continued until disease progression, even if chemotherapy has been interrupted earlier for any reason during first-line treatment, as it is assumed that bevacizumab monotherapy might be sufficient to prolong disease control achieved with combination induction therapy. In second-line treatment, however, bevacizumab as a single agent has very little activity [5]. As the optimal duration of bevacizumab during the course of first-line treatment has not been investigated before in randomized trials, we considered bevacizumab continuation to be a commonly used treatment strategy in clinical practice according to the overall respected treatment preference, which was influenced by the registration trial of bevacizumab [2] and the Swiss drug labelling of bevacizumab, which recommends bevacizumab continuation until disease progression. In our trial, the arm with the treatment holidays strategy [9, 10] was chosen as comparator.

A non-inferiority margin of a 6-week difference in TTP between bevacizumab continuation and no continuation was selected, in consultation with expert oncologists. Non-inferiority was not demonstrated in this trial, as the non-inferiority margin lies within the confidence interval for the HR. The observed difference in the median TTP of 5 weeks between the two treatment arms is below the chosen margin of a 6-week difference and indicates a difference of modest magnitude. This notion is further supported by a median difference of only 4 weeks in PFS.

There was no general consensus regarding the definition of a valid surrogate end point for OS when this trial was planned. Potential surrogate end points for OS include PFS or TTP. PFS differs from TTP in that PFS includes death as a result of any cause in its definition in addition to progression and appears as a more appropriate end point, because it is stronger associated with OS than TTP [11].

Detecting small differences in time-to-event end points such as TTP or PFS requires very close intervals between tumour assessments and/or a very large sample size. However, small differences in TTP or PFS become clinically meaningless in the context of an incurable disease unless OS is impacted. The survival analysis indicates a small, consistent but statistically non-significant trend towards longer OS in the bevacizumab continuation arm. Whether second and subsequent lines of therapy, which were very balanced between both arms, or the later use of bevacizumab, had any substantial impact on this secondary end point remains speculative but unlikely.

The disease progression patterns after cessation of bevacizumab therapy did not differ between treatment arms, in line with earlier observations [12].

Besides the selection requirement to achieve at least SD following induction therapy, a broad spectrum of patients, all with disease not amenable to curative surgery, was included into this trial. Patients were not selected by molecular markers, as cetuximab became available only 1 year before trial recruitment was completed. At that time, 80% of patients had already been recruited. We assume that *RAS* and *BRAF* mutations were distributed similarly in both arms.

Different chemotherapy regimens were used during induction treatment. This reflects the heterogeneity in clinical practice during the study period. To avoid potential imbalances between treatment arms, we used the chemotherapy backbones as stratification factors.

As demonstrated in another trial with mCRC patients [7], single-agent bevacizumab is associated with a low incidence of treatment-related severe adverse effects. No fatalities due to toxicity occurred. Low-grade adverse events were noticeably more frequent in the bevacizumab continuation arm. A quality-of-life assessment was not part of our trial, as we did not anticipate detecting meaningful differences.

We assessed the time interval between randomization and start of second-line treatment. Again we observed a minor and statistically non-significant difference for this end point between the two arms. Although the decision to start a new line of treatment and its timing are somewhat arbitrary and depend on many factors, it is interesting to note that there was a delay of nearly 2 months between the median TTP and this end point. Thus, diagnosing progressive disease does not necessarily trigger the immediate need for a new line of cancer treatment in all patients.

Oncology is becoming an increasingly value-based specialty [13]. Whereas incremental cost utility ratios using a lifelong quality-of-life-adjusted time horizon are preferred in health economic analyses [14], data required for such analyses are not always fully available. We used approximate unit costs for our analysis and found a difference of ~30 000 USD between bevacizumab continuation versus no continuation in the mean costs per patient until disease progression.

The rapid onset of drug resistance and subsequent treatment failure with bevacizumab monotherapy reinforces the need for alternative strategies. One approach is to offer patients a treatment-free interval, although criteria to select patients for this strategy are not known at this time. Another is to de-escalate induction chemotherapy and continue one component (usually fluoropyrimidines) in combination with bevacizumab, as shown to be effective in the CAIRO-3 trial [15]. Additional evidence regarding this latter approach comes from a recently reported three-arm randomized trial comparing no maintenance treatment versus bevacizumab continuation versus a combination of capecitabine and bevacizumab in patients who had completed induction chemotherapy [16]. In this non-inferiority trial, which enrolled 840 patients to induction chemotherapy plus bevacizumab, 473 patients were randomized after 6 months of induction treatment. The primary end point of this trial was 'time to failure of strategy' (TFS), comprising maintenance plus re-induction after first progression. The difference in the median PFS between bevacizumab alone versus no treatment until disease progression was 4 weeks (4.6 versus 3.6 months), which confirms the results of our trial. Continuing single-agent chemotherapy plus bevacizumab achieved a median PFS of 6.2 months. The PFS in the chemotherapy plus bevacizumab maintenance arm was significantly longer compared with the no treatment arm. This advantage in PFS however did not translate into a significantly prolonged survival in this trial.

In summary, we found no evidence that continuation of bevacizumab as a single agent after completion of first-line chemotherapy appears is of meaningful therapeutic value. Today's treatment preference for maintenance therapy, based on current knowledge, is to continue with fluoropyrimidines alone or in combination with bevacizumab, or to offer treatment holidays.

acknowledgements

We thank the Swiss health insurances and the Swiss Federal Government (SBFI) for financial support and santésuisse (Swiss Association of Social Health Insurance Companies) for making this study possible. Julia Balfour, Medical Writer/Consultant, Dundee, UK, provided English-language editing assistance, with funding from SAKK.

funding

This work was supported by Swiss health insurances of santésuisse (Swiss Association of Social Health Insurance Companies). Santésuisse provided financial support for the conduct of the study and financed bevacizumab continuation therapy. The State Secretariat for Education, Research and Innovation (SERI) provided additional financial support to SAKK. Neither funding body had any input into the design or conduct of the trial or were involved in the analysis/interpretation of the data. No grant number.

disclosure

DK reports advisory board member of Merck, Lilly, and Sanofi Aventis; RM reports grants and personal fees from Roche, grants and personal fees from Amgen, grants and personal fees from Merck, personal fees from Sanofi Aventis, personal fees from Pfizer; SA reports grants from Roche Pharma; PM reports personal fees from Amgen Advisory Board, personal fees from Celgene Advisory Board, non-financial support from Roche; AR reports personal fees from Roche Advisory Board; VH reports personal fees from Roche Pharma Schweiz, other from Roche, grants from Swiss National Science Foundation, outside the submitted work. The remaining authors report no conflicts of interest.

references

1. Berry SR, Cosby R, Asmis TR et al. Randomized controlled trials (RCTs) examining continuous (CS) versus intermittent strategies (IS) of delivering systemic treatment (Tx) for untreated metastatic colorectal cancer (mCRC): a meta-analysis from the Cancer Care Ontario program in evidence-based care (abstract). J Clin Oncol 2013; 31 (suppl; abstr 3534). http://meetinglibrary.asco.org/content/111397-132 (12 December 2013, date last accessed).
2. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335–2342.
3. Saltz LB, Clarke S, Diaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008; 26: 2013–2019.
4. Tebbutt NC, Wilson K, Gebski VJ et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol 2010; 28: 3191–3198.
5. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25: 1539–1544.
6. Bennouna J, Sastra J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013; 14(1): 29–37.
7. Díaz-Rubio E, Gómez-España A, Massutí B et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist 2012; 17(1): 15–25.
8. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer 2012; 12: 89. [epub ahead of print 13 March 2012]. doi: 10.1186/1471-2407-12-89.
9. Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009; 27: 5727–5733.
10. Adams R, Meade A, Saymour M et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial. Lancet Oncol 2011; 12: 642–653.
11. Tang PA, Bentzen SM, Chen EX, Siu LL. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol 2007; 25(29): 4562–4568.
12. Miles D, Harbeck N, Escudier B et al. Disease course patterns after discontinuation of bevacizumab: pooled analysis of randomized phase III trials. J Clin Oncol 2011; 29(1): 83–88.
13. Grusenmeyer PA, Wong YN. Interpreting the economic literature in oncology. J Clin Oncol 2007; 25(2): 196–202.
14. Tappenden P, Chilcott J, Ward S et al. Methodological issues in the economic analysis of cancer treatments. Eur J Cancer 2006; 42(17): 2867–2875.
15. Koopman M, Simkens L, Ten Tije AJ et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): the phase III CAIRO study of the Dutch Colorectal Cancer Group (DCCG). J Clin Oncol 2013; 31 (suppl; abstr 3502). http://meetinglibrary.asco.org/content/115023-132 (12 December 2013, date last accessed).
16. Arnold D, Graeven U, Lerchenmuller CA et al. Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (BEV) alone, or no treatment following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): a phase III non-inferiority trial (AIO KRK 0207). J Clin Oncol 2014; 32 (suppl; abstr 3503). http://meetinglibrary.asco.org/content/133066-144 (16 July 2014, date last accessed).