Compound(s): Zaltrap® / Aflibercept

Registry Title: Observational study to evaluate quality-of-life data in patients with metastatic colorectal cancer under Zaltrap® treatment

(Nicht - Interventionelle Studie zur Erfassung der Lebensqualität bei Patienten mit metastasiertem kolorektalen Karzinom unter Zaltrap® Therapie)

Registry number: AFLIBL06681 / 1774 (BfArM registry No)

Registry name: QoliTrap

Registry initiation date [date first patient in (FPI) = date of first patient's informed consent]: 03-Sep-2013

Registry completion date [last patient completed/last patient out (LPO)]: 31-Mar-2020

Registry design: This was a prospective, non-interventional study (NIS) which was conducted in Germany, Austria and Switzerland pursuant to §67 AMG (Germany) and § 2a Abs 3 AMG (Austria). The use of aflibercept (Zaltrap®) in oncological practice according to the summary of product characterization (SPC) was documented. Therapy data and quality of life of the patients with metastatic colorectal cancer (mCRC) were recorded**.**

Date of interim report: 4 interim analyses have been performed during study period:

1) 07-Apr-2016
2) 02-Mar-2017
3) 05-Dec-2017
4) 02-Jan-2019

Report date: 25-Jan-2021

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	Observational study to evaluate quality-of-life data in patients with metastatic colorectal cancer under Zaltrap® treatment (Nicht-Interventionelle Studie zur Erfassung der Lebensqualität bei Patienten mit metastasiertem kolorektalen Karzinom unter Zaltrap® Therapie) Registry number: AFLIBL06681 / 1774 (BfArM registry No)
Design:	Non-interventional, prospective, multicenter, multi-national
Objectives:	Primary objective: To document and analyze Quality of Life (QoL) data from patients with mCRC receiving treatment with Zaltrap® in combination with FOLFIRI in daily routine care according to EORTC QLQ-C30 as well as the percentage of patients whose QoL is reduced by less than 5% during treatment with aflibercept over the 12-week observation period. Separate evaluations with respect to RAS status (wild type, mutation and unknown) were performed. Regarding QoL, further secondary endpoints were analyzed: • Effects on other QoL dimensions/scales • Effects of toxicities on QoL • Effects of pre-existing symptoms on QoL • Predictive factors for improvement in QoL • Identification of serious adverse drug reactions/events • Comparison of QoL between responders and non-responders • Comparison of QoL in subgroups RAS WT and RAS mt Secondary objectives. • To evaluate progression-free survival (PFS) • To evaluate response rate (RR) • To evaluate overall survival (OS) • To evaluate safety • To evaluate the impact of RAS status on therapy.
Treatment:	Treatment of mCRC with aflibercept according to labeled indication:

	The recommended dose of aflibercept, administered as an intravenous (iv) infusion over 1 hour, is 4 mg / kg of body weight, followed by the FOLFIRI regimen. This is considered as one treatment cycle, which should be repeated every 2 weeks. The FOLFIRI regimen to be used is irinotecan 180 mg/m² iv infusion over 90 minutes and folinic acid (dl racemic) 400 mg/m² iv infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-fluorouracil (5-FU) 400 mg / m² iv bolus, followed by 5-FU 2400 mg / m² continuous iv infusion over 46 hours.
Scientific committee and members:	Not applicable.
Publications (reference):	• DGHO 2015 / Poster (P213): Derigs HG, et al. 2015 • DGHO 2016 / Talk (V648): Scholten F, et al. 2016 • ASCO 2016 / Poster: Hofheinz RD, et al. 2016 • DGHO 2017 / Poster (P578): Scholten F, et al. 2017 • DGHO 2018 / Poster (P893): Piringer G, et al. 2018 • DGHO - ESMO 2019 / Talk (V256): von Moos R, et al. 2019 • DKK 2016 / Poster (ID 0211): Derigs G, et al. 2016 • ESMO 2017 / Poster (595P): von Moos R, et al. 2017 • ESMO 2018 / Poster (575P): Hofheinz RD, et al. 2018 • WCGC-ESMO 2018 / Poster (P-260): Zahn MO et al, 2018 • WCGC 2019 / Poster: Hofheinz RD, et al. 2019 • DGHO 2020 / Presentation: Scholten F, et al. 2020 • SOHC 2020 / Poster: Von Moos R. et al. 2020 At regular intervals the participating sites were informed by country-specific newsletters about the progress of the study.
Introduction - Background/rationale:	Aflibercept is a recombinant fusion protein which blocks the activity of VEGFA, VEGFB, and placental growth factor (PlGF) by acting as a high-affinity ligand trap to prevent these ligands from binding to their endogenous receptors. A phase III, randomized trial (VELOUR trial) has been shown that patients with metastatic colorectal cancer (mCRC)

	previously treated with an oxaliplatin-based regimen achieved a significant increase in overall survival (OS) with aflibercept and FOLFIRI compared to FOLFIRI and placebo. Median OS in the aflibercept treatment arm was 13.50 months vs. 12.06 months in the control arm (HR=0.817; 95% confidence interval, 0.713–0.937; p=0.0032). Further, median PFS and response rate were also significantly improved in the aflibercept arm compared to placebo arm. These efficacy effects were also observed in the subset of bevacizumab pretreated patients. Regarding safety, 99.2% and 97.9% of patients in aflibercept and placebo arm, respectively, reported treatment-related adverse events (AEs). Grade 3/4 AEs were reported more often by patients in aflibercept arm than in placebo arm, 83.5% and 62.5%, respectively. Increase in AEs could be attributed both to chemotherapy and aflibercept. Grade 3/4 AEs with >2% higher incidence in the aflibercept arm compared to placebo were diarrhea, asthenia/fatigue, stomatitis/ulceration, infections, hypertension, gastrointestinal/abdominal pain, neutropenia/neutropenic complications, and proteinuria (Van Cutsem E, et al. 2012). Based on the data of the VELOUR trial aflibercept in combination with FOLFIRI was approved in the EU in February 2013 for the treatment of patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen (SPC Zaltrap®). However, no quality of life data were collected in the before mentioned trial. The QoLiTrap-study aimed to evaluate quality of life in patients under treatment with aflibercept plus FOLFIRI after oxaliplatin based therapy in routine practice. No diagnostic or therapeutic interventions were pre-specified. Since importance of RAS status in patients with mCRC has increased in recent years, e.g. it could be shown to influence efficacy results of treatment with EGFR inhibitors (Diaz-Rubio E, et al. 2017, Douillard JY, et al. 2013, Van Cutsem E, et al. 2011), RAS status was also recorded in the QoLiTrap-study. Thus, separate evaluations of patients with RAS wild type and RAS mutation were possible to investigate a potential impact of RAS mutations on aflibercept treatment and on quality of life. No consistent data existed so far regarding the prognostic impact of RAS mutations on the treatment with anti-angiogenics. Additionally, PFS, response rate (RR), OS as well as safety of aflibercept and FOLFIRI administered under real world conditions should be evaluated.
Methodology:	(a) Site and patient selection: The study was planned to be conducted in about 140 sites: 120, 10 and 14 sites in Germany, Austria and Switzerland, respectively. Clinics and medical practices in Germany, Austria and Switzerland with experience in the therapy of mCRC patients could participate. A total of approximately 1500 patients with mCRC into the trial should be enrolled, 1340, 75 and 85 patients in Germany, Austria and Switzerland, respectively. Except the conditions specified in the summary of product characteristics no further inclusion criteria were applied. (b) Data collection:

	For data capturing and data management, a web-based validated software was employed. Physicians documented the anamnesis, therapy and safety data into electronic case report forms (eCRF). Patients were asked to fill in the EORTC QLQ-C30 questionnaires on paper every 2 weeks. The filled in-questionnaires were forwarded by fax or e-mail or letter to the CRO (Alcedis GmbH), where double data entry into the CRF was carried out. (c) Safety data collection: All AEs (serious and non-serious, related and not-related) that occurred after first dose of aflibercept and until 28 days after last dose administered had to be reported by German and Austrian sites using the applicable eCRF. For Suisse sites all adverse drug reactions (ADRs) - serious and non-serious- causally related to aflibercept had to be reported during the above stated time period. All AEs / ADRs had to be documented within 24 hours after they had become known by the sites. After saving the form an automatically generated e-mail informed the Pharmacovigilance (PV) of the CRO and Sanofi PV about the AE. If electronic reporting was not possible, paper forms in the investigator's file were at the doctor's disposal for notification AEs by conventional fax to Sanofi PV. If also fax reporting was not possible, the AE could be reported by phone to Sanofi. If a conventional fax or phone call was received by Sanofi PV, the PV of the CRO was informed and asked the site to document the SAE into the eCRF. Reconciliation between the PVs of Sanofi and CRO were carried out at regular intervals. (d) Data management, review, validation: Validity of documented data was ensured by validations in the eCRF, which indicated missing or implausible data entries. Patients could only be registered if they had been informed about the trial by the treating physician and had given their written consent before start of aflibercept therapy. The date of informed consent was documented into the eCRF and had to be before the date of the first documented cycle. The documentation of patients which was completed and signed by the investigator was reviewed on a regular basis by the data management of the Alcedis GmbH. Queries were made directly in the eCRF and the sites were asked to answer these. To further ensure the validity of the data, quality control on-site was performed at about 5% of participating sites by monitors of Alcedis GmbH according to the guidelines of Sanofi: 15 sites in Germany and 1 site each in Austria and Switzerland which were randomly selected by Sanofi were visited by a monitor during the observation period, involving comparison of individual data from the eCRFs with the respective entries in the patient files. (e) Statistical considerations: In general, the analysis was carried out by using descriptive and exploratory statistical methods including exploratory confidence intervals and p-values. For categorical variables, frequency tabulations of the number and percentage within each category (with a category for missing data) of the parameter were presented. For continuous variables, the mean, median, Q1, Q3 standard deviation, minimum and maximum values were calculated as well as the number of missing values.

	Quality of life was addressed by analyzing the EORTC QLQ-C30 questionnaires. The global scale of the quality of life was measured according to the EORTC-LQ-Manual for each documented point in time. The questionnaire includes five functional scales and the global health status and furthermore a number of multi-item scales and single items assessing financial impact and a range of physical symptoms common among patients with cancer. The scales and single items were linearly transformed such that all scales/items range from 0 to 100, with a higher score representing a higher level of functioning/symptomatology/problems. All analyses were descriptive, and 95% CI were given. Missing values on the EORTC QLQ-C30 were handled according to the EORTC QLQ-C30 Scoring manual. All other missing values were not replaced. For analysis of primary endpoint, changes of the Global health status/Quality of life were presented with mean, 95% Blyth-Still-Casella confidence intervals, STD, median, Q1, Q3, minimum, maximum. Analysis was also performed according to RAS status. Furthermore, the percentage change to baseline was displayed as well as the number of patients whose global health status was reduced by less than 5% during treatment with aflibercept over the 12-week observation period. Change of mean global health was calculated as difference between mean of all post-baseline measurements of global health status until week 12 (at least two are necessary) and baseline global health divided by baseline global health status (in percent). To determine potential predictors for improvement of mean global health status in the first 12 weeks the dependent variable of global health status was categorized into yes (=Improvement of mean global health in the first 12 weeks) and no (=No improvement of mean global health in the first 12 weeks). For a first overview the following independent covariates - Responder (Responder/Non-Responder) - Toxicity (Yes/No) - Pre-existing symptoms (Yes/No) - Baseline ECOG (<2/≥2) - Age (<60/≥ 60) were looked at in a univariate regression. Afterwards, all above mentioned independent covariates were entered into a stepwise multivariate logistic regression. The entry level was p=0.5 and the stay level p=0.1. All covariates being significant were considered as potential predictors of the event in question. Response rate was defined as the proportion of patients with CR+PR as best response. OS in months was measured from the date of the first dose given until the date of death. Survival time for patients not known to be deceased were censored at their date of last contact. PFS was measured from the date of the first dose given until the date of progression or death, whichever came first. PFS for patients without progression were censored at the date of last contact. Age at start of therapy was calculated as: Year of start of therapy- Year of birth.

Analyses of adverse and serious adverse events were based on the Sanofi PV database. AEs were summarized in reference to NCI grade, CTCAE version 4.0. Causal relation to the study drug, severity grade, outcome and further information if the outcome was death as well as a description of the AE were given. Adverse events of special interest (AESIs) were thromboembolic event, peripheral motor neuropathy, peripheral sensory neuropathy and reversible posterior leukoencephalopathy syndrome.

Patients from all study centers were pooled.

The analyses were performed on the following data sets:
Safety population (SP) = Intent-to-treat (ITT): All patients with mCRC receiving treatment with aflibercept and / or FOLFIRI.

Primary and secondary endpoint set (PES): All patients who have been treated with aflibercept in combination with FOLFIRI and who have at least two evaluable QoL questionnaires in the first 12 weeks after start of therapy.

Analyses of primary and secondary endpoints were based on PES, except the analyses of safety and key secondary endpoints. Those and all further analyses were based on SP.

Sample size calculation was based on the hypothesis that 65% patients would have a global quality of life either improved or reduced by less than 5% (success rate) over a 12-week observation (primary endpoint). Based on previous studies, it was assumed that only 80% of the data sets would be provided by the treating physicians and that only 62% of patients would have at least 2 evaluable quality of life questionnaires at 12 weeks after the start of therapy. In order to obtain evaluable data sets for 750 patients, about 1500 patients would therefore need to be included in the study. The case number of 750 evaluable patients was also justified in order to perform valid statistical evaluations for the subgroups according to RAS status (RAS wild type, RAS mutation). According to current market data, in Germany about 1/3 of the patients treated with Aflibercept were RAS wild type and about 2/3 were RAS mutations. For 750 patients, this would result in approximately 250 RAS wild type patients and approximately 500 RAS mutation patients. The statistical accuracy of the estimates for the success rates were presented using 95% confidence intervals.

The respective confidence intervals for 750, 500 or 250 patients and for assumed success rates of 65% or 50% are shown in the following table:

Patient number	Success rate 65% 95% confidence interval (Blyth-Still-Casella)	Success rate 50% 95% confidence interval (Blyth-Still-Casella)
750	61.6% ; 68.5%	46.4% ; 53.6%
250	59.1% ; 71.1%	43.6% ; 56.4 %
500	60.8% ; 69,2%	45.5% ; 54.5%

RESULTS	
Participants (actual):	(a) Overall participation status: Between September 2013 and September 2019, a total of 1330 patients with mCRC for whom treatment with Aflibercept in combination with FOLFIRI was planned, were screened by 186, 12 and 12 clinics and medical practices in Germany, Austria and Switzerland, respectively. A total of 1293 patients was registered (First patient in: 03-Sep-2013, Last patient in: 30-Sep-2019). (b) Participation per period of the registry:

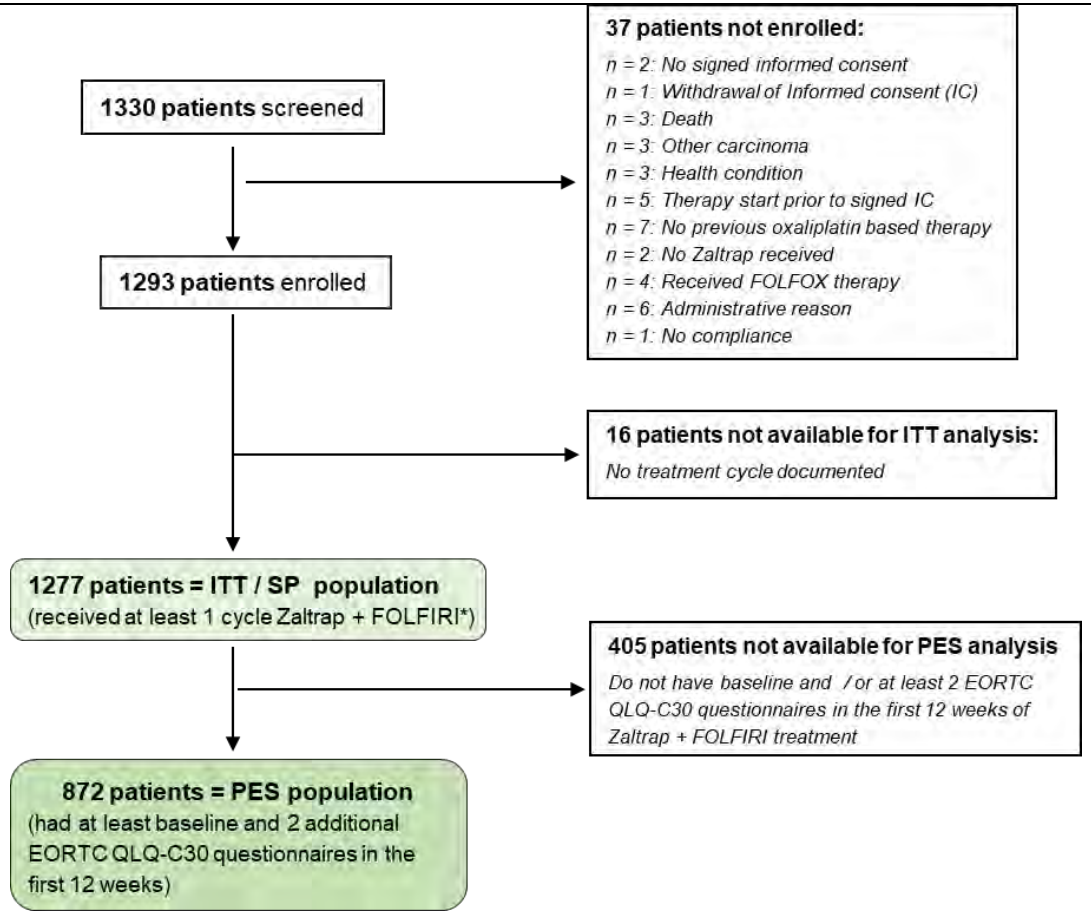


Figure 1: STROBE-Scheme (*1 patient with a maximum of 1 documented cycle received no Zaltrap)

Participant characteristics and primary analyses:	(a) Descriptive data Demographic and tumor data at baseline:

Overall, 1277 patients, 827 (64.8%) male and 450 (35.2%) female patients were exposed to at least one dose of study drug (ITT/safety set). Of them 74.4% were ≥60 years old. At study enrollment, median age was 66.0 years (min. 28.0, max: 90.0). There was no difference in median age between male and female patients. Median age increased with number of previous therapies (Table 1).

Table 1: Age [years], height [cm] and weight [kg] at baseline – ITT set (data source: Tables 101, 107, 124, 242 of QoLiTrap_Final Analysis_2020-08-26)

Parameter	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
Age											
Total	1277	65.45	9.75	41.00	59.00	66.00	73.00	84.00	28.00	90.00	0
Male - Age	827	65.70	9.45	43.00	60.00	66.00	73.00	84.00	28.00	90.00	0
Female - Age	450	64.99	10.28	34.00	59.00	66.00	73.00	82.00	31.00	84.00	0
1st line - Age	83	63.23	10.06	31.00	58.00	65.00	70.00	88.00	31.00	88.00	0
2nd line - Age]	642	65.53	9.87	41.00	60.00	66.00	73.00	84.00	28.00	87.00	0
3rd line - Age	295	65.81	9.45	33.00	60.00	67.00	73.00	82.00	31.00	84.00	0
>3rd line - Age	250	65.70	9.71	43.00	59.00	66.00	74.00	86.00	41.00	90.00	0
Non-determinable-Age	7	59.43	5.47	52.00	56.00	59.00	60.00	70.00	52.00	70.00	0
Height	1277	171.74	9.11	151.00	165.00	172.00	178.00	192.00	146.00	200.00	0
Weight	1277	76.86	17.30	44.00	65.00	75.00	87.00	129.00	36.00	150.00	0

Most patients in the ITT population had an ECOG of 0 and 1, namely 39.4% and 45.3%, respectively. 69.8% of patients suffered of concomitant diseases at baseline, mainly cardiovascular disorders (48.9%).

Tumor histology was adenocarcinoma in 96.2% of patients. 69.3% of patients had left-sided tumor localization. Grading was mainly G2 (61.7%). Greatest percentages for TNM classifications were T3 (50.6%), N2 (37.0% and M1 (63.7%). Metastases were mainly located in the liver (53.2%). About half of patients (50.7%) had a RAS mutation at baseline. Regarding previous therapy, 82.2% of patients had prior tumor surgery and 90.6% had received prior 1st line therapy. Additionally, 47.3% of patients had received a prior therapy at metastatic stage. 82.1% of ITT patients were pretreated with aVEGF/R (53.9%), aEGFR (13.2%) or a combination of both (15.1%). (Table 13).

Overall, 872 patients were analysed in the PES dataset. Baseline data for PES set were comparable to the ITT dataset. 64.3% and 35.7% of PES patients were men and women, respectively. Median age at enrollment was 66.0 years, 72.4%

were ≥60 years old (Table 2, Table 12). A majority of PES patients had an ECOG of 0 (44.0%) and 43.2% had an ECOG 1 (Table 12).

Table 2: Age [years] and height [cm] at baseline – PES set (data source: Tables 77, 80 of QoLiTrap_Final Analysis_2020-08-26)

Parameter	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
Age	872	64.81	9.88	41.00	59.00	66.00	72.00	83.00	28.00	88.00	0
Height	872	171.74	9.07	151.00	165.00	172.00	178.00	192.00	146.00	200.00	0

53.8%, 14.0% and 14.2% of PES patients were pretreated with aVEGF/R (bevacizumab), aEGFR (panitumumab, cetuximab) or a combination of both, respectively.

Tumor histology was adenocarcinoma in 96.4% of patients and 69.6% had a left sided tumor. 62.2% of PES patients had a grading of G2. Greatest percentages for TNM classifications wereT3 (50.5%), N2 (37.5% and M1 (64.9%). Metastases were mainly located in the liver (54.5%). Slightly more than half of patients (51.6%) had a RAS mutated tumor at baseline. (Table 13).
An overview of baseline data in both ITT and PES sets is shown in Table 12 and Table 13.

Study therapy data:

50.3% of ITT patients received Aflibercept as second line therapy, 23.1% as third-line therapy and 11.9% as fourth-line therapy. A majority of patients with RAS wild-type tumors received study treatment as third, fourth and ≥fifth-line compared to patients with RAS mutated tumor (Table 3).

Table 3: Therapy line of Aflibercept study treatment – ITT set (data source: Table 244 of QoLiTrap_Final Analysis_2020-08-26)

Therapy line of Aflibercept	RAS wild-type		RAS mutation		N/A		Total	
	N	%	N	%	N	%	N	%
First-line	20	4.02	48	7.41	15	11.36	83	6.50
Second-line	216	43.46	369	56.94	57	43.18	642	50.27
Third-line	124	24.95	145	22.38	26	19.70	295	23.10
Fourth-line	81	16.30	55	8.49	16	12.12	152	11.90

≥ Fifth-line	56	11.27	27	4.17	15	11.36	98	7.67
Non-determinable			4	0.62	3	2.27	7	0.55
Total	**497**	**100.00**	**648**	**100.00**	**132**	**100.00**	**1277**	**100.00**

A total of 10,197 cycles was documented, of these 83% contained the approved combination of aflibercept with Irinotecan, 5-Fluorouracil, Folinic acid (FOLFIRI). In 11% of cycles, aflibercept was given in combination with Irinotecan and Folinic acid only. Aflibercept was administered as monotherapy in 1.4% of cycles (Table 14). Aflibercept was administered at a median dose of 4 mg/kg (data source: Table 247 of QoLiTrap_Final Analysis_2020-08-26). The concomitant chemotherapeutic drugs were administered in about 2/3 of patients in the first 20 cycles as per SmPC (Table 15).
Deviations from recommended treatment protocol were documented for 6.3% of patients in the first cycle with increasing percentages in the following cycles. Highest percentage of patients with deviations was observed in cycle 7 with 51.7% (Table 16). Deviations consisted in dose modifications and dose delays. Dose modifications were documented from the first cycle of aflibercept, Irinotecan, 5-Fluorouracil and Folinic acid. Reasons for dose modifications were mainly 'non-hematological toxicity' and 'other'. Treatment delays were more common than dose modifications. Reasons for treatment delay were 'organizational reasons', 'patient request' and 'non-hematological toxicity' in almost equal percentages. Reasons and percentages of patients with dose delays and dose modifications for the first 7 cycles are presented in Table 17.
At each cycle, the concomitant use of antiemetic drugs, granulocyte-CSF, painkillers as well as 'other drugs' had to be documented. Antiemetic drugs were the most frequently used concomitant medication during study treatment; between 80% and 100% of patients received them at all cycles. Most often, a combination of 5HT3 receptor inhibitor and dexamethasone was administered. Painkillers were used by about 20% of patients and less than 10% of patients received granulocyte-CSF, mainly as primary prophylaxis; in contrast to antiemetic drugs, painkillers and granulocyte-CSF were not administered at all documented cycles (Table 18). In most cases, painkillers were not subject to narcotics law.

Median duration of study treatment was 12 weeks, median duration was slightly higher for RAS wild-type patients (12.0 weeks) compared to patients with RAS-mutation (11.6 weeks) (Table 4). Median number of cycles administered was 6, with a minimum of 1 cycle and a maximum of 66 cycles (Table 5).

Table 4: Duration of therapy [weeks] (Start of last cycle - Start of first cycle) – ITT set (data source: Table 246 of QoLiTrap_Final Analysis_2020-08-26)

Duration of therapy	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
RAS wild-type	497	17.76	19.35	0.00	6.00	12.00	23.00	107.00	0.00	145.00	0
RAS mutation	648	17.18	17.56	0.00	6.00	11.57	24.00	82.43	0.00	158.00	0
N/A	132	17.87	19.50	0.00	6.21	12.86	25.14	90.00	0.00	170.00	0
Total	**1277**	**17.48**	**18.47**	**0.00**	**6.00**	**12.00**	**23.57**	**90.71**	**0.00**	**170.00**	**0**

Table 5: Number of cycles per patient – ITT set (data source: Table 266 of QoLiTrap_Final Analysis_2020-08-26)

Number of cycles	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
RAS wild-type	497	7.98	7.31	1.00	3.00	6.00	10.00	42.00	1.00	61.00	0
RAS mutation	648	7.91	6.72	1.00	3.00	6.00	11.00	32.00	1.00	66.00	0
N/A	132	8.36	7.99	1.00	4.00	6.00	11.00	45.00	1.00	65.00	0
Total	**1277**	**7.98**	**7.09**	**1.00**	**3.00**	**6.00**	**11.00**	**35.00**	**1.00**	**66.00**	**0**

Reason for therapy termination was for 44.2% of patients disease progression, followed by adverse event / toxicity (21.2%) and patient's request (14.4%) (Table 6).

Table 6: Reason for therapy termination – ITT set (data source: Table 267 of QoLiTrap_Final Analysis_2020-08-26)

Reason for termination	RAS wild-type		RAS mutation		N/A		Total	
	N	%	N	%	N	%	N	%
Planned number of cycles given	20	4.07	22	3.41	11	8.46	53	4.19
Disease progression	221	45.01	296	45.89	42	32.31	559	44.15
Death	33	6.72	43	6.67	6	4.62	82	6.48
Adverse event / toxicity	96	19.55	139	21.55	33	25.38	268	21.17
Patient request	77	15.68	85	13.18	20	15.38	182	14.38
End of documentation	9	1.83	22	3.41	7	5.38	38	3.00
Other reasons	35	7.13	38	5.89	11	8.46	84	6.64
Total	**491**	**100.00**	**645**	**100.00**	**130**	**100.00**	**1266**	**100.00**

At the end of the study, about 30% of patients had died, mostly due to cancer (Table 19, Table 20). For the remaining 61% of alive patients, investigators planned further treatment (Table 21).

(b) Primary outcome (Evaluation for the Primary Endpoint Set)

For the analysis of QoL data according to EORTC QLQ-C30 (primary end-point) patients had to fill in a baseline questionnaire as well as at least 2 further questionnaires during the first 12 weeks of treatment. 872 patients fulfilled this criterion (=PES set).

Percentage of patients whose QoL was reduced by less than 5% (is QoL improved or reduced by less than 5%) during treatment with aflibercept over the 12-week observation period was defined as primary endpoint.

40.3% of patients had a global health status improved or reduced by less than 5% (including patients with no change), 55.7% of patients showed a decrease of ≥5% (Figure 2).

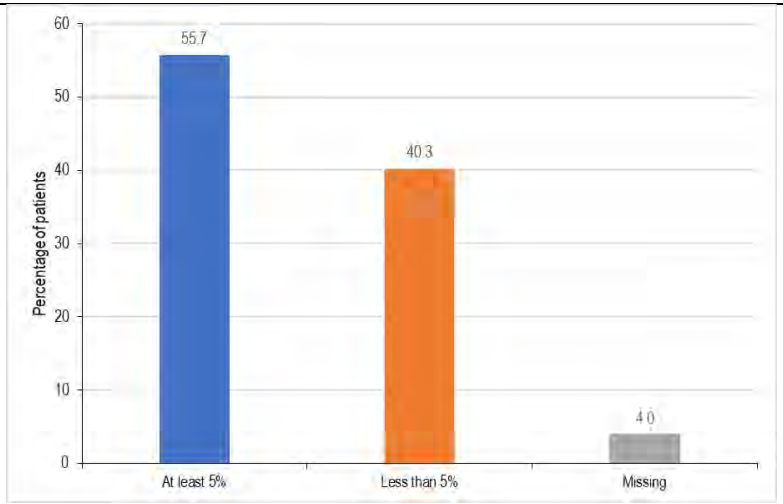
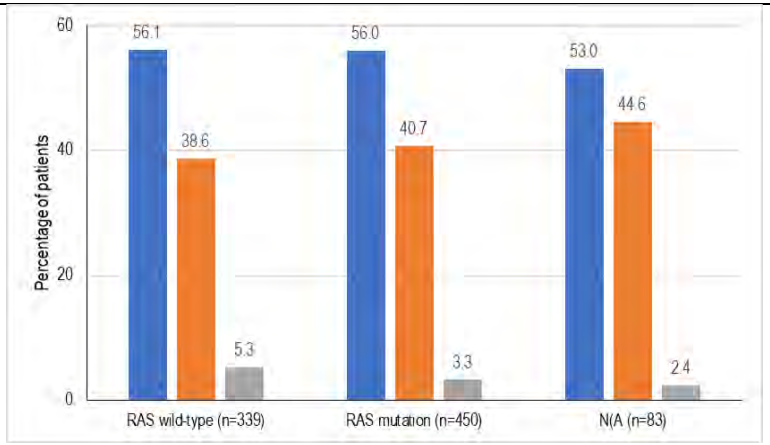
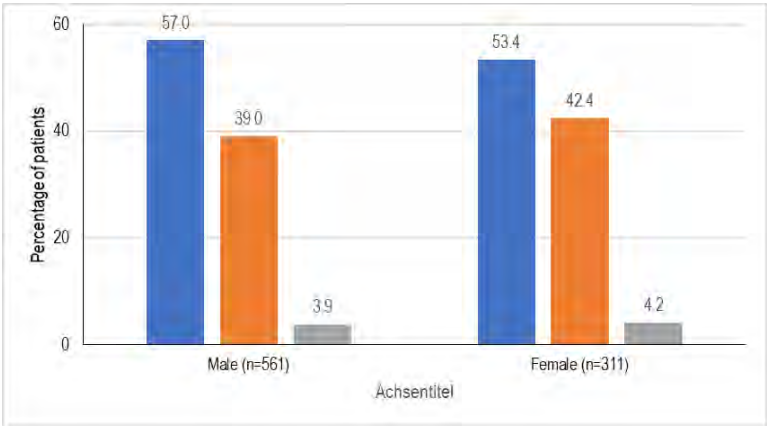
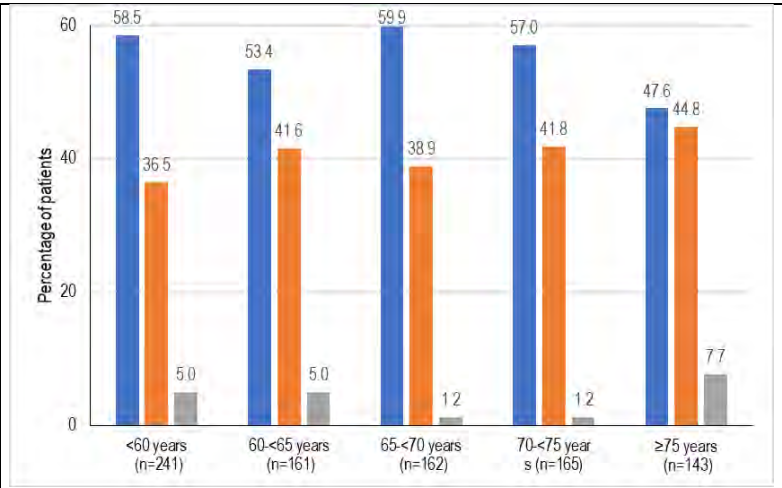


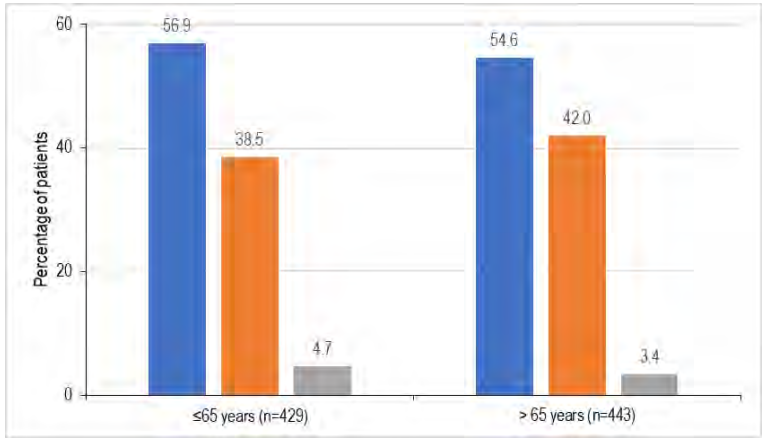
Figure 2: Percentage of patients having a decrease in global health status/Quality of life within the first 12 weeks by at least 5% versus less than 5% (ie QoL improved or reduced by less than 5%) (data source: Table 2 of QoLiTrap_Final Analysis_2020-08-26)

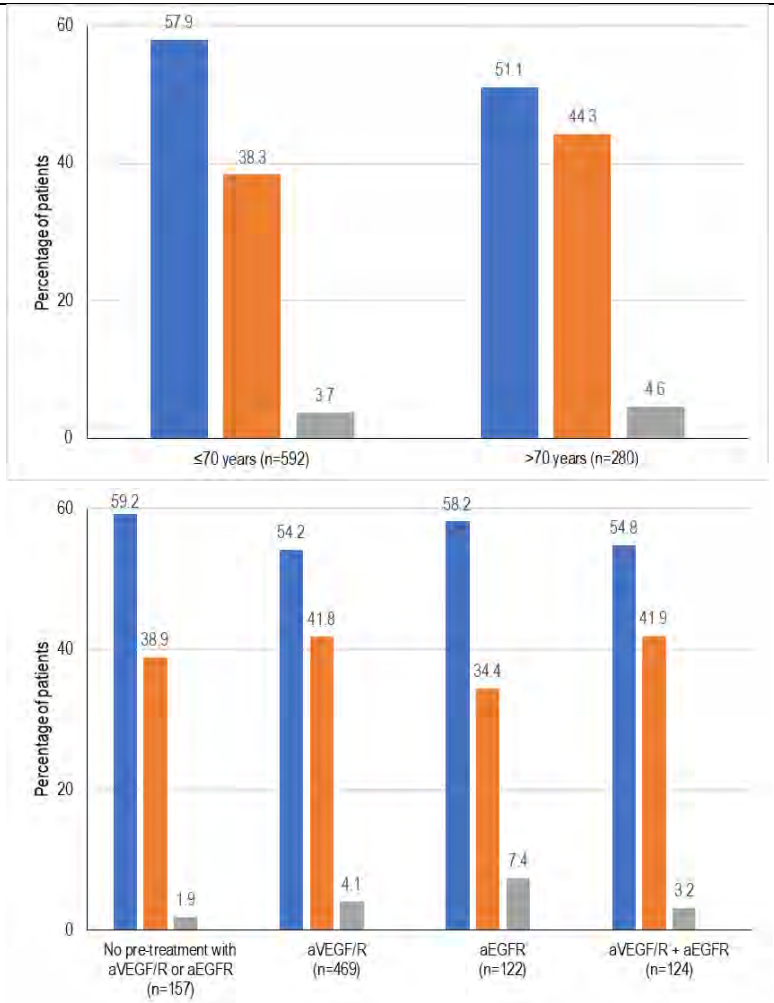
Stratification according to RAS-status, gender, age groups, pretreatment with aVEGF/R or EGFR, hypertension and line of study treatment is shown in the following Figure 3. Greater percentages of patients with RAS-mutation as well as female patients or older patients showed a global QoL improved or reduced by less than 5% of global health score than patients with RAS wild-type, men and younger patients. Lowest percentage of patients with global QoL improved or decreased by less than 5% in global health score was seen for EGFR-pretreated patients (34%).

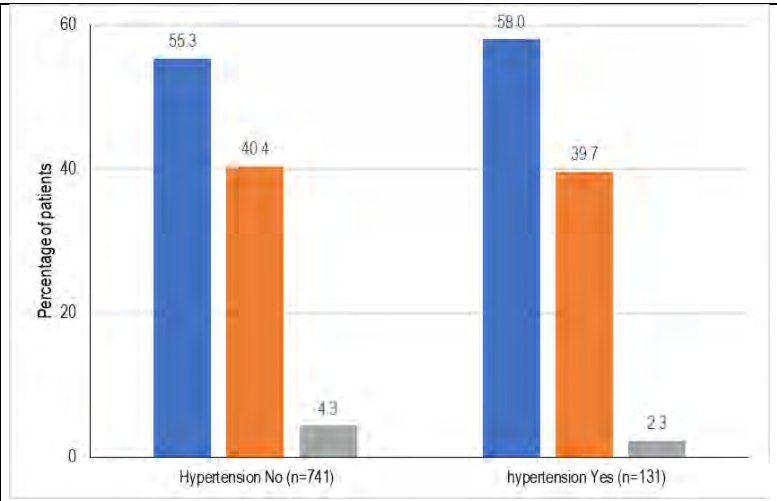

60
40
20
0
Percentage of patients
56.1
38.6
5.3
56.0
40.7
3.3
53.0
44.6
2.4
RAS wild-type (n=339)
RAS mutation (n=450)
N/A (n=83)


60
40
20
0
Percentage of patients
57.0
39.0
3.9
53.4
42.4
4.2
Male (n=561)
Female (n=311)
Achsentitel


Percentage of patients
60
40
20
0
58.5
36.5
5.0
53.4
41.6
5.0
59.9
38.9
1.2
57.0
41.8
1.2
47.6
44.8
7.7
<60 years (n=241)
60-<65 years (n=161)
65-<70 years (n=162)
70-<75 years (n=165)
≥75 years (n=143)


Percentage of patients
60
40
20
0
56.9
38.5
4.7
54.6
42.0
3.4
≤65 years (n=429)
> 65 years (n=443)


Percentage of patients
60
40
20
0
57.9
38.3
3.7
51.1
44.3
4.6
≤70 years (n=592)
>70 years (n=280)
59.2
38.9
1.9
54.2
41.8
4.1
58.2
34.4
7.4
54.8
41.9
3.2
No pre-treatment with aVEGF/R or aEGFR (n=157)
aVEGF/R (n=469)
aEGFR (n=122)
aVEGF/R + aEGFR (n=124)


60
40
20
0
Percentage of patients
55.3
40.4
4.3
58.0
39.7
2.3
Hypertension No (n=741)
hypertension Yes (n=131)

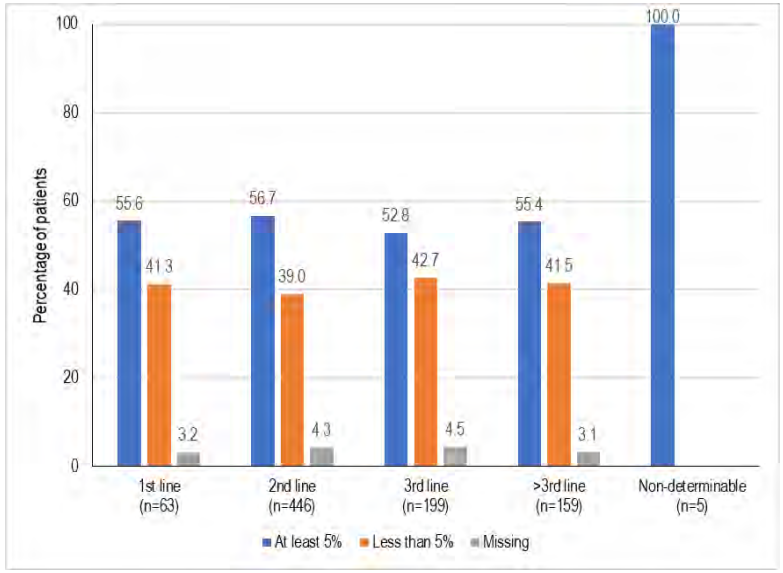
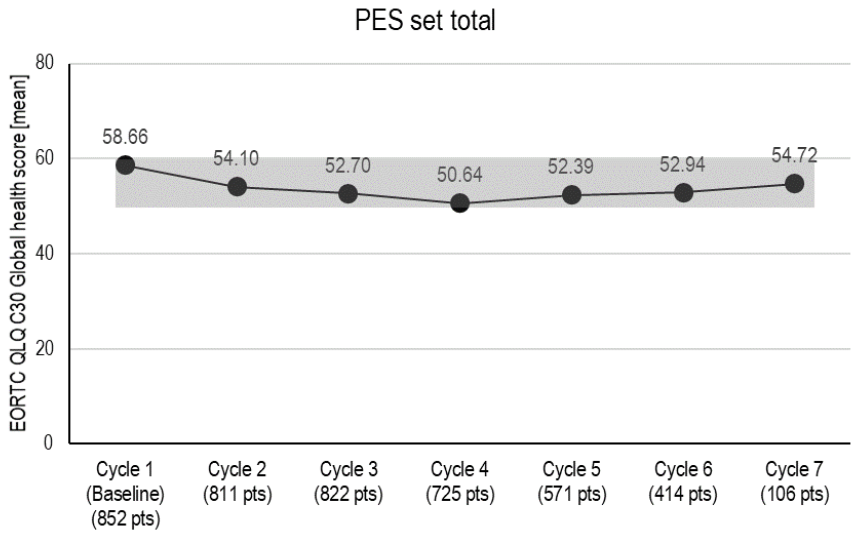
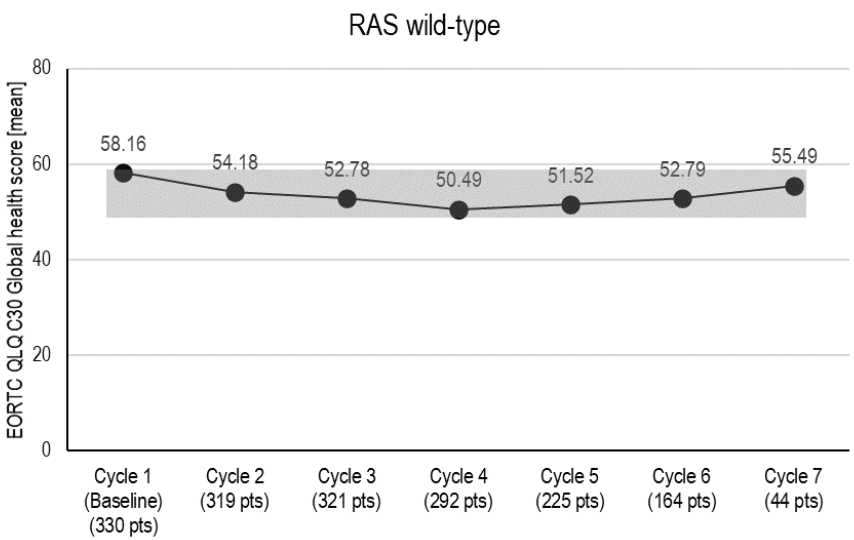

100
80
60
40
20
0
Percentage of patients
55.6
41.3
3.2
56.7
39.0
4.3
52.8
42.7
4.5
55.4
41.5
3.1
100.0
1st line (n=63)
2nd line (n=446)
3rd line (n=199)
>3rd line (n=159)
Non-determinable (n=5)
At least 5%
Less than 5%
Missing

	Figure 3: Decrease of global health status/QoL within the first 12 weeks by at least 5% versus less than 5% (ie QoL improved or reduced by less than 5%)) by stratification criteria (data source: Tables 2-9 of QoLiTrap_Final Analysis_2020-08-26) Course of mean global health status for the first 7 cycles is presented in 


RAS wild-type
EORTC QLQ C30 Global health score [mean]
80
60
40
20
0
58.16
54.18
52.78
50.49
51.52
52.79
55.49
Cycle 1 (Baseline) (330 pts)
Cycle 2 (319 pts)
Cycle 3 (321 pts)
Cycle 4 (292 pts)
Cycle 5 (225 pts)
Cycle 6 (164 pts)
Cycle 7 (44 pts)

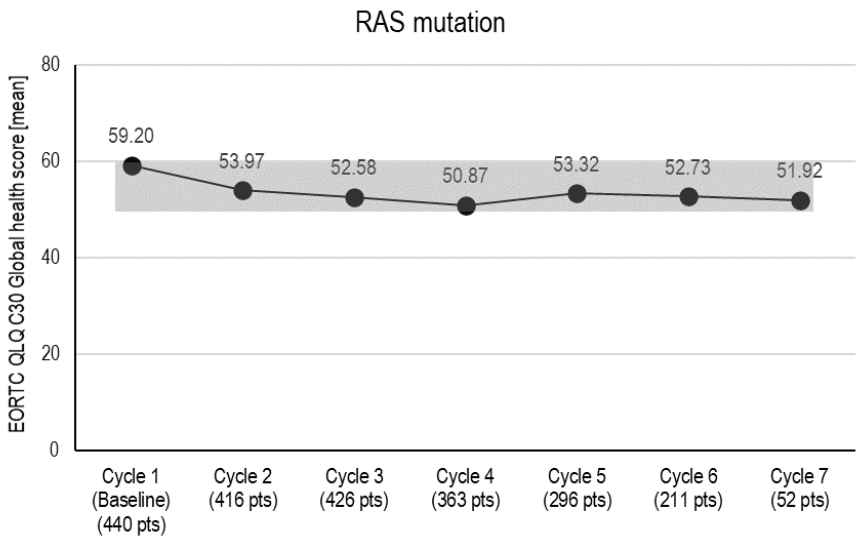
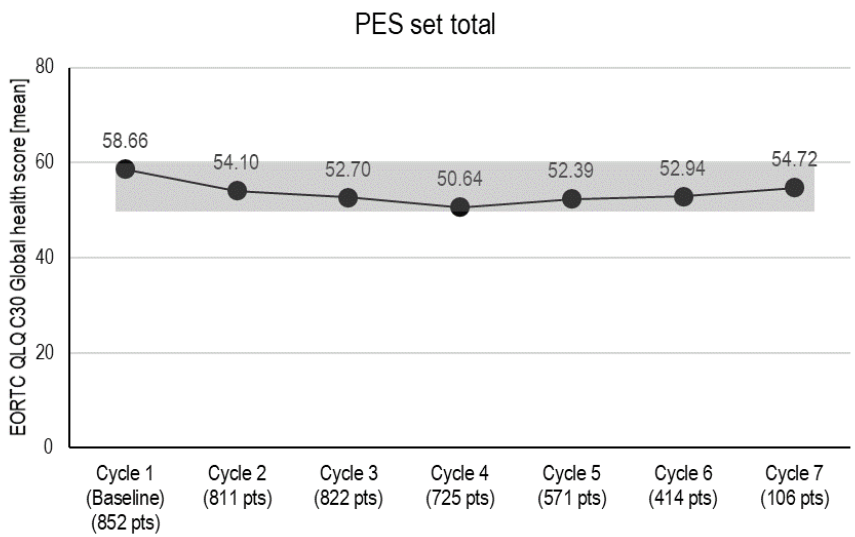
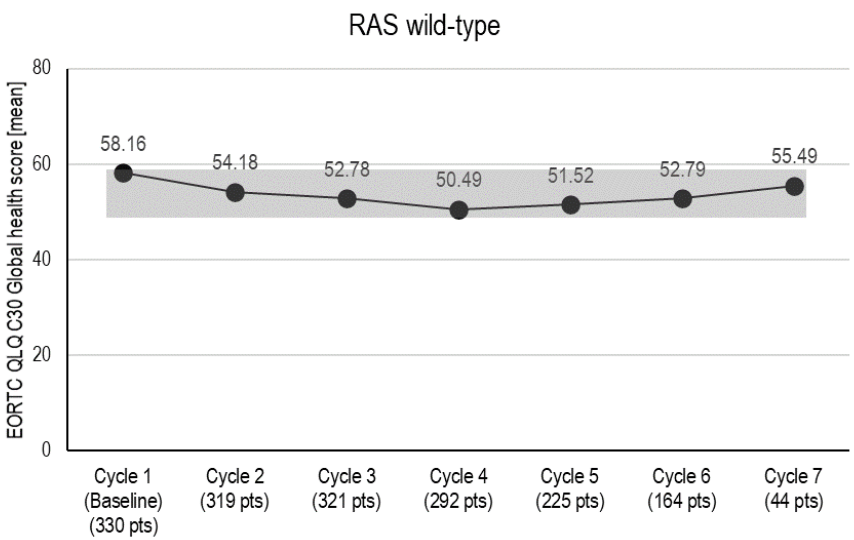


Figure 4. Due to number of evaluable patients per cycle of <10 from cycle 7 on, further cycles were not taken into account. For the analysis, the mean of all present and evaluable EORTC questionnaires for each point in time was calculated. Up to cycle 4 a decrease of mean Global health score was observed, in the following cycles an increase was seen for PES patients in total as well as for subgroup of RAS wild-type.


PES set total
EORTC QLQ C30 Global health score [mean]
80
60
40
20
0
58.66
54.10
52.70
50.64
52.39
52.94
54.72
Cycle 1 (Baseline) (852 pts)
Cycle 2 (811 pts)
Cycle 3 (822 pts)
Cycle 4 (725 pts)
Cycle 5 (571 pts)
Cycle 6 (414 pts)
Cycle 7 (106 pts)


RAS wild-type
EORTC QLQ C30 Global health score [mean]
80
60
40
20
0
58.16
54.18
52.78
50.49
51.52
52.79
55.49
Cycle 1 (Baseline) (330 pts)
Cycle 2 (319 pts)
Cycle 3 (321 pts)
Cycle 4 (292 pts)
Cycle 5 (225 pts)
Cycle 6 (164 pts)
Cycle 7 (44 pts)

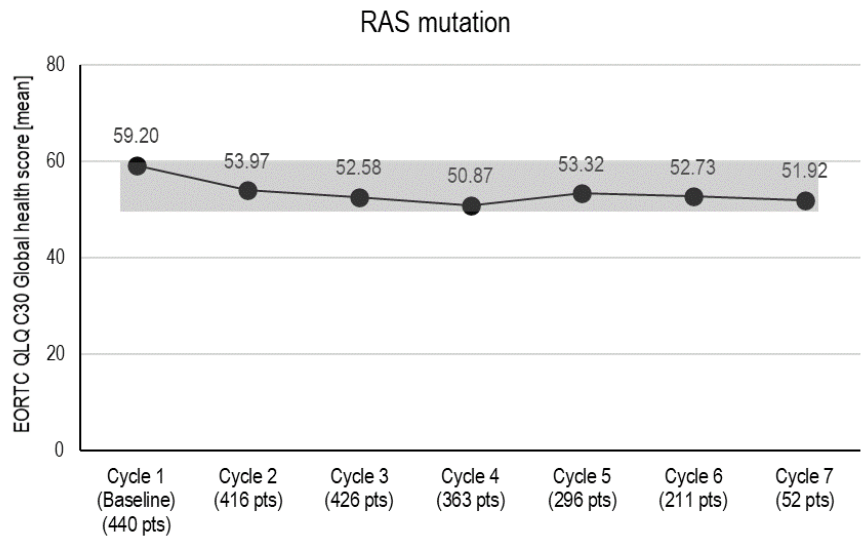
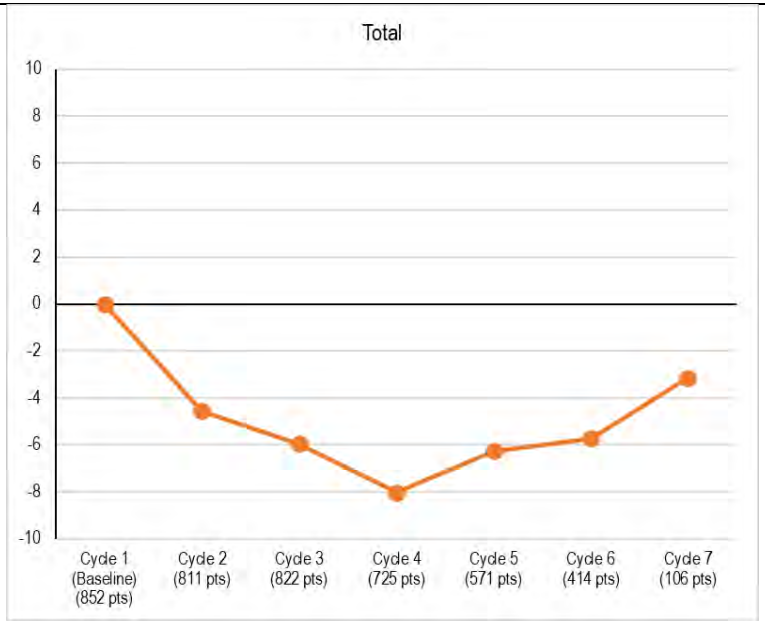
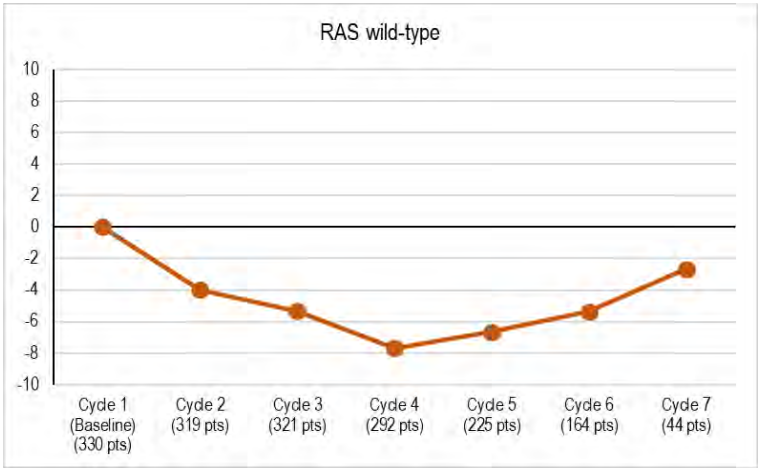


Figure 4: Course of mean global health status/QoL during the first 7 aflibercept-cycles [mean values +/- 95% CI] (data source: Table 10 of QoLiTrap_Final Analysis_2020-08-26)

Calculation of the change for each mean value from baseline value, which was taken as 0, is shown in Figure 5. Neither for total PES set nor for RAS wild-type or RAS mutation a clinically meaningful decline of -10 points from baseline was observed.


Total
10
8
6
4
2
0
-2
-4
-6
-8
-10
Cycle 1 (Baseline) (852 pts)
Cycle 2 (811 pts)
Cycle 3 (822 pts)
Cycle 4 (725 pts)
Cycle 5 (571 pts)
Cycle 6 (414 pts)
Cycle 7 (106 pts)


RAS wild-type
10
8
6
4
2
0
-2
-4
-6
-8
-10
Cycle 1 (Baseline) (330 pts)
Cycle 2 (319 pts)
Cycle 3 (321 pts)
Cycle 4 (292 pts)
Cycle 5 (225 pts)
Cycle 6 (164 pts)
Cycle 7 (44 pts)

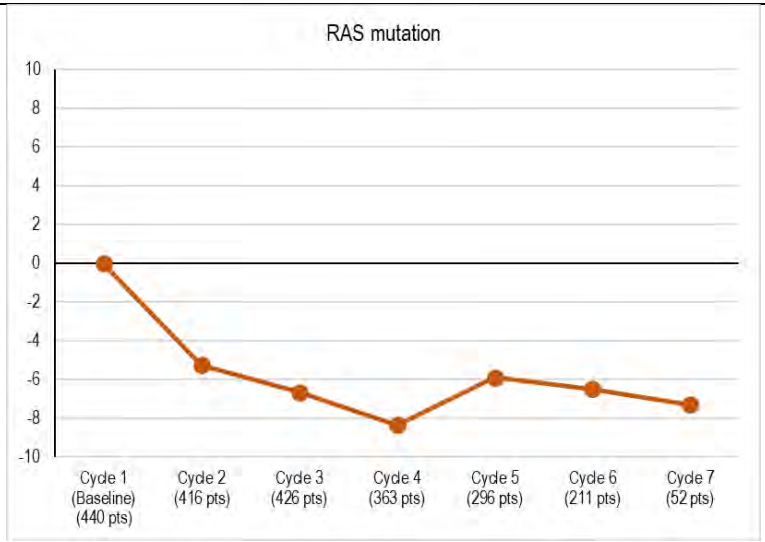


Figure 5: Course of change of global health status/QoL of mean values to baseline during the first 7 aflibercept-cycles (data source: Table 10 of QoLiTrap_Final Analysis_2020-08-26)

Mean change of global health status/QoL within the first 12 weeks was calculated by taking the mean of all evaluable EORTC questionnaires after baseline and within the defined time period for each patient and computing the difference in percent to baseline value. The mean change amounted to -4.60% for total PES patients. Patients with RAS mutation had a greater decline than patients with RAS wild-type, -6.05% and -3.39%, respectively. However, patients with RAS mutation started from a slightly higher mean baseline value than RAS wild-type patients, 59.2 and 58.2, respectively. Nearly stable global health status/QoL was observed for subgroups 'pretreatment with aVEGF/R + aEGFR' and 'aflibercept administered as >3rd line', with positive mean change of 1.45% and 0.01%, respectively. Highest percentage decrease in mean global health status/QoL was -23.89% for subgroup 'aflibercept administered as non-determinable Line' (Table 22).

Changes of functional scales within the first 12 weeks of aflibercept therapy are given in Table 23. An overview of mean change of functional scales within the first 12 weeks is shown in Figure 6. Except for 'emotional functioning' which increased within the observed time period thus representing a higher / healthier level of functioning, all other functioning

scales decreased. Highest decrease in mean change was seen for 'role functioning'. Patients with RAS mutation had greater mean changes of functional scales, positive as well as negative, compared to RAS wild-type.

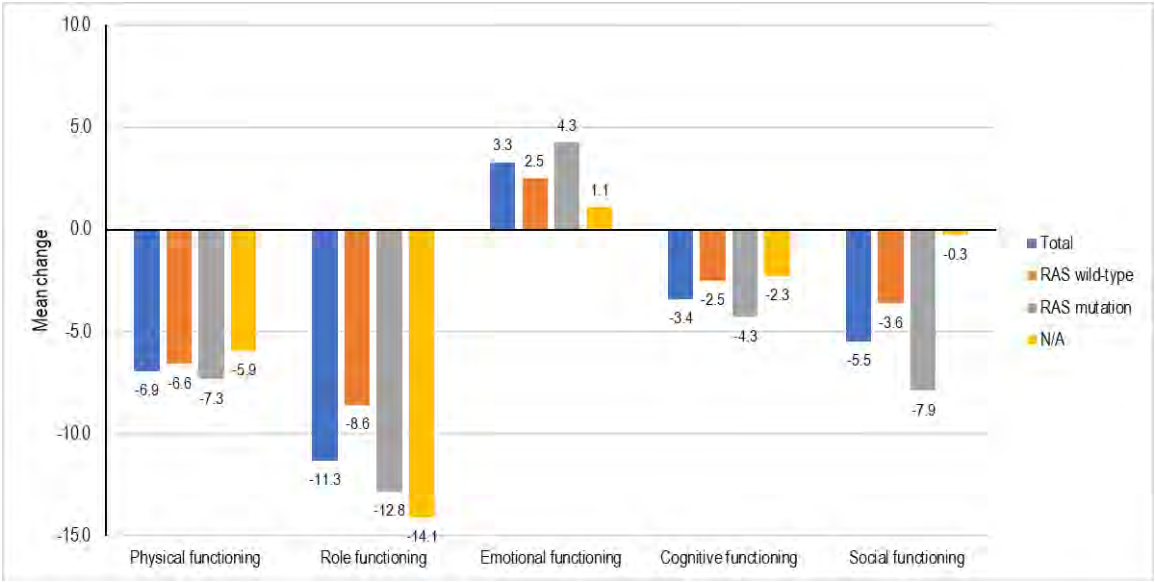


Figure 6: Mean change of functional scales of EORTC-QLQ-C30 within the first 12 weeks stratified by RAS mutation) (data source: Table 26 of QoLiTrap_Final Analysis_2020-08-26)

Additionally, the EORTC QLQ-C30 deals with 9 symptoms which are relevant for cancer patient. Table 24 gives a tabular overview of changes of symptom scales within the first 12 weeks of aflibercept therapy. Increasing scores represent deterioration of the respective symptom. An overview of mean change of the symptoms is presented in Figure 7. Six symptoms showed a deterioration, namely fatigue, nausea+vomiting, pain, dyspnea, appetite loss and diarrhea, with fatigue having the greatest worsening and diarrhea having the slightest deterioration. An improvement was noted for the other three symptoms with the greatest enhancement for constipation. Patients with RAS mutation had greater deterioration of fatigue and higher improvement of constipation than RAS wild-type patients, whereas latter ones showed greater deterioration of pain and appetite loss and greater improvement of sleep disturbances and financial impact than patients with RAS mutation.

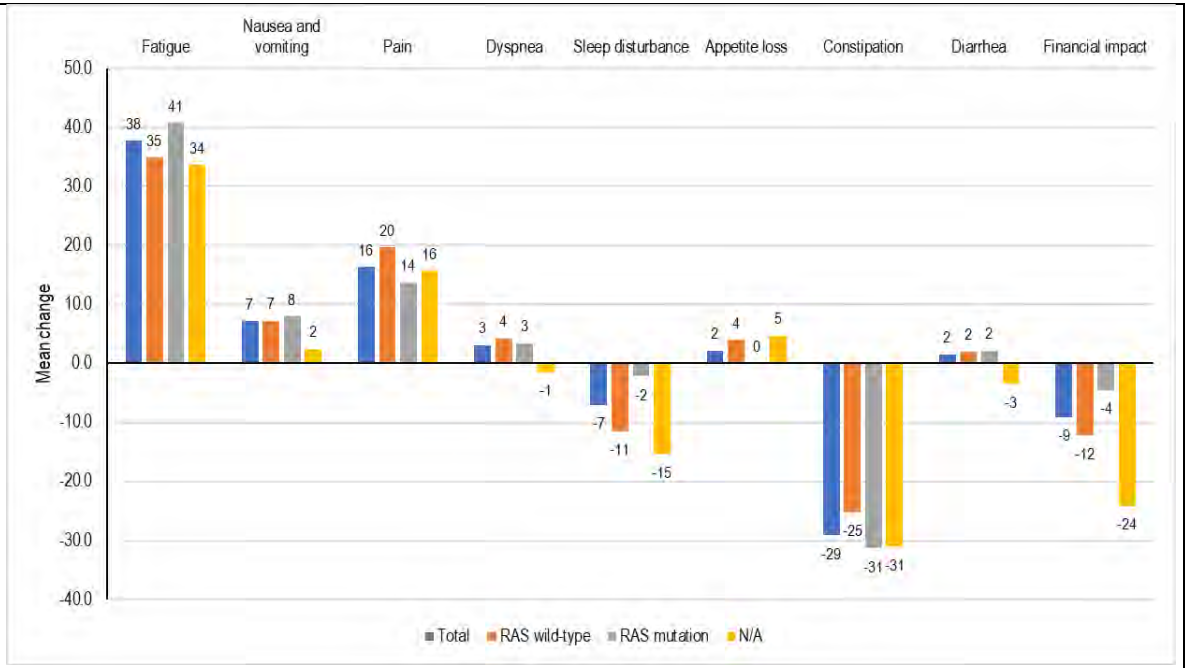


Figure 7: Mean change of symptom scales of EORTC-QLQ-C30 within the first 12 weeks stratified by RAS mutation) (data source: Table 34 of QoLiTrap_Final Analysis_2020-08-26)

To determine factors which might influence improvement of global health status/QoL, defined as increase by ≥1 point(s), the following parameters were analyzed: Disease control (yes, no, no imaging), Responder (yes, no, no imaging), hematological toxicity (yes, no), non-hematological toxicity (yes, no), pre-existing symptoms (yes, no, unknown), age (<60 years, ≥60 years), and ECOG (<2, ≥2, unknown). Table 7 gives an overview of change of global health with respect to the above listed parameters.

Table 7: Impact of selected variables on Change of global health status/QoL [%] within the first 12 weeks (data source: Table 42 of QoLiTrap_Final Analysis_2020-08-26)

Change of global health with respect to		N	Mean	95% CI lower	95% CI upper	Std	Median	Min	Max	NMiss
Disease control	Yes*	330	-2.69	-7.93	2.55	48.37	-9.72	-89.06	388.89	13
	No	206	-2.79	-9.04	3.45	45.47	-8.33	-77.92	311.11	4
	No imaging	301	-7.93	-12.55	-3.32	40.69	-12.50	-100.00	360.00	18
Responder	Yes**	122	-5.00	-12.52	2.52	41.97	-11.11	-89.06	277.78	1
	No	414	-2.06	-6.77	2.64	48.71	-8.45	-77.92	388.89	16
	No imaging	301	-7.93	-12.55	-3.32	40.69	-12.50	-100.00	360.00	18
Hematological toxicity	No	693	-4.53	-7.87	-1.19	44.78	-10.94	-100.00	360.00	29
	Yes	144	-4.96	-12.60	2.69	46.42	-6.25	-75.00	388.89	6
Non-hematological toxicity	No	397	-4.49	-8.22	-0.76	37.77	-8.33	-100.00	277.78	11
	Yes	440	-4.70	-9.46	0.05	50.75	-13.89	-89.06	388.89	24
Pre-existing symptoms	No	249	-7.96	-12.56	-3.35	36.89	-10.94	-100.00	266.67	8
	Yes	566	-3.05	-7.05	0.96	48.54	-10.00	-89.06	388.89	27
	Unknown	22	-6.67	-21.11	7.78	32.58	-9.52	-51.11	86.67	0
Age [years]	<60	229	-5.21	-10.64	0.23	41.73	-12.50	-100.00	266.67	12
	≥60	608	-4.37	-8.06	-0.69	46.25	-9.86	-89.06	388.89	23
ECOG	<2	733	-6.01	-9.23	-2.79	44.38	-11.11	-100.00	388.89	28
	≥2	33	5.44	-14.16	25.04	55.28	-0.00	-66.67	200.00	4

	Unknown	71	5.27	-5.48	16.03	45.44	-2.86	-57.50	206.25	3
Total		**837**	**-4.60**	**-7.66**	**-1.55**	**45.03**	**-10.00**	**-100.00**	**388.89**	**35**

* Patients with CR+PR+SD as best response / ** Patients with CR+PR as best response

Univariate logistic regression analysis (Type 3) yielded p-values for each analyzed parameter of <.0001, except for 'non-hematological toxicity' for which a p-value of 0.2232 was calculated. Further analysis showed that responders, patients with hematological toxicity and with ECOG ≥2 had a higher odds, whereas patients being ≥60 years old, patients with non-hematological toxicity and patients with pre-existing symptoms have a lower odds to achieve improvement of global health (Table 8).

Table 8: Univariate logistic regression- Improvement of global health- Estimates and Odds ratio (data source: Table 44 of QoLiTrap_Final Analysis_2020-08-26)

Univariate logistic regression- Estimates and Odds ratio	Parameter vs. reference value	Estimate (parameter)	Standard error	p-value	Odds ratio (parameter vs. reference)	CI 95%
Responder	Yes vs. no	0.4524	0.0872	<.0001	2.471	1.76 - 3.48
Hematological toxicity	Yes vs. no	0.6657	0.0715	<.0001	3.786	2.86 - 5.01
Non-hematological toxicity	Yes vs. no	-0.0826	0.0678	0.2232	0.848	0.65 - 1.11
Pre-existing symptoms	Yes vs. no	-0.8437	0.0885	<.0001	0.929	0.68 - 1.27
	Unknown vs. no	1.6135	0.1552	<.0001	10.841	6.35 - 18.51
Age	≥60 years vs. <60 years	-0.3286	0.0686	<.0001	0.518	0.40 - 0.68
ECOG	≥2 vs. <2	0.9271	0.2041	<.0001	6.566	4.11 - 10.48
	Unknown vs. <2	0.0276	0.1974	0.8889	2.671	1.73 - 4.12

In stepwise multivariate analysis (entry level: p=0.5, stay level: p=0.1), hematological toxicity and ECOG remained as factors which influence improvement of global health (Table 9).

Table 9: Stepwise multivariate logistic regression- Improvement of global health- Final model- Estimates and Odds ratio (Observations read: 872, Observations used: 553) (data source: Table 46 of QoLiTrap_Final Analysis_2020-08-26)

Multivariate logistic regression- Estimates and Odds ratio	Parameter vs. reference value	Estimate (parameter)	Standard error	p-value	Odds ratio (parameter vs. reference)	CI 95%
Hematological toxicity	Yes vs. no	0.2668	0.1028	0.0095	1.705	1.14 - 2.55
ECOG	≥2 vs. <2	0.8562	0.2771	0.0020	4.942	2.60 - 9.41
	Unknown vs. <2	-0.1146	0.2629	0.6628	1.872	1.06 - 3.31

Other analyses:

Key secondary objectives

Key secondary objectives included the evaluation of progression-free survival (PFS), response rate (RR), overall survival (OS) and safety.

(a) Progression-free survival (PES set):

PFS was calculated in the overall PES dataset and by subgroups. Patients known to have a progression but without progression date as well as patients known to have died but without death date were excluded from the analysis. A compilation of PFS data is given in Table 25.

Median PFS values were 8.8, 9.4, 8.1 and 12.7 months for total PES set, RAS wild-type, RAS mutation and RAS N/A, respectively. RAS wild-type and RAS mutant patients showed overlapping CI 95%, thus median PFS was not significantly different between the 2 subgroups. Between patients with RAS mutation and RAS N/A no overlapping CI 95% were observed, showing a significant difference (Figure 8, Table 25).

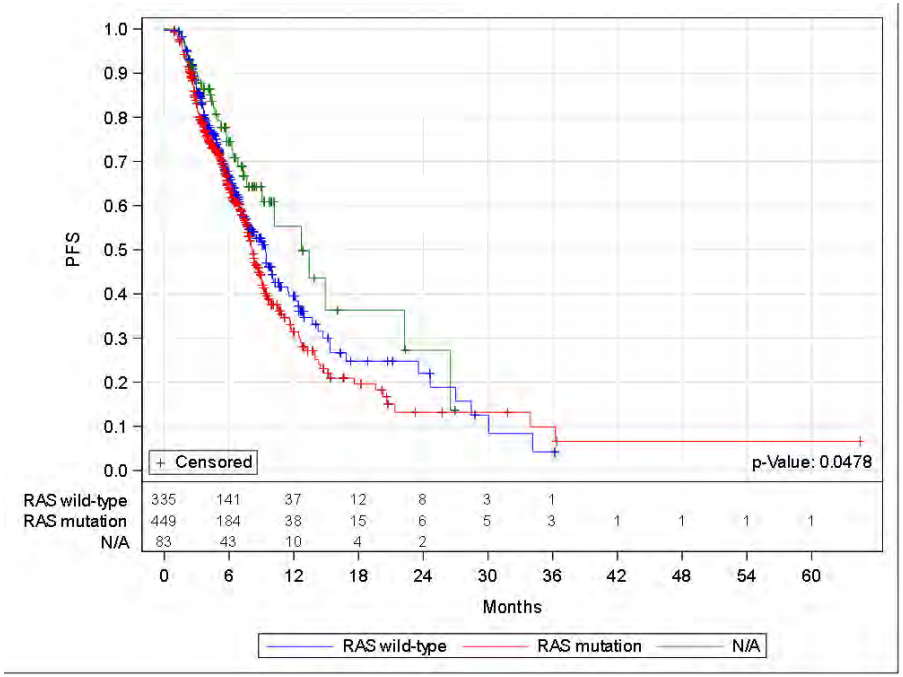


Figure 8: PFS stratified by RAS status (data source: Figure 1 of QoLiTrap_Final Analysis_2020-08-26)

Stratification according to gender, hypertension (yes/no) or age groups did not result in statistically different median PFS between subgroups.

Statistically significant differences in median PFS were observed according to type of prior targeted therapy and line of aflibercept therapy.
Patients pretreated with aEGFR and those without prior targeted therapy had higher median PFS, 12.9 months and 11.7 months, respectively, than the other subgroups. Lowest median PFS (6.9 months) was seen for patients receiving prior combination of aVEGF/R + aEGFR. Subgroups of patients having 'no prior targeted therapy' and those having prior 'aEGFR' had significantly longer PFS values than subgroups of patients with prior 'aVEGF/R' and those with prior 'aVEGF/R + aEGFR', due to non-overlapping CI 95% (Figure 9, Table 25).

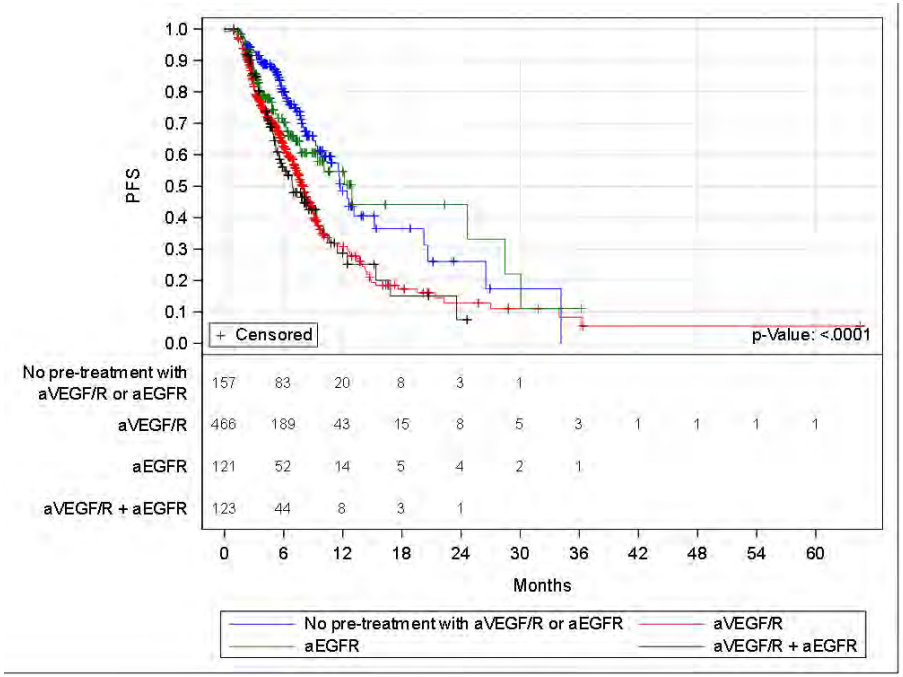


Figure 9: PFS stratified by prior targeted therapy (data source: Figure 6 of QoLiTrap_Final Analysis_2020-08-26)

Patients who received aflibercept as 1st line therapy had the highest median PFS (13.1 months) and this was significantly different from other groups since there was no overlapping CI 95% (Figure 10, Table 25).

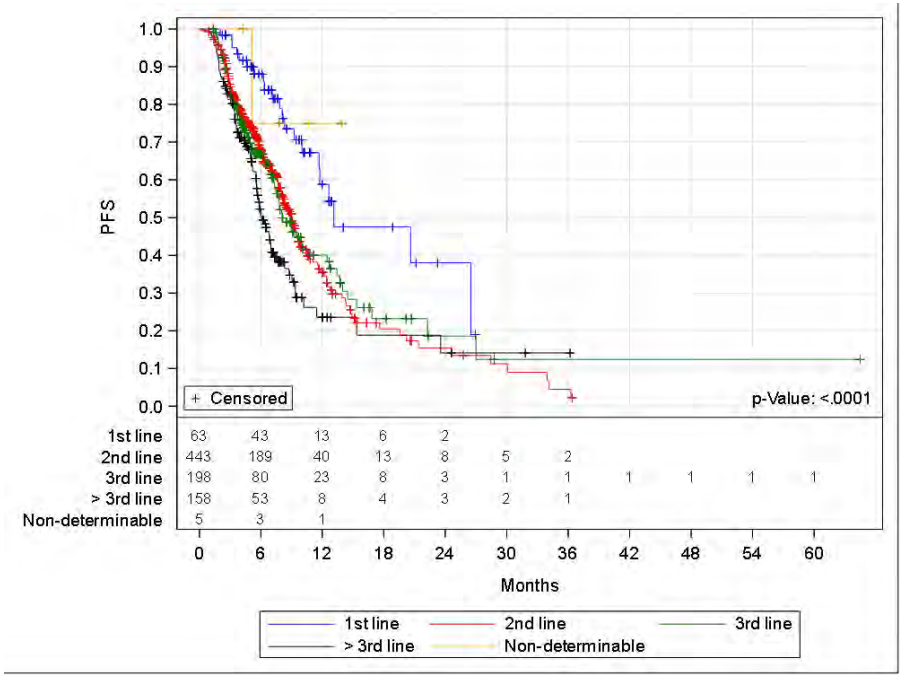


Figure 10: PFS stratified by line of treatment (data source: Figure 8 of QoLiTrap_Final Analysis_2020-08-26)

(b) Overall survival (PES set):

OS was calculated for PES set in total and for subgroups. Patients known to have died but without death date were excluded from the analysis. A total of 869 patients was included in the analysis. A compilation of OS data for total and subgroups is given in Table 26.

Median OS was 19.5, 23.6, 18.1 and 22.3 months for overall PES set, RAS wild-type, RAS mutation and RAS N/A, respectively. All subgroups showed overlapping CI 95%, thus median OS was not significantly different (Figure 11, Table 26).

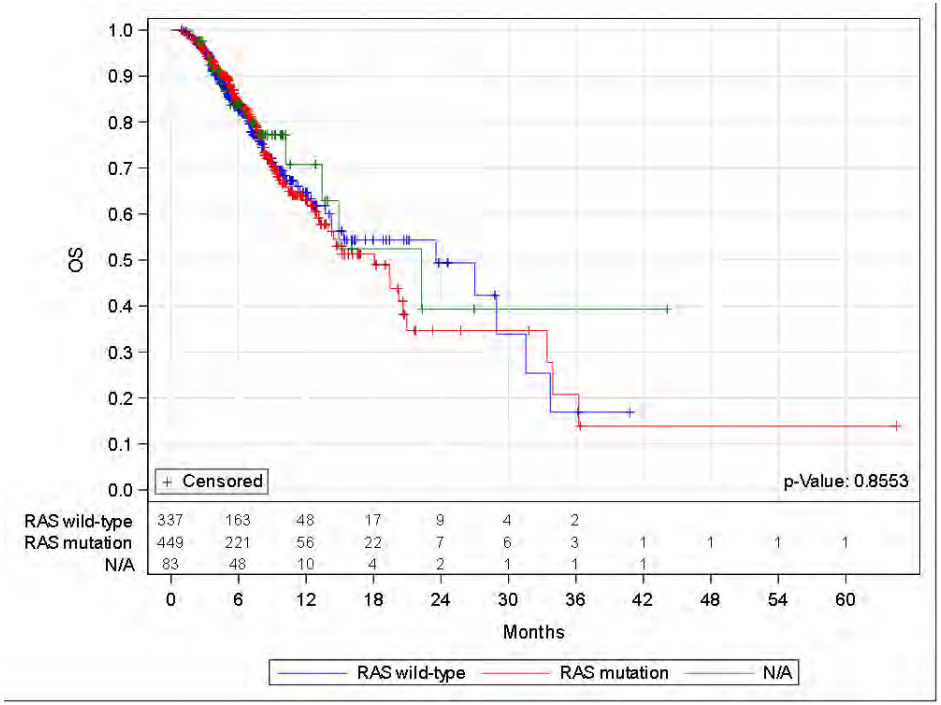


Figure 11: OS stratified by RAS status (data source: Figure 9 of QoLiTrap_Final Analysis_2020-08-26)

No statistically significant differences according to gender, hypertension and age groups were observed. However, median OS was higher for patients ≤65 years versus those >65 years, 22.3 and 14.7 months, respectively, and for patients ≤70 years versus those >70 years, 19.5 and 14.4 months, respectively (Table 26).

Significant differences in OS were observed according to type of prior targeted therapy,median OS being lowest for patients having received prior aVEGF/R + aEGFR and highest for those previously treated with aEGFR-, 11.5 months and 29.0 months, respectively (Figure 12,Table 26).

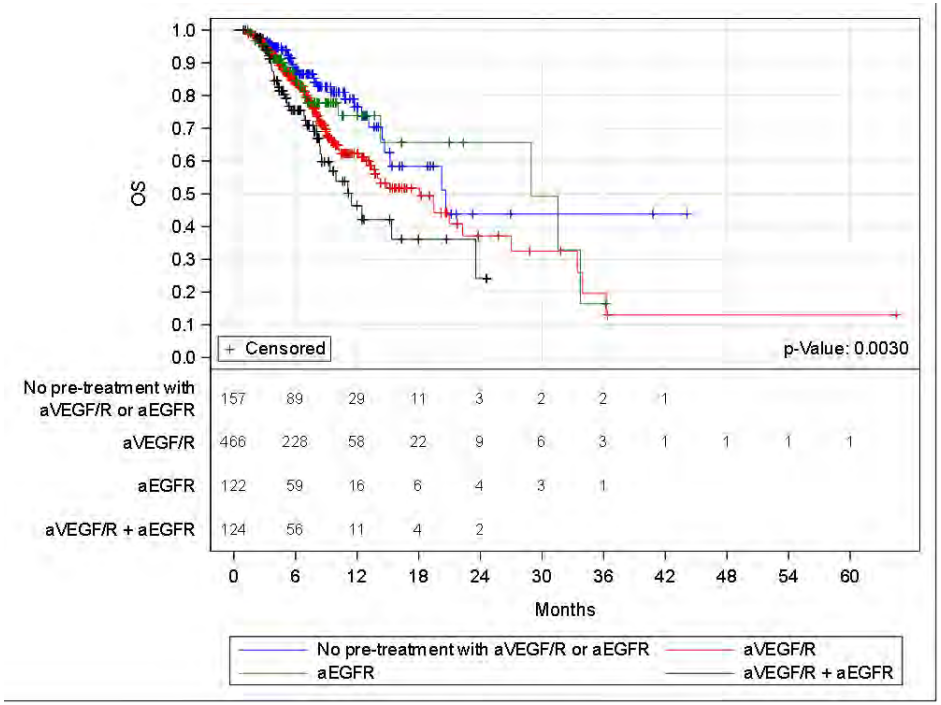


Figure 12: OS stratified by pretreatment (data source: Figure 14 of QoLiTrap_Final Analysis_2020-08-26)

Regarding stratification by line of aflibercept treatment, median OS was 19.4, 14.0 and 15.4 months for patients treated in 2nd line, 3rd line and >3rd line, respectively (Figure 13, Table 26). Median OS was not evaluable for patients treated in first line.

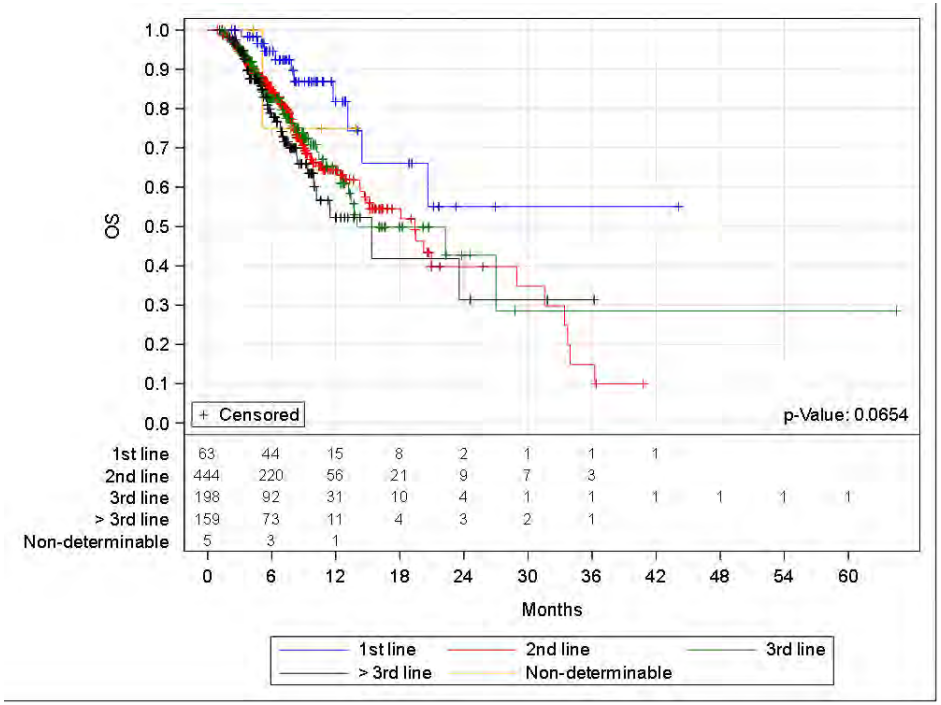


Figure 13: OS stratified by line of treatment (data source: Figure 16 of QoLiTrap_Final Analysis_2020-08-26)

(c) Response rate (PES set):

For determination of response rate, only patients with documented imaging results (CR, PR, SD, progression, non-evaluable) according to investigator's assessment were taken into account. Overall, 553 patients (63.4%) of PES set were evaluable. Of them, 123 patients (22%) had a documented best response of CR or PR (Table 27). Highest RR was observed for 1st line treatment with aflibercept and lowest for >3rd line treatment, 35% and 13%, respectively.

(d) Progression-free survival (ITT set):

PFS was also evaluated for ITT patients according to the type of prior targeted agent. A total of 1187 patients received a prior therapy during metastatic stage. More than 50% were pretreated with aVEGF/R only (Table 10).

Table 10: Patients with prior palliative therapy or prior therapy during metastatic stage (data source: Table 73 of QoLiTrap_Final Analysis_2020-08-26)

	N	%
Prior palliative therapy or prior therapy during metastatic stage with aEGFR only	168	14.15
Prior palliative therapy or prior therapy during metastatic stage with aVEGF/R and aEGFR	193	16.26
Prior palliative therapy or prior therapy during metastatic stage with aVEGF/R only	688	57.96
Prior palliative therapy or prior therapy during metastatic stage with other drugs only	138	11.63
Total	**1187**	**100.00**

Of these 1187 patients, 1175 patients were evaluable for PFS analysis. Median PFS (CI 95%) was 7.3 (6.28- 7.93), 9.4 (6.48- 12.93), 6.4 (5.20- 8.09) and 9.0 months (7.66- 11.97) for patients pretreated with aVEGF/R only, aEGFR only, aVEGF/R + aEGFR and other drugs, respectively (Figure 14, Table 28).

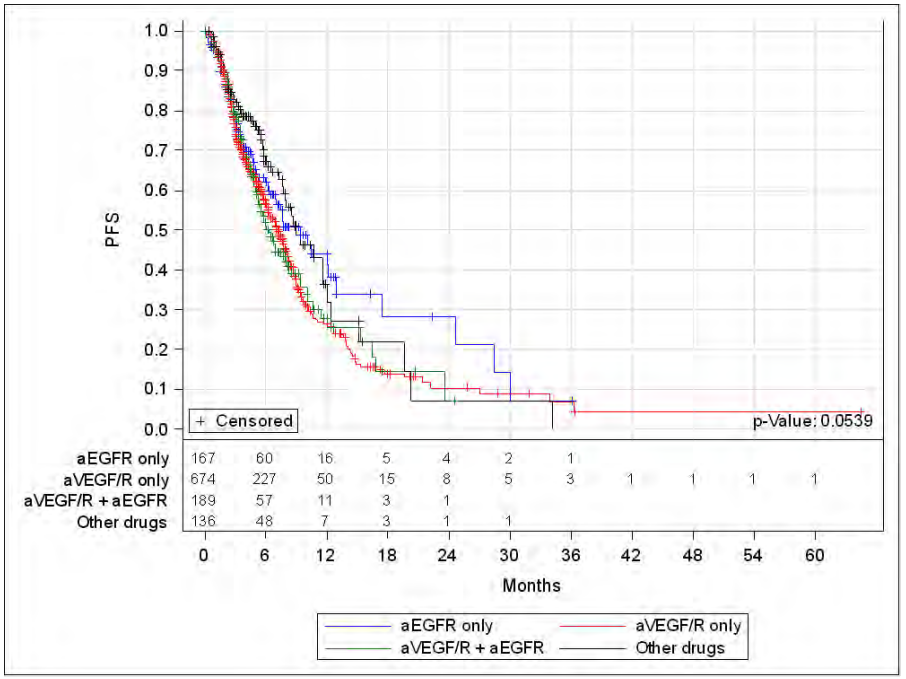


Figure 14: PFS stratified by prior palliative therapy or prior therapy during metastatic stage (data source: Figure 19 of QoLiTrap_Final Analysis_2020-08-26)

Excluding patients who received other drug as prior therapy, calculation of the p-value between the 3 remaining groups yielded 0.1764, thus no statistically significant difference in median PFS was observed for the differently pretreated subgroups (Table 28).

(e) Best response, Response rate and Disease control rate (ITT set):

Tumor response as assessed by the investigator was documented for 674 patients (52.8%) of ITT set. Best response in overall population as well as according to RAS status and line of aflibercept therapy is shown in Figure 15.

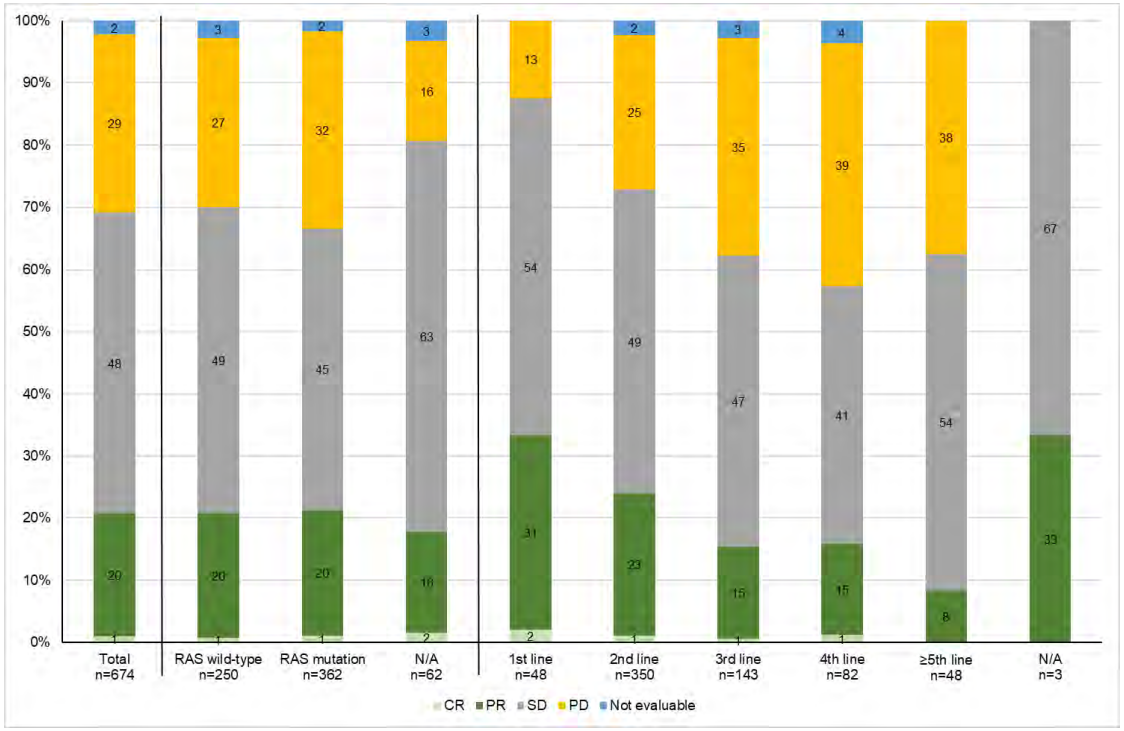


Figure 15: Percentage of patients with CR, PR, SD, PD and not evaluable as Best Response (data source: Tables 263, 264 of QoLiTrap_Final Analysis_2020-08-26)

Response rate (RR) was 20.8%, 20.8%, 21.3 and 17.7% for Total, RAS wild-type, RAS mutation and RAS N/A, respectively. Disease control rate (DCR, defined as percentage of patients with CR, PR and SD) yielded 70.0%, 69.1%, 66.6% and 80.6% for Total, RAS wild-type, RAS mutation and RAS N/A, respectively.

Regarding line of aflibercept therapy, RR declined with increasing line of treatment: 33.3%, 24.0%, 15.4%, 15.9% and 8.3% for 1st line, 2nd line, 3rd line, 4th line, and ≥5th line, respectively. The same was seen for disease control rate (DCR) with 87.5%, 72.9%, 62.2%, 57.3% and 62.5% for 1st line, 2nd line, 3rd line, 4th line, and ≥5th line, respectively.

Focusing exclusively on patients pretreated with aVEGF/R and/or aEGFR, 560 patients were evaluable for analysis. Best response is shown in Figure 16. RR and DCR were nearly in the same range as seen before for Total and according to RAS status: RR was 19.1%, 20.3%, 19.0% and 14.0%, and DCR was 66.6%, 68.9%, 63.4% and 76.7% for Total, RAS wild-type, RAS mutation and RAS N/A, respectively.

RR decreased with the line of aflibercept treatment reaching 23.1%, 16.1%, 16.0%, and 8.3% for 2nd line, 3rd line, 4th line, and ≥5th line, respectively. DCR was 71.4%, 63.5%, 56.8% and 62.5% for 2nd line, 3rd line, 4th line, and ≥5th line, respectively.

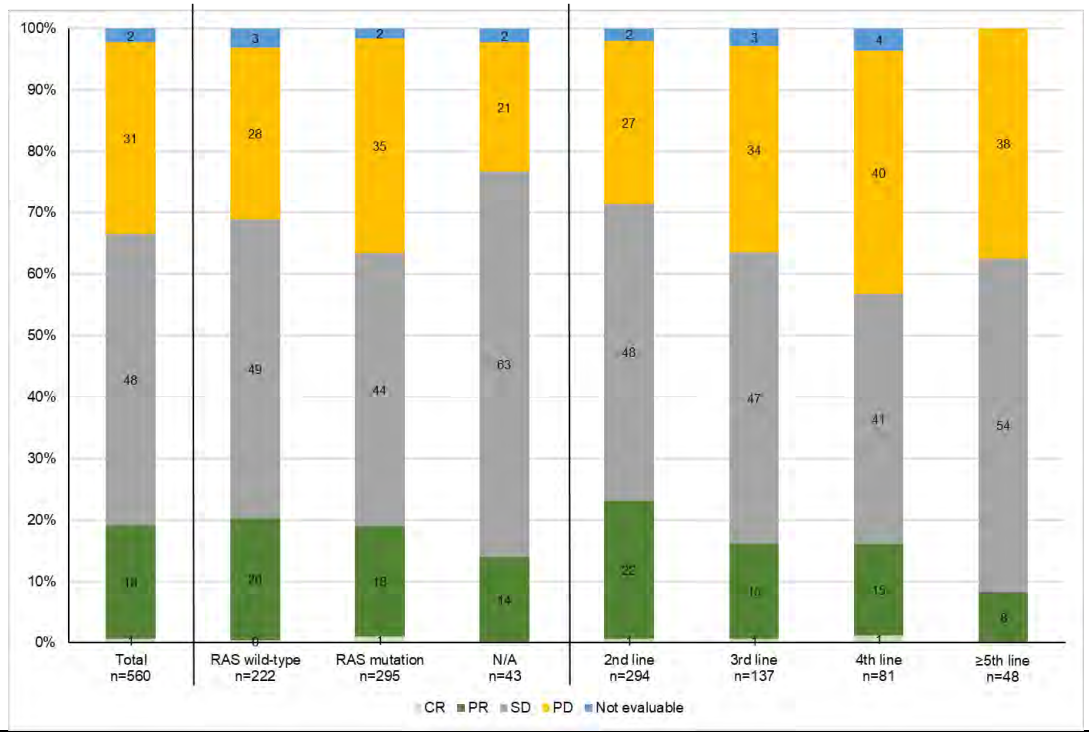


Figure 16: Best response of aVEGF/R and aEGFR pretreated patients [percentage of patients] (data source: Table 65 of QoLiTrap_Final Analysis_2020-08-26)

Taking into account the sidedness of the tumor location (right or left) for the patients pretreated with aVEGF/R and/or aEGFR, 542 patients were evaluable. RR and DCR were comparable for right- or left-sided tumors (Figure 17). RR was 19.6%, 20.7% and 19.1% and DCR was 67.4%, 66.7% and 67.6% for Total, right- and left-sided, respectively.

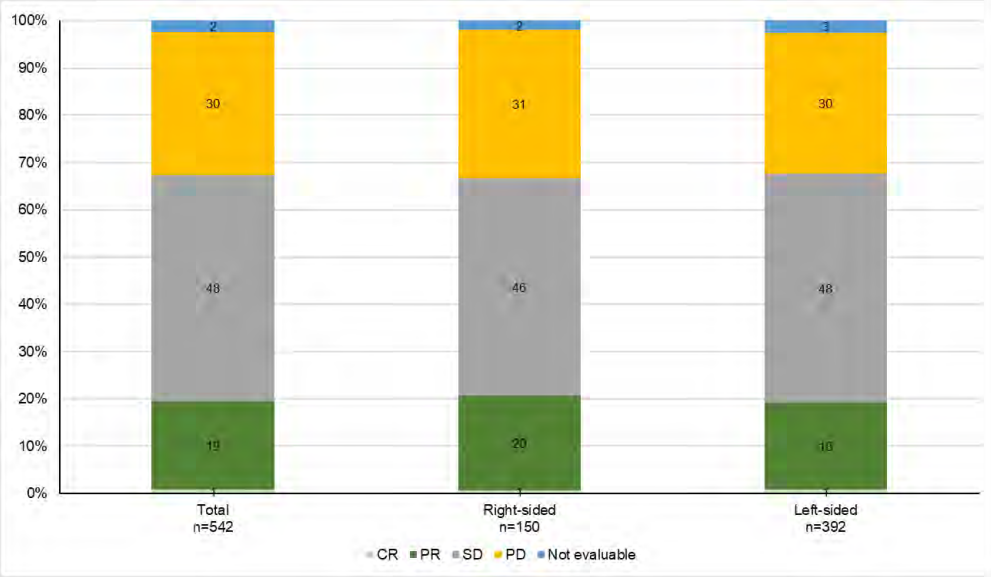


Figure 17: Best response of aVEGF/R and aEGFR pretreated patients with documented side of tumor location [percentage of patients] (data source: Table 66 of QoLiTrap_Final Analysis_2020-08-26)
Location right: Colon right (Cecum / Colon ascendens / Flexura coli dextra) and/or Transversum right and/or Transversum left and/or Transversum not further specified.
Location left: Colon left (Flexura coli sinistra / Colon descendens / Sigmoid), Rectosigmoid, Rectum

A compilation of data for best response, RR and DCR according to therapy line, tumor location and RAS status are presented in Table 29. There is a hint that patients with left-sided tumor have slightly better RR and DCR, however due to small number in right-sided stratification groups results should be interpreted with caution.

Additionally, RR was evaluated according to type of prior targeted therapy for the ITT set. Highest response rate (23.7%) was observed for patients with prior therapy with aEGFR only (Table 11).

Table 11: Patients with prior palliative therapy or prior therapy during metastatic stage – RR (data source: Table 74 of QoLiTrap_Final Analysis_2020-08-26)

Response rate	*CR+PR*		*No CR+PR*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
Prior palliative therapy or prior therapy during metastatic stage with aEGFR only	22	23.66	71	76.34	**93**	**100.00**
Prior palliative therapy or prior therapy during metastatic stage with aVEGF/R and aEGFR	12	13.19	79	86.81	**91**	**100.00**
Prior palliative therapy or prior therapy during metastatic stage with aVEGF/R only	73	19.41	303	80.59	**376**	**100.00**
Total	107	19.11	453	80.89	**560**	**100.00**

(f) Safety (ITT set):

Safety analysis was based on the AE-database of Sanofi. Due to regulatory reasons, centers in Germany and Austria had to report all AEs irrespective of causality whereas centers in Switzerland only had to report AEs with causal relationship to aflibercept.

A total of 5360 adverse events (AEs) was reported by 1056 patients of ITT set (82.7%). For 221 patients (17.3%) no adverse events were reported.
113 patients (10.7%) reported an AE of special interest, which was defined as thromboembolic event, peripheral motor neuropathy, peripheral sensory neuropathy and reversible posterior leukoencephalopathy syndrome.

The majority of AEs belonged to ‘Gastrointestinal disorders’ and ‘General disorders and administration site conditions’ with 1586 AEs and 648 AEs, respectively. The most frequently reported event were diarrhea with 12.0%, followed by

	nausea (5.3%). All other events occurred in less than 5% of cases (Table 30). More than 70% of AEs was not related to aflibercept, 26.6% of AEs were assessed by the investigator as related to aflibercept (Figure 18). Most AEs were of grade 1/2. Overall 173 patients (13.5%) developed grade 5 adverse events which were related to 'neoplasm progression' in 38 patients,(3.0%). Most common adverse events were diarrhea (34.2%), nausea (17.9%), stomatitis and fatigue (17.2% each) and hypertension (11.6%) (Table 31, AEs with highest percentages are marked grey). Summary of AEs occurring in more than 5% of patients is presented in Table 32. Most common ≥grade 3 adverse events were hypertension, diarrhea and general physical health deterioration with 9.24%, 6.73% and 4.86%, respectively. For more than 60% of AEs no action was taken regarding aflibercept and for 33% of AEs aflibercept was withdrawn. In 43% of patients, adverse events recovered/resolved, in 25% of patients, outcome was 'unknown'. 16% of patients had a fatal outcome (Figure 20). 23% of AEs (1233 / 5360) fulfilled seriousness criteria according to investigator's assessment; 43.8% of patients (559 / 1277) reported at least 1 SAE. Most frequently reported SAEs (>5%) were 'diarrhea' and 'general physical health deterioration' with 5.8% and 5.3%, respectively (Table 33, SAEs with highest percentages are marked grey). Reason for classification as serious was mainly 'hospitalization / prolongation of hospitalization' (69%), 'death' and 'important medical event' (14% each) (Figure 21). 21% of SAEs were assessed as related to aflibercept by the investigator. Regarding 'action taken', aflibercept was withdrawn for 54% of SAEs; no change of aflibercept administration was reported for 41% of SAEs. No 'Suspected Unexpected Serious Adverse Reactions' occurred.
Discussions:	<u>a) Key results</u> Between September 2013 and September 2019, 1293 patients with mCRC were enrolled by 210 sites in Germany, Austria and Switzerland and were treated with aflibercept according to licensed indication. There were no specifications concerning inclusion of patients or diagnostic and therapeutic measures, physicians could follow normal daily routine. However, patients were asked to fill in the EORTC QLQ-C30 before each cycle of treatment. 1277 of enrolled patients had received at least one cycle of aflibercept + FOLFIRI and were thus evaluable for analysis of therapy and safety data (ITT set). 872 patients of ITT set had filled in at least the baseline and 2 additional EORTC QLQ-C30 questionnaires in the first 12 weeks and were thus evaluable for analysis of primary endpoint (PES). Since no data on biological markers such as RAS status were available for aflibercept to determine the impact of RAS mutation on aflibercept treatment and on quality of life, there was an amendment to the observational plan which included the documentation of the RAS status. In each analysis set, ITT and PES; demographic patient data and tumor data were nearly the same: about 2/3 of patients were male; in median, patients were 66 years old. About 85% of patients had an ECOG of 0-1 at study enrollment. Nearly 70% of patients suffered from concomitant diseases, mainly cardiovascular disorders (about 50%).

	More than 80% of patients had prior surgery, and prior therapy had been administered to 90% of patients. Previous aVEGF/R treatment was administered to more than 50% of patients. Current RAS status of mCRC was 51% RAS mutation and 39% RAS wild-type. More than 60% of patients had distant metastases, primarily liver (>53%) and lung (>17%). Location of the tumor was mainly left-sided (about 70%). A total of 10,197 therapy cycles was documented, of these 83% contained the approved combination of aflibercept with Irinotecan, 5-Fluorouracil, Folinic acid. In 11% of cycles, aflibercept was given in combination with Irinotecan and Folinic acid only and as monotherapy in 1.4% of cycles. Study treatment was administered for a median of 12 weeks. Median number of cycles received was 6 (min: 1 cycle, max: 66 cycles). Main reason for therapy termination was disease progression, followed by adverse event / toxicity and patient's request with for 44.2%, 21.2% and 14.4%, respectively. No differences were observed between RAS wild-type and RAS mutant patients. Primary endpoint was the percentage of patients whose Global health status/QoL was either improved or reduced by less than 5% during treatment with aflibercept over the 12-week observation period. Overall, 40.3% of patients had a global QoL improved or decreased by less than 5%, 55.7% of patients showed a decrease of ≥5%. Stratification according to RAS-status, gender, age groups, pretreatment with aVEGF/R or EGFR, hypertension and line of study treatment showed that a greater percentage of patients with RAS-mutation as well as female patients or older patients had a global QoL improved or reduced by less than 5% as compared to patients with RAS wild-type, men and younger patients. Lowest percentage of patients with a global QoL either improved or decreased by less than 5% (34%) was seen for EGFR-pretreated patients. Course of mean global health status was evaluated for the first 7 cycles; for this analysis, the mean of all evaluable EORTC questionnaires for each point in time was calculated. Neither for total PES set nor for RAS wild-type or RAS mutation a clinically meaningful decline of 10 points from baseline was observed. The mean change of Global health status/QoL within the first 12 weeks amounted to -4.60% for total PES patients. Patients with RAS mutation had a greater decline than patients with RAS wild-type, -6.05% and -3.39%, respectively. However, patients with RAS mutation started from a slightly higher mean baseline value than RAS wild-type patients, 59.2 and 58.2, respectively. To determine factors which might influence improvement of global health status/QoL, defined as increase by ≥1 point(s), the following parameters were analyzed: disease control (yes, no, no imaging), responder (yes, no, no imaging), hematological toxicity (yes, no), non-hematological toxicity (yes, no), pre-existing symptoms (yes, no, unknown), age (<60 years, ≥60 years), and ECOG (<2, ≥2, unknown). Univariate and stepwise multivariate logistic regression analysis concluded that hematological toxicity (yes vs no) and ECOG (≥2 vs. <2) were independent factors influencing improvement of global health. Overall, there was a decrease in mean values of functional scales of EORTC QLQ-C30 questionnaire within the first 12 weeks of aflibercept therapy, with the exception of 'emotional functioning' which improved within the observed time period. Highest decrease/worsening in mean change was seen for 'role functioning'. Patients with RAS mutation had greater mean changes of functional scales, positive as well as negative, compared to RAS wild-type. Regarding cancer symptoms, six symptoms showed a deterioration, namely fatigue, nausea+vomiting, pain, dyspnea, appetite loss and

	diarrhea, with fatigue having the greatest worsening and diarrhea having the slightest deterioration. An improvement was noted for the other three symptoms with the greatest enhancement for constipation. Patients with RAS mutation had greater deterioration of fatigue and higher improvement of constipation than RAS wild-type patients. RAS wild-type patients showed a greater deterioration of pain and appetite loss and greater improvement of sleep disturbances and financial impact than patients with RAS mutation. PFS, RR / DCR, and OS were analyzed as secondary outcome objectives for PES and ITT set. For analysis of RR as well as DCR results of imaging assessment according to investigator's evaluation were considered. No specifications regarding time point or method for response evaluation were given in the observational plan. Median PFS (CI 95%) was 8.8 (8.03- 9.44), 9.4 (7.63- 10.10), 8.1 (7.66- 8.98) and 12.7 (9.05- 22.27) months in overall l PES set, RAS wild-type, RAS mutation and RAS N/A, respectively. RAS wild-type and RAS mutant patients showed overlapping CI 95%, thus median PFS was not significantly different between the 2 subgroups. Statistically significant differences were observed for stratification according to pretreatment and to line of aflibercept therapy. Patients pretreated with aEGFR and those without pretreatment with aVEGF/R or aEGFR had higher median PFS (CI 95%), 12.9 (7.66- 28.45) months and 11.7 (10.00- 20.23) months, respectively, versus patients receiving prior combination of aVEGF/R + aEGFR or aVEGF/R with median PFS of 6.9 (5.53- 9.38) and 8.0 (7.30- 8.75) months, respectively. Significant differences (p=<0.0001) were seen between subgroups 'no pretreatment with aVEGF/R or aEGFR' and subgroups 'aVEGF/R' or 'aVEGF/R + aEGFR', due to non-overlapping CI 95%. Stratification according to line of aflibercept treatment, showed median PFS (CI 95%) of 13.1 (11.68- not reached), 9.0 (8.09- 9.84), 8.1 (7.34- 10.63) and 6.1 (5.56- 7.01) months for 1st line, 2nd line, 3rd line and >3rd line, respectively. Patients who received aflibercept as 1st line therapy did not show overlapping CI 95% with the other subgroups, indicating a statistically significant difference (p= <0.0001). Median OS reached 19.5, 23.6, 18.1 and 22.3 months for evaluable PES set, RAS wild-type, RAS mutation and RAS N/A, respectively, with no statistically significant difference. Stratification according to pretreatment showed statistically significant results for OS, with lowest median OS for patients having received pretreatment with aVEGF/R + aEGFR and highest median OS for those with aEGFR-pretreatment, 11.5 months and 29.0 months, respectively (p= 0.0030). In addition to analysis of PES set, PFS was evaluated for ITT patients who received prior therapy, resulting in a total of 1187 evaluable patients. Median PFS (CI 95%) was 7.3 (6.28- 7.93), 9.4 (6.48- 12.93), 6.4 (5.20- 8.09) and 9.0 (7.66- 11.97) months for patients pretreated with aVEGF/R only, aEGFR only, aVEGF/R + aEGFR and 'other drugs', respectively. Observed differences were not statistically significant. Regarding evaluation of RR and DCR, evaluable patients of PES and ITT set were reduced by high number of missing results of imaging assessment. Only 553 patients of PES set (63.4%) and 674 patients of ITT set (52.8%) could be included in the analysis.

	Best response of CR or PR was documented for 123 patients of evaluable PES set, accounting for a RR of 22%. RAS status did not have an impact on RR. Regarding stratification according to pretreatment with aVEGF/R or aEGFR and line of aflibercept treatment, greatest differences in RR was observed for patients without pretreatment and lowest for patients pretreated with aVEGF/R + aEGFR, 32% and 13%, respectively, and for 1st line treatment and >3rd line treatment, 35% and 13%, respectively. RR of evaluable ITT patients amounted to 20.8%, 20.8%, 21.3 and 17.7% foroverall ITT population, RAS wild-type, RAS mutation and RAS N/A, respectively. DCR was 70.0%, 69.1%, 66.6% and 80.6% for overall ITT population RAS wild-type, RAS mutation and RAS N/A, respectively. No influence of RAS status could be observed. RR declined with increasing line of treatment: 33.3%, 24.0%, 15.4%, 15.9% and 8.3% for 1st line, 2nd line, 3rd line, 4th line, and ≥5th line, respectively. The same was seen for DCR with 87.5%, 72.9%, 62.2%, 57.3% and 62.5% for 1st line, 2nd line, 3rd line, 4th line, and ≥5th line, respectively. In the ITT population, 560 patients pretreated with aVEGF/R and/ or aEGFR, were evaluable. RR and DCR in RAS wild type and RAS mutant patients were comparable to the overall ITT population: RR was 19.1%, 20.3%, 19.0% and 14.0%, and DCR was 66.6%, 68.9%, 63.4% and 76.7% for overall ITT population, RAS wild-type, RAS mutation and RAS N/A, respectively. RR and DCR declined with line of treatment. Considering the sidedness of the tumor location (right or left) for the ITT patients pretreated with aVEGF/R and/or aEGFR, 542 patients were evaluable. RR and DCR were almost comparable for right- or left-sided tumors: RR was 19.6%, 20.7% and 19.1% and DCR was 67.4%, 66.7% and 67.6% for overall ITT, right- and left-sided, respectively. There is a trend that patients with left-sided tumor had slightly better RR and DCR, however due to small number in right-sided stratification groups results should be interpreted with caution. Evaluation of RR according to pretreatment yielded 23.7%, 19.4% and 13.2% for patients with prior therapy of aEGFR only, aVEGF/R only and aVEGF/R + aEGFR, respectively. Safety analysis was based on the AE-database of Sanofi. Due to regulatory reasons, centers in Germany and Austria had to report all AEs irrespective of causality whereas centers in Switzerland only had to report AEs with causal relationship to aflibercept. A total of 5360 adverse events (AEs) was reported by 1056 patients of ITT set (82.7%). For 221 patients (17.3%) no adverse events were reported. 113 patients (10.7%) reported an AE of special interest, which was defined as thromboembolic event, peripheral motor neuropathy, peripheral sensory neuropathy and reversible posterior leukoencephalopathy syndrome. Most AEs belonged to organ class 'Gastrointestinal disorders' and 'General disorders and administration site conditions' with 1586 AEs and 648 AEs, respectively. The most frequent reported event was diarrhea with 12.0%, followed by nausea (5.3%). All other events occurred in less than 5% of cases.

	Most of AEs were of grade 1/2. 173 patients (13.5%) developed grade 5, which were related to 'neoplasm progression' in 38 patients (3.0%). Most common adverse events were diarrhea (34.2%), nausea (17.9%), stomatitis and fatigue (17.2% each) and hypertension (11.6%). The majority of AEs (>70%) was not related to aflibercept and 26.6% of AEs were assessed by the investigator as related to aflibercept. No action regarding aflibercept administration was taken in more than 60% of AEs and for 33% of AEs aflibercept was withdrawn. Overall, AEs recovered in 43% of patients, 25% of patients had an 'unknown' outcome and 16% had a fatal outcome. 23% of AEs (1233 / 5360) fulfilled seriousness criteria according to investigator's assessment and 43.8% of patients (559 /1277) reported at least 1 SAE. Most frequently reported SAEs (>5%) were 'diarrhea' and 'general physical health deterioration' with 5.8% and 5.3%, respectively. Reason for classification as serious was mainly 'hospitalization / prolongation of hospitalization' (69%), followed by 'death' and 'important medical event' (14% each). 21% of SAEs were assessed as related to aflibercept by the investigator. Regarding 'action taken', aflibercept was withdrawn for 54% of SAEs; no change of aflibercept administration was reported for 41% of SAEs. No 'Suspected Unexpected Serious Adverse Reactions' occurred. <u>b) Interpretation and Generalizability</u> In contrast to clinical trials which include highly selected patients, observational studies include less selected patients which are older and have associated comorbidities, thus reflecting better general population. Demographic data of patients enrolled in this study were in line with general patient population suffering from mCRC, which encompass mainly patients with a median age >68 years (Oppelt KA, et al. 2019). As expected, median age of 66.0 (min:28.0, max:90.0) years of patients included in this study was greater than in VELOUR randomized clinical trial (median 61 years, range 21-82) which was the basis for regulatory approval of aflibercept + FOLFIRI (Velour study; Van Cutsem E, et al. 2012). Accordingly, percentage of age groups ≥65 years and ≥75 years was greater in this observational study (56% and 8%, respectively) than in the Velour trial (28% and 5.4%, respectively). Patients of this study were also older than patients enrolled in another observational study evaluating safety and effectiveness of FOLFIRI + aflibercept (OZONE study; Chau I, et al. 2020) in which median age was 64 (min:26.0, max:88.0) years. Patients in the present study had also a worse ECOG than in the Velour and OZONE studies with about 85%, 97% and 95% of patients having an ECOG of 0-1, respectively. Regarding RAS status, about 39% and 51% of patients were RAS wild-type and mutant, respectively; this is similar to the KRAS status in the OZONE study (35% wild-type and 52% mutant). Patients in this study received in median less treatment cycles than patients in the OZONE study, with 6 (min:1, max:66) and 7 (min:1, max:46) cycles, respectively. For the Velour study, a median of 9 cycles was recorded for patients in the aflibercept arm. Median duration of study therapy was 12 weeks (min:0, max:170) in QoLiTrap versus 16

	weeks (min.2, max:108) in OZONE observational study. No influence of RAS status on treatment was observed in this study. Regarding primary endpoint, 40.3% of evaluable patients had global health status either improved or decreased by less than 5%) during treatment with aflibercept over the 12-week observation period. This value is lower than the expected 50% to 65% after a 12-week observation period as stated in the observational plan. This may be due to the fact that the study enrolled patients treated in third, fourth and > fifth line setting. Slightly greater percentage of global health score improved or reduced by less than 5% was observed in RAS mutant patients, female patients and older patients. In contrast to this, patients with RAS mutation had a greater percentage decline than patients with RAS wild-type, -6.05% and -3.39%, respectively. Diagram of mean global health status/QoL during the first 7 aflibercept-cycles showed a similar course for total PES set and RAS wild-type, with a decrease up to cycle 4 and an increase afterwards; RAS mutant subgroup showed an additional decrease after to cycle 5. However, no clinically significant decrease by 10 points was observed. A similar course of global health status/QoL was seen in the Italian cohort of the ASQoP observational study, which focused on safety and health-related quality of life. However mean values in the ASQoP study were higher (between 60 and 70 points) than in Qolitrap (between 50 and 60). This may be due to lower median age of patients (63.0 years) and better performance status with nearly 100% of patients having an ECOG of 0-1 compared to patients in this study (Pastorino A, et al. 2018). Regarding PFS and OS, median time for both parameters was higher in this study than observed for the aflibercept - arm of Velour study. Median PFS and OS in QoLitrap were 8.8 and 19.5 months versus 6.9 and 13.5 months in Velour study (Van Cutsem E, et al. 2012). Considering only patients receiving aflibercept + FOLFIRI in 2nd line in QoLiTrap (in order to have a more reliable comparison with Velour patients treated exclusively in second line), , median PFS and OS were 9.0 and 19.4 months, respectively. This probably reflects the fact that management of mCRC has improved since VELOUR study with more life-extending therapies available. The improved outcomes observed in QoLitrap versus VELOUR may be unexpected, because patients enrolled into this observational study were not selected by several inclusion or exclusion criteria regarding e.g. concomitant diseases or pretreatment. Higher median PFS may be explained by that timing of visits and assessments as well as assessment methods were not prespecified. As such, PD might be detected later than in a clinical trial with timely and methodological specifications for tumor assessments. Higher median OS may be partly explained by long duration of this observational study, which allows documentation of date of death even years after documented end of aflibercept therapy; further, introduction of new therapy options (e.g. pembrolizumab) in the meantime may contribute to improved OS. Within this observational study an impact of pretreatment (aEGFR and/or aVEGF/R) and of line of aflibercept therapy on PFS and OS was observed. Patients without pretreatment with aVEGF/R or aEGFR and those with aEGFR pretreatment as well as patients receiving aflibercept in 1st line therapy had higher median PFS values than the other

	subgroups. Median OS was highest in subgroups for patients without pretreatment with aVEGF/R or aEGFR, those with aEGFR pretreatment and patients receiving aflibercept in 2nd line therapy. Gender, RAS status and age did not show an impact on either PFS or OS. Ruff P, et al. 2018, who performed an age-based analysis of the Velour study data also did not find an impact of age on OS. Additionally, influence of line of aflibercept + FOLFIRI treatment on efficacy is shown in another clinical trial in which the therapy was administered in >2nd line in patients with mCRC (Auvrey M, et al. 2020). Results for PFS, OS and response rate were worse compared to those in the Velour trial, in which treatment was given in 2nd line only. Auvrey M, et al. 2020, also demonstrated negative effect of prior bevacizumab on efficacy. These results, too, are in line with the findings of this observational study. Regarding best response, most patients in this observational study as well as in the Velour study had SD as best response, 48% and 66%, respectively. RR was slightly higher in this observational study than in the aflibercept arm of the Velour study, 20.8% and 19.8%, respectively. In general, the safety profile was in line with the known toxicities of aflibercept in combination with FOLFIRI. Percentage of patients who reported at least one AE of any grade amounted to 83%, 99% and 98% in the present study, the Velour study and the OZONE study, respectively. Most frequent reported AEs in this study, namely diarrhea, nausea, stomatitis, and hypertension, were also among the most often stated AEs in the Velour study and in the OZONE study (Van Cutsem E, et al. 2012; Chau I, et al. 2020). However, percentages in this study were lower than observed in VELOUR and OZONE. Partly, this could be an effect of the daily routine treatment documented in this study, in which investigators may not ask patients at each visit about potential AEs. On the other hand, this may be the consequence of the improved knowledge to treat AEs during aflibercept + FOLFIRI treatment. Furthermore, for 82 patients enrolled by Suisse sites, only ADRs related to aflibercept as per investigator judgment were reported. No new safety issues occurred.

Conclusions:	Given the effectiveness results of this non-interventional study, aflibercept + FOLFIRI can be considered as effective treatment for mCRC patients in daily routine, as per licensed modalities. Treatment efficacy was not influenced by gender, tumor sidness, RAS status and age. Additionally, no deleterious effect on quality of life was observed during for the first 7 cycles. In general, aflibercept + FOLFIRI was well tolerated. The safety profile reported in this study was in line with the known safety profile of aflibercept and FOLFIRI. No new safety signals were identified.
Date of report:	11-Dec-2020