Horizon Scanning in Oncology

Aflibercept (Zaltrap®) in addition to FOLFIRI for the 2nd line therapy of metastatic colorectal cancer

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 38
ISSN online 2076-5940

Horizon Scanning in Oncology

Aflibercept (Zaltrap®) in addition to FOLFIRI for the 2nd line therapy of metastatic colorectal cancer

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, May 2013

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors:	Dr. med. Eleen Rothschedl
Internal review:	Dr. med. Anna Nachtnebel, MSc Mag. Johanna Breuer
Project leader:	Dr. med. Anna Nachtnebel, MSc
External review:	Prof. Dr. med Markus Borner Chefarzt Onkologie, Spitalzentrum Biel

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 publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

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 Nr. 38
ISSN-online: 2076-5940

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

1 Drug description

Generic/Brand name/ATC code:

Aflibercept/Zaltrap®/S01LA05

Developer/Company:

Regeneron Pharmaceuticals/Sanofi

Description:

aflibercept inhibits angiogenesis by binding to all VEGF-A isoforms and placental growth factor

Aflibercept/Zaltrap® (ziv-aflibercept) is a recombinant fusion protein composed of Vascular Endothelial Growth Factor Receptors (VEGFR) 1 and 2 fused to human IgG1 [1]. By binding to all VEGF-A isoforms and to placental growth factor aflibercept prevents these factors from stimulating angiogenesis which leads to reduced vascularisation of neoplasms and further to inhibition of tumour growth [2]. Aflibercept is manufactured by recombinant DNA technology in a Chinese hamster ovary K-1 mammalian expression system. It is available in single-use vials of 100 mg/4ml or 200 mg/8 ml [1].

intravenous infusion, administered prior to FOLFIRI regimen

For the treatment of metastatic colorectal cancer (mCRC), patients receive aflibercept in combination with FOLFIRI treatment (consisting of 5-fluorouracil, leucovorin and irinotecan) whereby aflibercept is to be administered prior to the FOLFIRI regimen as an intravenous infusion (4 mg/kg) over one hour every two weeks [1]. The FOLFIRI treatment consists of administration of irinotecan 180 mg/m^2 intravenous infusion over 90 minutes, folinic acid (leucovorin) 400 mg/m^2 intravenous over 2 hours, followed by 5-fluorouracil 400 mg/m^2 intravenous bolus and 5-fluorouracil 2,400 mg/m^2 continuous intravenous infusion over 46 hours [3].This procedure should be repeated every two weeks until disease progression or unacceptable toxicity [3].

2 Indication

indicated in adults with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen

Aflibercept (Zaltrap®) combined with FOLFIRI (5-fluorouracil/irinotecan/leucovorin) treatment is indicated in adult patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen [3].

3 Current regulatory status

approved by the FDA and the EMA

Aflibercept (Zaltrap®) has been approved by the FDA for the treatment of mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen, used in combination with FOLFIRI treatment in March 2012 [1].

In February 2013 the EMA granted marketing authorization for Zaltrap® for the same indication like the FDA in the European Union.

For the treatment of wet macular degeneration the EMA approved aflibercept (Eylea®) in November 2012 [3].

4 Burden of disease

incidence rate in Austria 28.1 per 100,000 people per year

CRC develops in the tissues of the colon and/or rectum. It is the third most common cancer and the third leading cause of cancer-related mortality in men and women in the United States [4]. In Austria, CRC is the third most common malignancy diagnosed in men and the second most common malignancy diagnosed in women. In 2010, the incidence rate in Austria for both men and women was 28.1 (per 100,000 people per year), mortality rate was 11.9 (per 100,000 people per year) [5].

median age at diagnosis: 69 years

Median age at diagnosis for cancer of the colon and rectum is about 69 years and the overall 5-year relative survival rate (for 2003-2009) is 64.9% [6].

Histologically, more than 95% of CRCs are adenocarcinomas. Less common types occurring are carcinoid tumors, gastrointestinal stromal tumors, lymphomas or sarcomas [7].

Risk factors for CRC are increasing age, colorectal polyps, a family history of CRC and hereditary conditions (such as familial polyposis, hereditary nonpolyposis colon cancer, Lynch syndrome variants I and II, personal history of ulcerative colitis or Crohn colitis). Moreover, diet (high in fat, low in calcium, folate and fiber) and cigarette smoking do appear to increase the risk of developing colorectal cancer [4].

approximately 20% of patients have metastasis at the time CRC is diagnosed

Common symptoms of CRC are bloody or tarry stool, abdominal pain, otherwise unexplained iron deficiency anemia, a change in bowel habits, weakness and/or weight loss. Symptoms manifest themselves usually at rather advanced stages of the disease due to tumor growth into the intestinal lumen. CRC is a potentially metastatic disease, the most frequently affected sites are the regional lymph nodes, liver, lungs, and peritoneum. Approximately 20% of patients have metastasis at the time CRC is diagnosed. For the staging of CRC the TNM classification (primary tumour -T, status of the regional nodes – N, distant metastasis -M) is applied [8].

5 Current treatment

An abundance of treatment options are available for CRC. Selection of therapy depends on the site and extent of metastatic disease, performance status, organ function, comorbidity of the patient and KRAS mutation status [9].

chemotherapy doublets as first-line therapy

In general, patients who are able to tolerate it should receive chemotherapy doublets as first-line therapy. Oxaliplatin-based options for the first-line therapy are, for example, FOLFOX (=fluorouracil, leucovorin, oxaliplatin) or CapeOX-based (capecitabine, oxaliplatin) regimens with or without bevacizumab, FOLFOX ± panitumab for (KRAS wild-type gene only) or FOLFOXIRI (=fluorouracil plus leucovorin, oxaliplatin, and irinotecan).

In case of disease progression after these first-line therapies, treatment options will be selected according to the first-line regimen received and include [10, 11]:

several therapy options in case of disease progression

- FOLFIRI ± bevacizumab
- FOLFIRI ± aflibercept
- Irinotecan ± bevacizumab
- Irinotecan ± aflibercept
- Cetuximab or panitumumab (KRAS WT gene only) +irinotecan
- Regorafenib (not yet licenced in the European Union).

If bevacizumab has been administered in combination with first-line chemotherapy, continuation of bevacizumab with second-line fluoroyrimidine-based chemotherapy is a commonly used regimen [11].

Alternatively, the first-line therapy can be started by using an irinotecan containing regimen (FOLFIRI); in case of disease progression further treatment options would contain oxaliplatin-based regimens.

6 Evidence

To identify relevant literature, a literature search was conducted in April 2013 in medical databases (Embase, Medline, CRD Database, The Cochrane Library). Search terms used were “Aflibercept”, “AVE0005”, “AVE 0005”, “Zaltrap”, “eylea”, “vascular endothelial growth factor trap”, “vasculotropin trap” and “VEGF Trap” in combination with “Colorectal Neoplasms” (MeSH), “colorectal cancer”, “mCRC”, “(refractory or relapsed) near colorectal cancer”. Inclusion criteria were phase III study (full text articles, abstracts) and phase II studies (full text). Overall, 99 references were identified of which two were included in this report:

one phase III study and one phase II study were identified

- a phase III trial, evaluating the effect of adding aflibercept to FOLFIRI in patients with mCRC previously treated with an oxaliplatin – based regimen [12].

and

- a phase II study evaluating the safety and efficacy of aflibercept in pretreated patients with mCRC [13].

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an Oxaliplatin-based regimen [10].			
Study identifier	NCT00561470, EudraCT Number: 2007-000820-42, VELOUR trial		
Design	Prospective, multinational, randomized, double-blind, parallel-arm		
	Duration	*Enrolment:* November 2007 to March 2010 *Median follow-up:* 22.28 months *Cut-off dates for analyses:* 2011-02-07	
Hypothesis	Superiority		
Funding	Sanofi (in collaboration with Regeneron Pharmaceuticals)		
Treatment groups	Intervention (n=612)	4 mg/kg Aflibercept IV over 1 hour every 2 weeks followed immediately by FOLFIRI (irinotecan 180 mg/m² IV over 90 minutes, with leucovorin 400 mg/m² over 2 hours, followed by fluorouracil 400 mg/m² bolus and fluorouracil 2400 mg/m² continuous infusion over 46 hours) Patients received a median of seven cycles of aflibercept	
	Control (n=614)	Placebo and FOLFIRI (irinotecan 180 mg/m² IV over 90 minutes, with leucovorin 400 mg/m² over 2 hours, followed by fluorouracil 400 mg/m² bolus and fluorouracil 2400 mg/m² continuous infusion over 46 hours Patients received a median of eight cycles of placebo	
Endpoints and definitions	Overall survival (primary outcome)	OS	The time interval from randomization to death from any cause
	Progression-free survival	PFS	The interval from randomization to the first observation of disease progression (according to independent review committee review) or death from any cause
	Objective response	OR	Complete response and partial response
	Treatment-emergent adverse events	–	–
	Laboratory abnormalities	–	–
Results and analysis			
Analysis description	Intention-to-treat (ITT analysis) Primary Endpoint: overall survival, log rank test Response rate between control arm and aflibercept arm was compared using Cochrane-Mantel-Haenszel test.		
Analysis population	Inclusion	❁ Age (years) ≥ 18 ❁ Histologically or cytologically proven colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment ❁ Patients who experienced relapse within 6 months of completion of oxaliplatin—based adjuvant therapy ❁ Prior administration of bevacizumab ❁ ECOG performance status 0-2 ❁ Adverse events from prior anticancer therapy were to have recovered to grade ≤ 1 [NCI-CTCAE version 3.0]	

Analysis population	Exclusion	❁ Known prior malignancies or known brain metastases, patients with adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or any other cancer from which the patient had been disease-free for more than 5 years were permitted ❁ Prior administration of irinotecan ❁ Major surgery within 28 days ❁ Uncontrolled hypertension within 3 months before enrolment ❁ Deep vein thrombosis within 4 weeks before randomization ❁ Pregnant and breast-feeding women	
	Characteristics	*Median age (years):* 61 (19-86) vs. 61 (21-82) *Male (%):* 57.5 vs. 59.6 *Prior bevacizumab (%):* 30.5 vs. 30.4 *ECOG (%)0/1/2:* 57.0/40.7/2.3 vs. 57.0/40.8/2.1 *Prior hypertension (%):* 43.6 vs. 43.5	
Results	Treatment group	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Number of subjects	N = 614	N = 612
	Survival Median, months 95.34% CI	 12.06 11.072-13.109	 13.50 12.517-14.949
	Survival probability, % 12 months 95.34 % CI 18 months 95.34% CI 24 months 95.34% CI 30 months 95.34% CI	 0.503 0.462-0.543 0.309 0.269-0.348 0.187 0.149-0.225 0.120 0.080-0.160	 0.561 0.521-0.602 0.385 0.343-0.427 0.280 0.237-0.324 0.223 0.178-0.268
	PFS median, months 95% CI	 4.67 4.21-5.36	 6.90 6.51-7.2
	Best overall response, % Complete response Partial response Stable disease Response rate, % (complete response + partial response) 95% CI	 0.4 10.8 64.9 11.1 8.5-13.8	 - 19.8 65.9 19.8 16.4-23.2
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	OS	HR	0.817
		95.34% CI	0.713-0.937
		P value	0032
	PFS	HR	0.758
		95% CI	0.661-0.869
		P value	< .0001
	Response rate	HR	NR
		95% CI	NR
		P value	< .001

Abbreviations: OS= overall survival, PFS= progression-free survival, CI= confidence interval, HR= Hazard ratio, n= number, ECOG= Eastern Cooperative Oncology Group, NR= not reported

Table 2: Most frequent adverse events

NCT00561470						
Adverse Event (according to NCI-CTCAE version 3.0)	Placebo/FOLFIRI (n=605)			Aflibercept/FOLFIRI (n=611)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Any	97.9	45.1	17.4	99.2	62.0	21.4
Diarrhea	56.5	7.6	0.2	69.2	19.0	0.3
Asthenic conditions	50.2	10.4	0.2	60.4	16.0	0.8
Stomatitis and ulceration	34.9	5.0	-	54.8	13.6	0.2
Nausea	54	3.0	-	53.4	1.8	-
Infections and infestations	32.7	6.1	0.8	46.2	11.0	1.3
Hypertension	10.7	1.5	-	41.4	19.1	0.2
Hemorrhage Epistaxis	19 7.4	1.7 -	- -	37.8 27.7	2.8 0.2	0.2 -
GI and abdominal pains	29.1	3.1	0.2	34	5.1	0.3
Vomiting	33.4	3.5	-	32.9	2.6	0.2
Decreased appetite	23.8	1.7	0.2	31.9	3.4	-
Weight decreased	14.4	0.8	-	31.9	2.6	-
Alopecia	30.1	-	-	26.8	-	-
Dysphonia	3.3	-	-	25.4	0.5	-
Constipation	24.6	1.0	-	22.4	0.8	-
Headache	8.8	0.3	-	22.3	1.6	-
Palmar-plantar erythrodysesthesia syndrome	4.3	0.5	-	11.0	2.8	-
Arterial thromboembolic event	1.5	0.5	-	2.6	0.8	1.0
Venous thromboembolic event	7.3	2.6	3.6	9.3	3.1	4.7
Fistula from GI origin	0.3	0.2	-	1.1	0.3	-
Fistula from other than GI origin	0.2	-	-	0.3	-	-
GI perforation	0.5	0.2	0.2	0.5	0.2	0.3
Anemia	91.1	3.5	0.8	82.3	3.3	0.5
Neutropenia	56.3	19.1	10.4	67.8	23.1	13.6
Neutropenic complications	3.0	1.7	1.2	6.5	4.4	1.3
Thrombocytopenia	33.8	0.8	0.8	47.4	1.7	1.7
Proteinuria	40.7	1.2	-	62.2	7.5	0.3
ALT increased	37.1	2.2	-	47.3	2.5	0.2

Abbreviations: NCI= National Cancer Institute, CTCAE= Common Terminology Criteria of Adverse Events, GI= gastrointestinal, ALT=alanine transaminase

In this prospective, multinational, randomized, double-blind, parallel-arm phase III trial a total of 1,226 patients were included. The aim of the study was to evaluate the efficacy and safety of the combination of aflibercept plus FOLFIRI versus placebo plus FOLFIRI in patients with mCRC. All enrolled patients had disease progression with an oxaliplatin-based regimen.

aflibercept/FOLFIRI was compared to placebo/FOLFIRI in 1,226 patients

Patients were randomly assigned to either the FOLFIRI/aflibercept group (n=612) or to FOLFIRI/placebo group (n=614). Thus, patients received 4mg/kg of aflibercept or placebo intravenously, followed subsequently by administration of the FOLFIRI (irinotecan, leucovorin and fluorouracil) regimen. Patients of FOLFIRI/aflibercept group received a median of nine cycles overall (with a median of seven cycles of aflibercept) versus eight cycles overall (median of eight cycles of placebo) in the FOLFIRI/placebo group. 30.5% of patients in the FOLFIRI/placebo arm and 30.4% of patients in the aflibercept/FOLFIRI arm received prior bevacizumab.

approximately one third of patients received prior bevacizumab

The primary endpoint of the phase III trial was overall survival; secondary endpoints were progression-free survival, objective response, treatment emergent adverse events and laboratory anomalies. Analyses after a median follow up time of 22.28 months showed that adding aflibercept to FOLFIRI led to a significantly improved median overall survival: median survival was 13.50 versus 12.06 months in aflibercept/FOLFIRI versus placebo/FOLFIRI arm yielding a hazard ratio of 0.817 (95.34% CI, 0.713 to 0.937; P=.0032). Two-year survival rates were 28.0% (aflibercept group) compared to 18.7% (control group).There was also a significant increase in median progression-free survival (6.9 months in the aflibercept group compared to 4.7 months in the control group). Response rate (complete response + partial response) was 19.8% in the aflibercept arm compared to 11.1% in the control arm. However, no patient in the aflibercept group and only 0.4% of patients in the control group achieved complete response. In contrast, 19.8% of patients in the aflibercept arm and 10.8% of patients in the control arm achieved partial response.

overall survival was extended by 1.44 months in the aflibercept group

significant increase in progression-free survival in the aflibercept group

In the context of the described phase III study, a subgroup analysis of the effects of prior bevacizumab use was conducted. The results indicated that adding aflibercept to FOLFIRI led to a consistent trend of increased overall survival and progression free survival, regardless of prior administration of bevacizumab. Furthermore, prior bevacizumab treatment did not appear to affect the safety profile of aflibercept [14].

In the aflibercept/FOLFIRI arm treatment-emergent adverse events occurred in 99.2% of patients and led to discontinuation from study treatment in 26.8% of patients. In comparison, 97.9% of control arm patients showed treatment-emergent adverse events which led to treatment discontinuation in 12.1% of patients. There were more patients affected by adverse events of grade 3 and grade 4 in the aflibercept arm (83.5%) than in the control arm (62.5%), in particular hypertension, hemorrhage, arterial thromboembolic events and venous thromboembolic events were more frequent. A higher incidence in the aflibercept arm was also reported for diarrhea, asthenic conditions, stomatitis and ulceration, infections, palmar-plantar erythrodysesthesia, neutropenia and thrombocytopenia. The incidence of serious adverse events was 49% in the aflibercept group compared to 33% in the placebo group. Adverse events with a fatal outcome affected 13 patients in the aflibercept arm and 6 patients in the placebo arm. Adverse events, toxicity-related deaths, dose modifications and treatment-related withdrawals were also more frequent in the aflibercept arm [1]. Most common adverse events leading to study discontinuation were asthenic conditions, infections, diarrhea and hypertension.

high rate of treatment-emergent adverse events in both groups

grade 3 and grade 4 adverse events were more common in the aflibercept group

6.2 Efficacy and safety – further studies

phase II trial of pretreated patients with mCRC evaluated safety and efficacy of aflibercept monotherapy

An open-label, 2-stage, phase II clinical trial evaluated the safety and efficacy of aflibercept monotherapy in patients with mCRC pretreated with chemotherapy and/or EGFR inhibitors [13]. A total of 75 patients were assigned to either the bevacizumab-naive (n=24) or the prior bevacizumab cohort (n=51). Patients of both cohorts (n=74, one patient has been excluded due to appearance of brain metastasis) received 4 mg/kg intravenous aflibercept in two-week cycles.

aflibercept did not show positive results in single-agents use

The authors defined the endpoint as a combination of objective response rate and 16-week progression-free-survival. In the bevacizumab-naive cohort, 8 of 24 patients (33.3%) achieved stable disease at 8 weeks and 5 of 24 patients (20.8%) achieved stable disease at ≥ 16 weeks. No cases of partial response were reported in this group. In the prior bevacizumab cohort, 21 of 50 patients (42.0%) obtained stable disease at 8 weeks and 6 of 50 patients (12.0%) achieved stable disease at ≥ 16 weeks. One patient in this group achieved a partial response. The median progression-free survival times were 2 months (95% CI: 1.7-8.6 months) in the bevacizumab-naive group and 2.4 months (95% CI: 1.9-3.7 months) in the prior bevacizumab cohort. Within this study, aflibercept did not show positive results in single-agents use.

adequate availability of aflibercept to bind endogenous VEGF has been shown

Median overall survival was 10.4 months (95% CI: 7.6-15.5) in the bevacizumab-naive cohort vs. 8.5 months (95% CI: 6.2-10.6) in the prior bevacizumab cohort. Additionally the plasma levels for free and VEGF-bound aflibercept were analyzed: mean free to VEGF-bound aflibercept ratio was 1.82. This result suggests adequate availability of aflibercept to bind endogenous VEGF [13].

7 Estimated costs

Aflibercept (Zaltrap®, 4mg/kg) is administered as an intravenous infusion over one hour every two weeks, in combination with FOLFIRI (5-fluorouracil, leucovorin and irinotecan) treatment. Aflibercept is available in single-use vials of 100 mg/4ml (25 mg/ml) or 200 mg/8ml (25 mg/ml) [1].

costs for one month range between € 2,490 and € 2,714

The costs for one cycle of aflibercept (assuming a body weight of 70kg) are estimated to range between € 1,245 (manufacturer´s price) [15] and € 1,358 (Austrian health insurance) [16] resulting in monthly costs of € 2,490 and € 2,714, respectively. In addition to that, costs for FOLFIRI treatment incur.

According to manufacturer´s information, the estimated cycle number per patient is six [15], whereas a median of seven cycles were administered in the VELOUR trial. Applying these numbers would yield overall treatment costs between € 7,470 (manufacturer's price) and € 8,142 (health insurance) for six cycles and between € 8,715 (manufacturer's price) and € 9,506 (health insurance) for seven cycles.

8 Ongoing research

A search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu for trials concerning "metastatic colorectal cancer" and "aflibercept" was conducted in May 2013 with the following results:

different studies evaluating the effect of aflibercept on mCRC are ongoing

- *NCT01661270:* the aim of this multinational, randomized, double-blind phase III study is to evaluate the improvement in progression-free survival of aflibercept versus placebo in patients with mCRC (treated with FOLFIRI after failure of an oxaliplatin-based regimen. The estimated study completion date is January 2016.
- *NCT01571284 (EudraCT Number: 2011-005724-17):* a multicenter, single-arm, open label phase III study to evaluate the safety and health-related quality of life of aflibercept in patients with mCRC (previously treated with an oxaliplatin-containing regimen). The estimated study completion date is June 2015.
- *NCT01670721:* a multicenter, single arm, open label, phase III study to assess the safety of aflibercept in patients with (mCRC) treated with irinotecan/5FU combination (FOLFIRI) after failure of an oxaliplatin-based regimen. Furthermore, this study aims to evaluate the health-related quality of life (HRQL) of aflibercept within the patient population. The estimated study completion date is June 2014.
- *NCT01754272:* a non-interventional Follow-up study to the VELOUR trial (NCT00561470). The archived colorectal cancer and metastasized tissue tumor blocks of patients who have participated in the VELOUR trial will be analyzed. The aim of the study is to identify proteins or markers which represent individual response to treatment. The estimated study completion date is December 2013.
- *NCT01646554:* a randomized phase II/III study to evaluate the efficacy of FOLFOX alone versus FOLFOX and aflibercept in K-ras mutant in patients with resectable liver metastasis from CRC. The estimated study completion date is December 2016.

Furthermore, several phase I and phase II studies were identified assessing single use of aflibercept or combined with capecitabine, OPTIMOX, FOLFIRI and modified FOLFOX6) in either pretreated or previously untreated patients.

further studies for different types of cancer are ongoing

There are numerous partly ongoing, partly completed phase II and phase III studies evaluating the efficacy of aflibercept on further types of cancer including metastatic thyroid cancer, ovarian cancer, metastatic non-small-cell lung cancer, advanced esophageal/gastric, metastatic pancreatic cancer or metastatic androgen-independent prostate cancer to name but a few.

9 Commentary

FDA and EMA granted marketing authorization for 2nd line therapy of mCRC

Aflibercept (Zaltrap®) has been approved by both the EMA (in February 2013) and the FDA (in March 2012) in combination with FOLFIRI for the treatment of mCRC after disease progression on an oxaliplatin-based treatment. The marketing authorization was based on the results of the above-mentioned phase III study (VELOUR trial), which showed significantly increased overall survival as well as progression-free survival [12]. In particular, median survival was 13.50 months versus 12.06 months in the aflibercept and the placebo group respectively, yielding a gain of 1.44 months (HR 0.817; 95.34% CI, 0.713-0.937; P=.0032). Median progression-free survival was 6.9 months in the aflibercept group and 4.7 months in the control group.

survival benefit stands in contrast with higher incidence of adverse events

These positive results are in contrast to the higher incidence of grade 3 and grade 4 adverse events reported in the aflibercept arm (83.5%) than in the control arm (62.5%). Also, serious adverse events occurred in 49% of patients in the aflibercept group compared to 33% in the placebo group. Adverse events with a fatal outcome affected 13 patients in the aflibercept arm and 6 patients in the placebo arm. Adverse events, toxicity-related deaths, dose modifications and treatment-related withdrawals were also more frequent in the aflibercept arm [1]. 26.8% of patients receiving aflibercept and 12.1% receiving placebo discontinued from study treatment due to adverse events.

studies evaluating quality-of-life are missing

Rather modest gains in overall survival and progression-free survival in addition to a higher number of adverse events, question if patients with this incurable disease will actually benefit from combining FOLFIRI with aflibercept, foremost since studies evaluating quality-of-life are still missing. Even though a study evaluating safety and health related quality-of-life of aflibercept in combination with FOLFIRI (NCT01670721) is currently recruiting patients, results will not be available before June 2014. Moreover, these results are achieved at monthly costs of € 2,716 (for two cycles), cost arising in addition to expenses for FOLFIRI treatment, premedication and treatment of side effects.

bevacizumab might have been a more meaningful comparator

Further, instead of comparing FOLFIRI + aflibercept to FOLFIRI + placebo, the combination with bevacizumab would have been a more meaningful comparator, thus, gains achieved in efficacy outcomes are further questioned. Similarly, only 30.4% of patients (aflibercept-arm) had previously been treated with bevacizumab, a therapy commonly administered as first-line therapy for mCRC. Even though results of a subgroup analysis yielded no statistically significant difference between patients previously treated with bevacizumab and patients without prior bevacizumab therapy, the findings indicate that previously treated patients may benefit less from aflibercept [1].

As already mentioned, the use of bevacizumab is a standard treatment option for the second line therapy of mCRC. Safety profiles of aflibercept and bevacizumab seem to be rather consistent, with the exception of hypertension and proteinuria which are more frequent in the aflibercept arm [1]. However, a detailed comparison of aflibercept and bevacizumab is not possible as long as direct comparative studies are missing. Also treatment selection based on costs proves difficult since the monthly costs for bevacizumab range, depending on the regimen used, between € 2,400 (7.5 mg/kg every 3 weeks) and € 5,580 (10mg/kg every 2 weeks) in comparison to about € 2,700 for aflibercept [16].

In summary, it can be stated that the positive effects of aflibercept regarding increased overall survival and progression-free survival are to be balanced against the high incidence of adverse events. Currently there are no data available concerning aflibercept and quality-of-life, results of an ongoing study may give more information about this essential parameter.

data concerning aflibercept and quality-of-life are needed

References

1. U.S. Food and Durg Administration. *Drugs@FDA*. 2013 [cited 2013 01.May]; Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo.
2. National Horizon Scanning, C., *Aflibercept (VEGF-Trap) for metastatic colorectal cancer – second line* 2009, Birmingham: National Horizon Scanning Centre (NHSC).
3. European Medicines Agency. *Zaltrap: EPAR – Product information* 2013 [cited 2013 17. April]; Available from: http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002532/human_med_001617.jsp&mid=WC0b01ac058001d124.
4. National Cancer Institute. *Colon and Rectal Cancer* 2013 [cited 2013 01.May]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page9#Section_269.
5. Statistik Austria. *Dickdarm und Enddarm – Krebsinzidenz und Krebsmortalität*. 2013 [cited 2013 01.May]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/dickdarm_enddarm/index.html.
6. National Cancer Institute. *Surveillance Epidemiology and End Results*. 2013 [cited 2013 20.May]; Available from: http://seer.cancer.gov/statfacts/html/colorect.html.
7. American Cancer Society. *Colorectal Cancer*. 2013 [cited 2013 02.May]; Available from: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/index.
8. UpToDate. *Clinical manifestations, diagnosis, and staging of colorectal cancer*. 2013 [cited 2013 05.May]; Available from: http://www.uptodate.com.
9. The Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of colorectal cancer*. 2013 [cited 2013 05.May]; Available from: http://www.sign.ac.uk/pdf.sign126.pdf.
10. National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2013*. 2013 [cited 2013 20.May]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
11. Schmoll, H.J., et al., *Esmo consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making.* Annals of Oncology, 2012. **23**(10): p. 2479-2516.
12. Van Cutsem, E., et al., *Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen.* Journal of Clinical Oncology, 2012. **30**(28): p. 3499-506.
13. Tang, P.A., et al., *Phase II clinical and pharmacokinetic study of aflibercept in patients with previously treated metastatic colorectal cancer.* Clinical Cancer Research, 2012. **18**(21): p. 6023-31.
14. Allegra, C.J., et al., *Effects of prior bevacizumab (B) use on outcomes from the VELOUR study: A phase III study of aflibercept (Afl) and FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) after failure of an oxaliplatin regimen.* Journal of Clinical Oncology, 2012. **30**(15).
15. Windisch, I., *Zaltrap – angefragte Unterlagen Aflibercept*, A. Nachtnebel, Editor 2013-05-24.
16. Warenverzeichnis Apothekerverlag Online. 2013 [cited 2013 20.May]; Available from: http://warenverzeichnis.apoverlag.at.