IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Aflibercept (Zaltrap) – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Aflibercept (Zaltrap) – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 29.05.2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Aflibercept (Zaltrap) – Benefit assessment according to § 35a Social Code Book V

Contracting agency:
Federal Joint Committee

Commission awarded on:
01.03.2013

Internal Commission No.:
A13-08

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Robert Dengler, Haematology and Oncology Practice and Daytime Clinic, Regensburg, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Anette Minarzyk
- Catharina Brockhaus
- Tatjana Hermanns
- Thomas Kaiser
- Michaela Florina Kerekes
- Stefan Lhachimi
- Corinna ten Thoren
- Volker Vervölgyi

Keywords: aflibercept, colorectal neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

[3]Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
ECOG-PS	Eastern Cooperative Oncology Group performance status
FOLFIRI	Irinotecan + 5-fluorouracil + folinic acid
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
i.v.	intravenous
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PT	MedDRA Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	MedDRA System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug aflibercept (Zaltrap). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 01.03.2013.

Research question

The aim of this report is to assess the added benefit of aflibercept in combination with a chemotherapy consisting of irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in comparison with FOLFIRI as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (mCRC) that has progressed during or after an oxaliplatin-containing regimen. The comparator therapy chosen by the company concurs with the ACT specified by the G-BA.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were to be included in the assessment.

Results

One relevant study (VELOUR) was included in the benefit assessment. This was a multinational, randomized, parallel, placebo-controlled, double-blind phase-III study comparing aflibercept + FOLFIRI with placebo + FOLFIRI. The participants enrolled were 1226 adult patients with histologically or cytologically proven adenocarcinoma of the colon or rectum with inoperable metastases who had recurrence within 6 months of completion of an oxaliplatin-containing chemotherapy. The treatment – both in combination with aflibercept and FOLFIRI alone – was administered in 14-day cycles.

The risk of bias was rated as low both at study level and at outcome level.

Mortality

There was a statistically significant prolongation of overall survival (OS) in favour of the treatment with aflibercept + FOLFIRI versus the treatment with placebo + FOLFIRI (HR = 0.82 [0.71; 0.93], p = 0.003). For OS, this led to an indication of an added benefit for the combination of aflibercept + FOLFIRI in comparison with FOLFIRI alone.

Adverse events

The overall rates of serious adverse events (SAEs), severe adverse events (AEs) (AEs with CTCAE [Common Terminology Criteria for Adverse Events] Grade 3 and 4) and treatment discontinuations due to AEs all were statistically significantly higher in the aflibercept arm than in the placebo arm (SAEs: RR [relative risk] = 1.47 [1.28; 1.69], p < 0.001; AEs with

CTCAE Grade 3 und 4: RR = 1.34 [1.24; 1.43], p < 0.001; treatment discontinuations due to AEs: RR = 2.22 [1.73; 2.86], p < 0.001).

There was proof of an effect modification by the characteristic “age” for the outcome SAEs (p = 0.002). In both subgroups (patients < 65 years and ≥ 65 years), there were statistically significantly more SAEs under aflibercept + FOLFIRI than under placebo + FOLFIRI. But the effect was more pronounced in the older patients (RR 1.88 [1.51; 2.35]) than it was in the younger patients (RR 1.27 [1.06; 1.52]).

In summary, there is therefore an indication of greater harm from aflibercept + FOLFIRI compared with the ACT FOLFIRI for several outcomes of the category "side effects".

Morbidity and health-related quality of life

No results, or no evaluable results, were available for the outcome categories morbidity and health-related quality of life. Hence an added benefit of aflibercept in comparison with the ACT is not proven for these outcome categories.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug aflibercept in the treatment of patients with mCRC compared with the ACT is assessed as follows:

In summary, there are both positive and negative effects with the same certainty of results (indication) for patients < 65 years and for patients ≥ 65 years.

On the positive side, there is an added benefit in the category mortality with the extent "considerable" for both age strata. On the negative side, there is greater harm with the extent "major" in the category serious/severe AEs (outcome “discontinuation due to AEs”) for both age strata. The differences in extent, which result from a proof of an effect modification regarding the characteristic “age” in the outcome SAEs (for patients < 65: "minor", for patients ≥ 65 years: "major") can therefore be neglected when balancing the positive and negative effects. So the overall conclusion on added benefit is derived for the total population as a whole.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

The added benefit of aflibercept versus the ACT is downgraded from "considerable" to "minor" because of the major risk of harm for severe and serious AEs. This does not affect the certainty of results.

In summary, there is an indication of a minor added benefit of aflibercept + FOLFIRI versus the ACT FOLFIRI for the treatment of adult patients with mCRC that has progressed during or after an oxaliplatin-containing regimen.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.2 Research question

The assessment of the added benefit of aflibercept was conducted according to the approval status [3] for the following therapeutic indication: aflibercept in combination with a chemotherapy consisting of irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in adult patients with mCRC that has progressed during or after an oxaliplatin-containing regimen.

The G-BA specified the combination chemotherapy consisting of 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) as the ACT.

The company accepted the ACT specified by the G-BA. It was also used for this assessment.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were to be included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on aflibercept for the treatment of patients with mCRC (studies completed up to 10.01.2013)
- Search in trial registries for studies on aflibercept for the treatment of patients with mCRC (last search 10.01.2013)

The Institute's own search:

- Search in trial registries to check the search results of the company (last search 18.03.2013)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The study VELOUR listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
VELOUR (EFC10262)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment concurred with the study pool of the company.

The study VELOUR was an RCT with aflibercept + FOLFIRI in comparison with placebo + FOLFIRI.

Section 2.6 contains a reference list for the VELOUR study.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Characteristics of the study and of the interventions

Table 3 and Table 4 describe the VELOUR study. This was the approval study for aflibercept (Zaltrap).

Table 3: Characteristics of the studies included – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VELOUR	RCT, double-blind, parallel	Adults (> 18 years) with proven metastatic adenocarcinoma of the colon or rectum for whom no curative treatment is available after failure of an oxaliplatin-based therapeutic regimen	FOLFIRI + aflibercept (N = 612) FOLFIRI + placebo (N = 614)	Treatment duration: Treatment until disease progression, inacceptable toxicity, discontinuation of study medication by patient or doctor Observation duration: Corresponding to treatment duration; survival was follows-up until death or end of study (cut-off upon occurrence of 863 deaths)	178 centres in Western and Eastern Europe, North and South America, Australia, New Zealand, South Africa and Korea 11/2007 until 02/2011	Primary outcome: prolongation of OS Secondary outcomes: AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

AE: adverse event; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; N: number of randomized patients; OS: overall survival; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study	Intervention	Comparison	Concomitant medication
VELOUR	FOLFIRI + aflibercept 4 mg/kg administered i.v. over 1 hour Composition of FOLFIRI: folinic acid[a] 400 mg/m² over 120 minutes irinotecan 180 mg/m² over 90 minutes 5-FU 400 mg/m² bolus given over 2 - 4 minutes 5-FU 2400 mg/m² infusion over 46 hours Treatment regimens administered every 2 weeks	FOLFIRI + placebo	Concomitant medication: All supportive interventions to guarantee the optimum care of the patient could be administered during the study. Systemic oncologic drugs other than the study medication, radiotherapy and anticonvulsants from the group of CYP3A4 inducers were not permitted.
a: As D, L racemate, in case of using it as L-isoform, the dosage was to be halved CYP3A4: cytochrome P450 3A4; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; 5-FU: 5-fluorouracil; i.v.: intravenous; RCT: randomized controlled trial; vs.: versus			

The study VELOUR was a multinational, randomized, parallel, placebo-controlled and double-blind phase-III study. The participants enrolled were adult patients with histologically or cytologically proven adenocarcinoma of the colon or rectum with inoperable metastases who had recurrence within 6 months of completion of an oxaliplatin-containing chemotherapy.

A total of 1226 patients were randomly assigned in a ratio of 1:1, 612 patients to aflibercept + FOLFIRI, and 614 patients to placebo + FOLFIRI. Overall, the criteria of the approved therapeutic indication of aflibercept were regarded as being fulfilled for the patients enrolled in the study. The study as a whole was therefore relevant for the benefit assessment. This concurs with the company's assessment.

The study treatments were administered according to a regimen described in the Summary of Product Characteristics (SPC) [3]. For aflibercept, this means an intravenous (i.v.) infusion of 4 mg/kg over one hour in each treatment cycle. Accordingly, the patients in the placebo arm received an intravenous placebo infusion over one hour. Immediately after the administration of aflibercept or placebo, all patients received FOLFIRI in the following scheme: Infusions of irinotecan 180 mg/m^2 i.v. over 90 minutes und leucovorin (folinic acid) 400 mg/m^2 i.v. over 2 hours, followed by a bolus of 5-FU (5-fluorouracil) 400 mg/m^2 i.v. over 2 to 4 minutes with a subsequent infusion of 5-FU 2400 mg/m^2 i.v. over 46 hours. The study medication was administered every 2 weeks. All supportive interventions to guarantee the optimum care of the patient could be administered as concomitant medication. Only systemic oncologic drugs other than the study medication, radiotherapy and anticonvulsants from the group of CYP3A4 inducers were explicitly excluded.

Study treatment was continued until the occurrence of either disease progression or inacceptable toxicity or the doctor's or patient's decision.

OS was recorded as patient-relevant primary outcome in the study. AEs were patient-relevant secondary outcomes.

The treatment duration (including follow-up) was 22.6 (17.9) weeks on average (standard deviation) in the aflibercept arm, and 24.2 (17.4) weeks in the placebo arm. AEs were recorded up to 30 days after the last administration of study medication. OS was recorded until the end of the follow-up phase.

The VELOUR study was a placebo-controlled study. According to the SPC, aflibercept for the treatment of mCRC is only approved in combination with FOLFIRI. Hence the comparison of aflibercept + FOLFIRI versus (placebo) + FOLFIRI performed in the study concurs with the comparison relevant for this research question. The study was therefore suitable for assessing the added benefit of aflibercept in comparison with the ACT.

Characteristics of the study population

Table 5 shows the characteristics of the patients in the study included.

Table 5: Characteristics of the study populations – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study **Characteristics** **Category**	**Aflibercept + FOLFIRI** **N = 612**	**Placebo + FOLFIRI** **N = 614**
VELOUR		
Age [years]: mean (SD)	59.5 (10.5)	60.2 (10.8)
Sex: [f/m], %	40.4 / 59.6	42.5 / 57.5
ECOG-PS, n (%)		
0	349 (57)	350 (57)
1	250 (40.8)	250 (40.7)
2	13 (2.1)	14 (2.3)
Disease duration: time from first diagnosis to randomization [months] mean (SD)	21.0 (24.1)	20.9 (21.1)
Location of primary tumour, n (%)		
Colon	289 (47.2)	302 (49.2)
Recto sigmoid	123 (20.1)	136 (22.1)
Rectum	197 (32.2)	174 (28.3)
Other	3 (0.5)	2 (0.3)
Liver metastases only, n (%)		
Yes	153 (25.0)	146 (23.8)
No	459 (75.0)	468 (76.2)
Treatment discontinuations, n (%)		
Complete treatment discontinuation	593 (96.9)	598 (97.4)
Discontinuation of aflibercept/placebo only	95 (15.5)[a]	14 (2.3)[a]

a: In relation to safety population, aflibercept + FOLFIRI: N = 611, placebo + FOLFIRI: N = 605)
ECOG-PS: Eastern Cooperative Oncology Group performance status, f: female, FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; m: male; N: number of randomized patients; n: number of patients in category, RCT: randomized controlled trial, SD: standard deviation; vs.: versus

There were no relevant differences between the treatment groups for the following characteristics: age, sex, Eastern Cooperative Oncology Group performance status [ECOG-PS], disease duration, location of primary tumour, and proportion of patients who only had liver metastases. On average, the patients were 60 years old and had been diagnosed with the disease for about 21 months. About 41% of the patients were women. In almost half of the patients, the primary tumour was located in the colon, about one quarter only had liver metastases.

The overall rate of the patients who discontinued treatment was about 97% in both treatment arms. However, this number also includes those patients who discontinued treatment because of disease progression or inacceptable toxicity or after decision made by the doctor or the

patient. Additionally, the clinical study report (CSR) also included information on the proportion of patients who only discontinued individual components of the study treatment (i.e. aflibercept/placebo or FOLFIRI). In relation to the safety population (aflibercept arm N = 611, placebo arm N = 605), this affected 134 (21.9%) of the patients in the aflibercept arm, and 27 (4.5%) of the patients in the placebo arm. The proportion of patients who only discontinued treatment with aflibercept or placebo was 95 (15.5%) (aflibercept) and 14 (2.3%) (placebo). The reason most commonly given for this treatment discontinuation was "AE" for both treatment arms (93 [15.2%] in the aflibercept arm, and 12 [2.0%] in the placebo arm).

Although according to the approval, treatment with aflibercept, in principle, also is an option for patients with other tumour types of colorectal cancer (such as neuroendocrine tumours or sarcomas), the VELOUR study only included patients with adenocarcinomas, which, with more than 95%, constitute the vast majority of colorectal carcinomas. It is unclear to what extent the results also apply to patients with rarer types of tumour.

Risk of bias at study level

Table 6 shows the risk of bias at study level. This was rated as low for the VELOUR study. This concurs with the company's assessment.

Table 6: Risk of bias at study level – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
VELOUR	yes	yes	yes	yes	no	yes	low
FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; vs.: versus							

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (OS)
- Adverse events
  - overall rate of AEs
  - SAEs
  - severe AEs (CTCAE Grade 3 and 4)
  - treatment discontinuations due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used additional outcomes in the dossier (Module 4), namely progression-free survival (PFS) and objective response rate (ORR), both as outcomes for morbidity (see Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the study included. Table 8 shows the risk of bias for these outcomes.

Table 7: Matrix of outcomes – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study	Outcomes						
	Overall survival	Morbidity	Health-related quality of life	Overall rate of AEs	SAEs	Severe AEs (CTCAE Grade 3 and 4)	Discontinuation due to AEs
VELOUR	yes	no	no	yes	yes	yes	yes

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; SAE: serious adverse events; vs.: versus

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study		Outcomes					
	Study level	Overall survival	Health-related quality of life	Overall rate of AEs	SAEs	Severe AEs (CTCAE Grade 3 and 4)	Discontinuation due to AEs
VELOUR	low	low	–[a]	–[b]	low	low	low

a: Not recorded
b: Results on the overall rate of AEs were not interpretable. Therefore no assessment of risk of bias.
AE: adverse event; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

No data on morbidity and health-related quality of life were recorded in this study.

The risk of bias for the outcome OS was rated as low. This concurs with the company's assessment. The risk of bias was also rated as low for the outcomes on AEs. This also concurs with the company's assessment. However, the company did not make an assessment at outcome level, but on overall AEs.

Further information about the choice of outcome and risk of bias at the outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 9 and Table 10 summarize the results on the comparison of aflibercept + FOLFIRI vs. placebo + FOLFIRI in patients with mCRC. Table 11 contains additional information on the most common severe AEs (CTCAE Grade ≥ 3) that occurred in at least 5% of the patients (referring to the Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class [SOC]) or in at least 2% of the patients (referring to MedDRA Preferred Term [PT]) in one treatment arm.

Table 9: Results on OS – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study Outcome	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Aflibercept + FOLFIRI vs. placebo + FOLFIRI	
	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI]	p-value
VELOUR						
OS	612	13.5 [12.52; 14.95]	614	12.1 [11.07; 13.08]	0.82 [0.71; 0.93]	0.003[a]

a: P-value from log-rank test

CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; N: number of analysed patients; OS: overall survival; RCT: randomized controlled trial; vs.: versus

Table 10: Results on AEs – RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study Outcome category Outcome	Aflibercept + FOLFIRI N = 611	Placebo + FOLFIRI N = 605	Aflibercept + FOLFIRI vs. placebo + FOLFIRI
	Patients with events n (%)	Patients with events n (%)	RR [95% CI]; p-value
VELOUR			
Adverse events			
Overall rate of AEs	606 (99.2)	592 (97.9)	
SAEs	294 (48.1)	198 (32.7)	1.47 [1.28; 1.69] < 0.001
Severe AEs (CTCAE Grade 3 and 4)	510 (83.5)	378 (62.5)	1.34 [1.24; 1.43] < 0.001
Treatment discontinuations due to AEs	164 (26.8)	73 (12.1)	2.22 [1.73; 2.86] < 0.001

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 11: Results on AEs – AEs with CTCAE Grade ≥ 3 that occurred in a treatment arm in ≥ 5% of the patients in SOC, and in ≥ 2% of the patients in PT

SOC **PT**	**Aflibercept + FOLFIRI** **N = 611**	**Placebo + FOLFIRI** **N = 605**
	Patients with at least one event **n (%)**	**Patients with at least one event** **n (%)**
VELOUR		
Infections and infestations	75 (12.3)	42 (6.9)
Blood and lymphatic system disorders	179 (29.3)	146 (24.1)
Neutropenia	153 (25.0)	133 (22.0)
Febrile neutropenia	26 (4.3)	10 (1.7)
Metabolism and nutrition disorders	58 (9.5)	21 (3.5)
Decreased appetite	21 (3.4)	11 (1.8)
Dehydration	26 (4.3)	8 (1.3)
Nervous system disorders	51 (8.3)	33 (5.5)
Vascular disorders	145 (23.7)	31 (5.1)
Hypertension	117 (19.1)	9 (1.5)
Deep vein thrombosis	13 (2.1)	11 (1.8)
Respiratory, thoracic and mediastinal disorders	46 (7.5)	29 (4.8)
Pulmonary embolism	28 (4.6)	21 (3.5)
Gastrointestinal disorders	232 (38.0)	139 (23.0)
Diarrhoea	118 (19.3)	47 (7.8)
Nausea	11 (1.8)	18 (3.0)
Stomatitis	78 (12.8)	28 (4.6)
Vomiting	17 (2.8)	21 (3.5)
Abdominal pain	27 (4.4)	14 (2.3)
Intestinal obstruction	8 (1.3)	12 (2.0)
Skin and subcutaneous tissue disorders	24 (3.9)	9 (1.5)
Palmar-plantar erythrodysaesthesia syndrome	17 (2.8)	3 (0.5)
Renal and urinary disorders	32 (5.2)	8 (1.3)
Proteinuria	18 (2.9)	0
General disorders and administration site conditions	134 (21.9)	88 (14.5)
Fatigue	77 (12.6)	47 (7.8)
Asthenia	31 (5.1)	18 (3.0)
Progression of a disease	19 (3.1)	16 (2.6)
Examinations	38 (6.2)	21 (3.5)
Decreased weight	16 (2.6)	5 (0.8)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; N: number of analysed patients; n: number of patients with event; PT: MedDRA Preferred Term; SOC: MedDRA System Organ Class; vs.: versus

There was only one relevant study for the assessment of aflibercept in the treatment of patients with mCRC. The available study VELOUR did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most "indications" could be derived from the data.

Overall survival

The treatment with aflibercept + FOLFIRI resulted in a statistically significant prolongation of OS in comparison with placebo + FOLFIRI. There is therefore an indication of an added benefit of aflibercept + FOLFIRI compared with the ACT FOLFIRI for OS. This deviates from the company's assessment, which claimed proof of an added benefit.

Morbidity

The company's dossier contained no relevant results on morbidity. Hence an added benefit of aflibercept in comparison with the ACT is not proven. This assessment deviates from that of the company, which derived an added benefit in this outcome category on the basis of the outcomes PFS and ORR.

Health-related quality of life

The VELOUR study did not record any data on health-related quality of life. Hence an added benefit of aflibercept + FOLFIRI in comparison with the ACT FOLFIRI is not proven. This concurs with the company's assessment.

Adverse events

The overall rates of SAEs, severe AEs (CTCAE Grade 3 and 4) and treatment discontinuations due to AEs were higher under aflibercept + FOLFIRI than under placebo + FOLFIRI. The differences were statistically significant. There is an indication of greater harm from aflibercept + FOLFIRI compared with the ACT FOLFIRI for these outcomes.

This assessment deviates from that of the company, which rated the AEs recorded in the study as typical AEs of antineoplastic treatment that could be managed by an experienced oncologist. It presented the results of different operationalizations of the category side effects in Module 4 of the dossier, but did not explicitly consider them in the overall conclusion on added benefit.

Subgroup analyses

There were subgroup analyses both on the outcome OS and on the outcomes on the category "AEs" on the following characteristics: ECOG-PS, prior treatment with bevacizumab, age, and sex. The only relevant result from the subgroup analyses was proof of an interaction (p-value 0.002) regarding the outcome SAE for the characteristic "age" (patients $< / \geq 65$ years). The results on this subgroup analysis are shown in Table 12.

Table 12: Subgroups: RCT, direct comparison – aflibercept + FOLFIRI vs. placebo + FOLFIRI

Study Outcome Characteristic Subgroup	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Aflibercept + FOLFIRI vs. placebo + FOLFIRI	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
SAEs						
Age						
< 65 years	406	173 (42.6)	372	125 (33.6)	1.27 [1.06; 1.52]	
≥ 65 years	205	121 (59.0)	233	73 (31.3)	1.88 [1.51; 2.35]	
					Interaction:	0.002[b]

a: Interaction test in the Cox model with factor, treatment effect and interaction effect of treatment and factor
b: Chi-square test (Cochran's Q-statistics) for investigating the subgroup differences
CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

For both age strata, the risk of an SAE was statistically significantly higher under aflibercept + FOLFIRI in comparison with placebo + FOLFIRI. However, the effect to the disadvantage of aflibercept + FOLFIRI was greater in patients ≥ 65 years than in patients < 65 years. It was therefore examined for the overall conclusion on the extent of added benefit whether the conclusion changes when the different effects are considered (see Section 2.5.2).

In addition, the company described different prespecified subgroup analyses for the outcome OS in Module 4 (Section 4.3.1.3.5.1.1). The interaction test performed by the company resulted in an indication ($0.05 \leq$ p-value < 0.2) for the characteristics "pre-existing hypertension", "liver metastases only", and "location of primary tumour". These results were not considered any further in this benefit assessment because there was only an indication of effect modification and because analyses for these three characteristics were only available for OS, but not for the outcomes on AEs.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2. and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in an indication of an added benefit of aflibercept + FOLFIRI versus the ACT FOLFIRI for the outcome OS. In contrast, there were indications of greater harm from aflibercept regarding the outcomes SAEs and severe AEs (CTCAE Grade 3 and 4). There was proof of an effect modification by the characteristic age for the outcome treatment discontinuation due to AEs. The results of the total population of the VELOUR study are supplemented by the subgroup results relevant for the assessment in the following Table 13.

Table 13: Extent of added benefit at outcome level: aflibercept + FOLFIRI vs. placebo + FOLFIRI

Outcome		**Effect estimator [95% CI]** **Median survival time / proportion of events aflibercept + FOLFIRI vs. placebo + FOLFIRI** **p-value** **Probability**	**Derivation of extent[b]**
Mortality			
OS		HR 0.82 [0.71; 0.93] 13.5 vs. 12.1 months p-value = 0.003 Probability: "indication"	Outcome category: survival time $0.85 < CI_o < 0.95$ Added benefit, extent: "considerable"
Morbidity			
no evaluable data available			
Health-related quality of life			
no evaluable data available			
Adverse events			
SAEs	Age < 65 years	RR 1.27 [1.06; 1.52] RR[c] 0.79 [0.66; 0.94] 42.6 % vs. 33.6 % p-value = 0.010[d] Probability: "indication"	Outcome category: serious/severe AEs $0.90 < CI_o < 1.00$ greater harm, extent: "minor"
	Age ≥ 65 years	RR 1.88 [1.51; 2.35] RR[c] 0.53 [0.43; 0.66] 59.0 % vs. 31.3 % p-value < 0.001[d] Probability: "indication"	Outcome category: serious/severe AEs $CI_o < 0.75$ greater harm, extent: "major"
Severe AEs (CTCAE Grade 3 and 4)		RR 1.34 [1.24; 1.43] RR[c] 0.75 [0.70; 0.81] RR[e]: 0.44 [0.36; 0.54] 83.5 % vs. 62.5 % p-value < 0.001 Probability: "indication"	Outcome category: serious/severe AEs $0.75 < CI_o < 0.90$ greater harm, extent: "considerable"[f] to "major"
Treatment discontinuations due to AEs		RR 2.22 [1.73; 2.86] RR[c] 0.45 [0.35; 0.58] 26.8 % vs. 12.1 % p-value < 0.001 Probability: "indication"	Outcome category: serious/severe AEs[h] $CI_o < 0.75$ greater harm, extent: "major"

(continued on next page)

Table 13: Extent of added benefit at outcome level: aflibercept + FOLFIRI vs. placebo + FOLFIRI (continued)

a: Probability provided if statistically significant differences were present
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_o).
c: Proportion of events aflibercept plus FOLFIRI vs. placebo plus FOLFIRI (reversed direction of effect to enable direct use of limits to derive extent of added benefit)
d: Institute's calculation, unconditional exact test (CSZ method according to [5])
e: Institute's calculation: RR, CIs, and p-value for the comparison of the proportions of patients without events (aflibercept + FOLFIRI vs. placebo + FOLFIRI)
f: On the basis of the comparison of the proportions of patients with at least one event (aflibercept + FOLFIRI vs. placebo + FOLFIRI)
g: On the basis of the comparison of the proportions of patients without event (aflibercept + FOLFIRI vs. placebo + FOLFIRI)
h: Classification as serious/severe AE because 75.6% of the AEs leading to discontinuation in the aflibercept arm, and 72.6% in the placebo arm were severe AEs (CTCAE Grade ≥ 3).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; CI_o: upper limit of the confidence interval; CSZ: convexity, symmetry, z score; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; RR: relative risk; vs.: versus

It is to be noted that different upper limits of the 95% confidence interval result for the outcome severe AEs (CTCAE Grade 3 and 4), depending on whether the proportions of the patients with at least one event is considered or the proportions or of the patients without events. As a result, greater harm from aflibercept + FOLFIRI with the extent "considerable" would be derived for the comparison of the proportions of patients with at least one event, and greater harm with the extent "major" would be derived for the comparison of the proportions of patients without events. This is taken into account in the derivation of the overall conclusion on added benefit.

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment: aflibercept + FOLFIRI vs. FOLFIRI

Positive effects	**Negative effects**
Indication of an added benefit – extent: “considerable” (Mortality: OS)	Indication of greater harm – Patients < 65: extent: "minor" Patients ≥ 65: extent: "major" (serious/severe AEs: SAEs)
	Indication of greater harm – extent: "considerable"[a] to "major"[b] (serious/severe AEs: severe AEs [CTCAE Grade 3 and 4])
	Indication of greater harm – extent: “major” (serious/severe AEs: discontinuation due to AEs)
a: On the basis of the comparison of the proportions of patients with at least one event (aflibercept + FOLFIRI vs. placebo + FOLFIRI) b: On the basis of the comparison of the proportions of patients without event (aflibercept + FOLFIRI vs. placebo + FOLFIRI) AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; OS: overall survival; SAE: serious adverse events; vs.: versus	

In summary, there are both positive and negative effects with the same certainty of results (indication) for patients < 65 years and for patients ≥ 65 years.

On the positive side, there is an added benefit in the category mortality with the extent "considerable" for both age strata. On the negative side, there is greater harm with the extent "major" (treatment discontinuation due to AEs) in the category serious/severe AEs for both age strata. The differences in extent, which result from a proof of an effect modification regarding the characteristic “age” in the outcome SAEs can therefore be neglected when balancing the positive and negative effects. So the overall conclusion on added benefit is derived for the total population as a whole.

For this reason, the differences in extent described in Section 2.5.1 for the outcome severe AEs (CTCAE Grade 3 and 4), depending on whether the proportions of patients with at least one event are viewed, or the proportions of patients without event, have no effects on the overall conclusion on added benefit.

The added benefit of aflibercept + FOLFIRI versus the ACT FOLFIRI, based on OS, is downgraded from "considerable" to "minor" because of the major risk of harm, particularly for treatment discontinuations due to AEs. This does not affect the certainty of results.

In summary, there is an indication of a minor added benefit of aflibercept + FOLFIRI versus the ACT FOLFIRI for the treatment of adult patients with mCRC that has progressed during or after an oxaliplatin-containing regimen.

This deviates from the company's assessment, which claimed proof of a major added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

VELOUR (EFC10262)

1. Sanofi. Aflibercept versus placebo in combination with irinotecan and 5-FU in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin based regimen (VELOUR): full text view [online]. In: Clinicaltrials.gov. 27.09.2012 [accessed 25.01.2013]. URL: http://www.clinicaltrials.gov/show/NCT00561470.

2. Sanofi-Aventis. A multinational, randomized, double-blind study, comparing the efficacy of aflibercept once every 2 weeks versus placebo in patients with metastatic colorectal cancer (MCRC) treated with irinotecan / 5-FU combination (FOLFIRI) after failure of an oxaliplatin based regimen: study EFC10262; clinical study report [unpublished]. 2011.

3. Sanofi-Aventis Recherche & Développement. A multinational, randomized, double-blind study, comparing the efficacy of aflibercept once every 2 weeks versus placebo in patients with metastatic colorectal cancer (MCRC) treated with irinotecan / 5-FU combination (FOLFIRI) after failure of an oxaliplatin based regimen [online]. In: EU Clinical Trials Register. [accessed 25.01.2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000820-42/DE.

4. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T 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. J Clin Oncol 2012; 30(28): 3499-3506.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. European Medicines Agency. Zaltrap 25 mg/ml concentrate for solution for infusion: European public assessment report; product information [online]. 02.2013 [accessed 08.05.2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002532/WC500139484.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_08_afliberc ept_zaltrap_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3358.html.