POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS)

COMPOUND: ZALTRAP® (aflibercept or ziv-aflibercept in the US)

STUDY NUMBER: OBS13597

STUDY NAME: OZONE

The Study is conducted by Sanofi-Aventis group - 54. rue La Boétie 75008 - Paris, France, hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

Version Number:	1
Date:	04-Dec-2018

PASS Information

Title	Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS)
Version identifier of the final study report	1
Date of last version of the final study report	04-Dec-2018
EU PAS register number	ENCEPP/SDPP/4836
Active substance	Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents Aflibercept (or ziv-aflibercept in the US) ATC code: L01XX44
Medicinal product	ZALTRAP® 25 mg/mL concentrate for solution for infusion The recommended dose of ZALTRAP®, administered as an intravenous infusion over 1 hour, is 4 mg/Kg of body weight, followed by the FOLFIRI regimen, every 2 weeks.
Product reference	EU/1/12/814
Procedure number	EMEA/H/C/2532/MEA 002
Marketing authorization holder(s)	sanofi-aventis groupe 54, rue La Boétie 75008 Paris France
Joint PASS	No
Research question and objectives	• To describe long term safety, and clinical outcomes of the ZALTRAP® + FOLFIRI combination in patients treated in daily practice for a metastatic colorectal cancer (mCRC) after failure of an oxaliplatin-based regimen; • To assess safety and effectiveness of the ZALTRAP® + FOLFIRI combination in the following specific patient cohorts: - elderly patients (≥65 years old); - patients with renal or hepatic impairment (acknowledging the limits of irinotecan label); - non Caucasian patients; - number and type of prior anti-cancer therapy (eg, prior bevacizumab). • To describe utilization of health resources in patients treated with the ZALTRAP® and FOLFIRI combination.
Countries of study	Europe and US

Authors	Marina Celanovic Sanofi-aventis groupe 50 Binney Street Cambridge, MA 02142 - United States of America e-mail: marina.celanovic@sanofi.com Pascaline Picard Sanofi-aventis groupe 54, rue La Boétie 75008 Paris France e-mail:pascaline.picard-ext@sanofi.com Jesse Johnson Sanofi-aventis groupe 50 Binney Street Cambridge, MA 02142 - United States of America e-mail: jesse.johnson2@sanofi.com Juan Ramón Martínez Linical Spain C/ Rosa de Lima 1 bis - Edificio Alba 28290 Las Matas (Madrid) - Spain e-mail: juan.ramon.martinez@linical.com

Marketing authorization holder(s)

Marketing authorization holder(s)	sanofi-aventis groupe 54, rue La Boétie 75008 Paris France
MAH/MAH REPRESENTATIVE contact person	Lena Pedraut EU Oncology Regulatory Affairs Manager 1 Avenue Pierre Brossolette 91385 Chilly-Mazarin Tel: +33 1 60 49 53 79 e-mail: lena.pedraut@sanofi.com

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1 ABSTRACT

Title

Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS).

Date of abstract: 22-Oct-2018

Authors: Jesse Johnson (Sanofi-aventis groupe) and Juan Ramón Martínez (Linical, Spain)

Keywords

metastatic colorectal cancer, aflibercept, post-authorisation safety study, current clinical practice, observational

Rationale and background

For patients with metastatic colorectal cancer (mCRC) having failed a prior oxaliplatin-based regimen for first-line treatment of mCRC, the preferred treatment is an irinotecan based regimen (most often irinotecan combined with bolus/infusional 5-fluorouracil and leucovorin: FOLFIRI).

Following the European Medicines Agency (EMA) evaluation, Sanofi was requested to conduct a PASS in real life to assess safety and effectiveness of ZALTRAP® administered in the approved indication. The sponsor proposed to conduct an observational cohort non-comparative study, of which primary objective was to better characterize the safety and effectiveness of ZALTRAP® in the real life setting, particularly in subpopulations such as elderly patients or patients with hepatic or renal impairment (within the limits of the irinotecan label) or non-Caucasian patients. This study prospectively collected safety and effectiveness data in patients treated with ZALTRAP® in clinical practice.

Research question and objectives

Primary objective

- To describe long term safety, and clinical outcomes of the ZALTRAP® + FOLFIRI combination in patients treated in daily practice for a mCRC after failure of an oxaliplatin-based regimen.
- To assess safety of the ZALTRAP® + FOLFIRI combination in the following patient cohorts:
  - Elderly patients (≥65 years old);
  - Patients with renal or hepatic impairment (within the limits of irinotecan label);
  - Non Caucasian patients,
  - Number and type of prior anti-cancer therapy (eg, prior bevacizumab).

Secondary objectives

- To describe effectiveness of the ZALTRAP® + FOLFIRI combination (eg, progression free survival [PFS], overall survival [OS], response rate [RR]) in the following patient cohorts:
  - Elderly patients (≥65 years old);
  - Patients with renal or hepatic impairment (within the limits of irinotecan label);
  - Non Caucasian patients,
  - Number and type of prior anti-cancer therapy (eg, prior bevacizumab).
- To describe utilization of health resources in patients treated with the ZALTRAP® + FOLFIRI combination.

Study Design

This was a prospective, international, multicenter observational cohort non-comparative study. It included a cohort of patients treated with ZALTRAP® + FOLFIRI in the clinical setting (not as part of an interventional clinical trial) and followed for a maximum of 24 months after initiation of ZALTRAP®. The design of the study mirrored real life management of these patients. It was expected that collected data represent realistic characterization of the patient population treated with ZALTRAP® and a rational evaluation of clinical outcome measures related to effectiveness and safety as assessed by the physicians in routine clinical practice.

There was no fixed study visit schedule. The study visits occurred according to the treating physician's clinical practice and judgement. Physicians were asked to record data for study endpoint assessments every 3 months.

Setting

Site and patient selection: Oncologists and gastroenterologists with a recognized competency in oncology who prescribed ZALTRAP® + FOLFIRI after failure of an oxaliplatin-based regimen. The physicians were randomly selected based on physicians' lists in each participating countries. The random process was stratified on country-specific criteria in order to accurately reflect

routine clinical practices within each country. Each site which declined to participate was replaced by the following one selected by the same random selection process in the same country.

Patients enrolled in the study were selected among the patients for whom the physician decided to prescribe ZALTRAP® independently from study entry. Each physician included consecutive patients until the targeted number of patient in his/her country was reached. A screening form was implemented at each site to document the consecutive enrolment in order to help to limit bias related to physician-led patient selection, and captured why an eligible patient was not included.

Overall participation status: OZONE study was planned to involve approximately 750 patients in approximately 170 sites of 14 countries in Europe and the United States (US) during a recruitment period of 28 months.

Patients and study size, including dropouts

Patients, aged ≥18 years old who were planned to be treated with ZALTRAP® in combination with a 5FU plus irinotecan regimen (FOLFIRI) for mCRC after failure of an oxaliplatin based regimen (including bevacizumab pretreated patients). Patients for whom the treating physician decided to prescribe ZALTRAP® independently from entry into the study. Patient's availability of a written informed consent.

The study planned to enroll approximately 750 patients in 170 centers in 14 countries; within this population, it was expected to have:

- About 40% of patients in the elderly (≥65 years old) group,
- Around 10% to 15% of patients in the non-Caucasian group,
- Around 30% of patients in renal impairment group,
- Around 18% of patients in hepatic impairment group.

Variables and evaluation criteria

Safety:

Treatment emergent adverse events (TEAE), related TEAE and serious TEAE, serious related TEAE, TEAE leading to premature or permanent treatment discontinuation, TEAE leading to death.

Effectiveness:

Effectiveness variables included OS, PFS and objective response (OR)

OS was defined as the time interval from the date of 1st administration of ZALTRAP® or FOLFIRI to the date of death due to any cause.

PFS was defined as the time from the date of the 1st administration of ZALTRAP® or FOLFIRI to the date of tumor progression or death due to any cause, whichever came first.

Best overall response during treatment period, defined as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE).

All evaluations were performed according to the participating institutions practice and outcomes were based on the treating physician judgment.

Health resource utilization:

Emergency Room visits, cumulated length of stay (days) and type of hospitalization.

Source

Data collection: For each patient, the investigator entered the information requested by protocol in an electronic case report form (eCRF). Details on eCRF completion were explained to the investigator.

Safety data collection included all adverse events (AEs), regardless of seriousness or relationship to ZALTRAP® and/or FOLFIRI, spanning from the signature of the informed consent form through 30 days after the last administration of ZALTRAP® and/or FOLFIRI, recorded on the corresponding page(s) of the eCRF.

After this 30-day period only AEs (including serious AE [SAEs]) considered by the physician to be caused by ZALTRAP® and/or FOLFIRI with a reasonable possibility were collected.

Results

Overall participation status: The OZONE study included 766 treated patients from 11 countries in Europe and North America. Up to 84.3% of the treated patients were included in Europe and 15.7% were included in North America (United States and Puerto Rico).

Participation per period of the study: A total of 601 (78.5%) patients did not complete the 24 months follow-up. The main reason for not completing the 24 months follow-up was death reported in 558 (92.9%) patients.

Study population and exposure to study treatment: The treated patients were included from both genders: male (59.5%) and female (40.5%). Median age of patients was 64 years ranging from 26 to 88 years. Of the treated patients, 48.3% were ≥65 years old, 9.2% were non-Caucasian, 35.0% had renal impairment, and 19.6% had hepatic impairment, matching the protocol assumptions. ECOG PS was 0 or 1 for the vast majority of the patients (94.8%). Colon was the primary site for 73.5% of the patients and rectum for 25.6%. All patients had metastatic disease at baseline, 55.48% had more than 1 metastatic site; the most frequent metastatic sites were liver (67.5%) and lung (51.4%). Half of the patients (51.5%) had a KRAS mutated status. All treated patients were administered previous chemotherapy (97.8% including oxaliplatin), with 35% of them with more than one line for advanced disease. 58.6% of the patients had a prior exposure to bevacizumab.

In the overall population the median (Q1;Q3) duration of treatment was 16.4 (9.6-30.0) weeks. The median number of treatment cycles was 7 (4.0; 12.0) with median number of cycles with

aflibercept, irinotecan and 5-FU of 6 (3.0; 11.0), 6 (4.0; 12.0) and 6 (4.0; 12.0), respectively and relative dose intensities of 79.0% (63.8; 92.8), 81.4% (67.6; 93.8) and 82.9% (70.4; 94.5), respectively.

Primary objective:

During the study treatment period, almost every patient reported at least one TEAE (98.3%). Grade ≥3 TEAEs were reported in 523 patients (68.3%).TEAEs considered possibly related to the study medication were reported in 692 patients (90.3%). Serious TEAEs were reported in 334 patients (43.6%) and TEAEs leading to death, outside of a context of disease progression were reported in 14 patients (1.8%).

TEAEs most frequently reported were asthenic conditions (HLT) (58.4% of the patients) diarrhea (56.3%), stomatitis and ulceration (HLT) (39.3%), infections (SOC) (35.1%), nausea (33.4%), hemorrhage (grouped term) (29.5%), hypertension (grouped term) (29.1%), decreased appetite (22.7%), abdominal pain (21.7%) and vomiting (21.5%). Neutropenia was reported as a TEAE in 24.7% of patients, but there was no systemic collection of laboratory abnormalities in this study.

Corresponding Grade ≥3 TEAEs were reported in more than 5% of the patients for neutropenia as a TEAE (15.1%), asthenic conditions (HLT) (12.7%), hypertension (HLT) (10.3%), diarrhea (9.5%), infections (SOC) (9.0%) and stomatitis and ulceration (5.4%).

Other anti-VEGF class events were infrequent, with GI perforation reported in 0.9% of the patients (grouped term), GI fistula in 1.2%, fistula from other origin in 0.8%, osteonecrosis of the jaw in 0.4%, posterior reversible encephalopathy syndrome in 0.4%. Nephrotic syndrome was reported in one patient and no case of thrombotic microangiopathy was reported.

Overall serious TEAEs were reported in 334 patients (43.6%). The most frequently reported serious TEAEs were diarrhea (4.6%), general physical health deterioration (3.3%) and abdominal pain (2.9%). Possibly related serious TEAEs were reported in 185 patients (24.2%).

A total of 563 patients (73.5%) died at any time during the study. Of them, 530 patients (69.2%) died due to disease progression and 14 patients (1.8%) due to a TEAE not in relation with disease progression and 19 (2.5%) for reason “other”. Of the 14 patient who died due to a TEAE, 13 (1.7%) died within 30 days from the last dose of study treatment and the other one post 30 days after last dose. The most frequent TEAEs leading to death were infections (5 patients) and GI perforation (3 patients).

- Safety in the elderly population:

Among the 766 patients, 370 (48.3%) were aged 65 or more. All grades TEAEs were reported in 98.4% of the patients aged 65 or more and in 98.2% of the patients aged less than 65; with severe events (Grade ≥3) reported in 69.5% and 67.1% of the patients, respectively.

Only few TEAEs were more frequent (by ≥5%, all grade) in the elderly population. Asthenia and decreased appetite were more frequent: asthenia (all grade: 43.5% vs 35.9%; Grades ≥3: 11.9% vs 6.6%), decreased appetite (all grade: 25.4% vs 20.2%; Grades ≥3: 3.0% vs 2.5%).

Of importance for the elderly population, no increases by at least 5% in incidence were noted for diarrhea, dehydration, hemorrhages (grouped term), hypertension (grouped term) and renal failure events (grouped term).

- Safety in patients with impaired renal function at baseline

Among the 738 patients with renal status documented at baseline, 258 (34.9%) were reported with creatinine clearance ≤80 mL/min.

No TEAEs were more frequently (by ≥5%, all grade) reported in the patients with impaired renal function by comparison to these with normal renal function.

- Safety in patients with impaired liver function at baseline

Among the 657 patients with liver function documented at baseline, 129 (19.6%) had an impaired liver function (defined as, total bilirubin >UNL or AST or ALT >1.5 UNL).

At the SOC level, there was an excess in incidence (by ≥5%, all grade) for "any TEAE" in the patients with an impaired liver function for the Hepatobiliary disorders SOC, by comparison to the patients with normal liver function (11.6% vs 6.1%). This difference was not driven by any particular type of events.

At the PT level, all grades constipation was more frequent in patients with impaired liver function (23.3% vs 14.2%).

Hemorrhages, as a grouped term, were reported in more patients with impaired liver function population (all grades: 37.2% vs 30.1%; Grades ≥3: 5.5% vs 2.1%). The most frequent events were epistaxis (23.3% vs 18.9%) and hemorrhage of gastrointestinal origin (16.3% vs 12.1%).

- Safety in the non-Caucasian population

Among the 762 patients with race documented at baseline, only 70 (9.2%) were non-Caucasian.

By decreasing order of incidences, the following events were reported more frequently (by ≥5%, all grade) in the non-Caucasian population by comparison to the Caucasian population: nausea (41.4% vs 32.7%), vomiting (31.4% vs 20.7%), fatigue (31.4% vs 20.1%), abdominal pain (27.1% vs 21.2%), palmar-plantar erythrodysaesthesia syndrome (15.7% vs 6.1%), dehydration (14.3% vs 4.5%), cough (14.3% vs 5.8%), dizziness (11.4% vs 4.2%) and edema peripheral (11.4% vs 3.2%).

Hemorrhages (grouped term) and (hypertension, as grouped term) were reported less frequently in the non-Caucasian population than in the Caucasian population (20.0% vs 30.2% and 15.7% vs 30.5%, respectively).

Renal failure (grouped term) and proteinuria (grouped term) were reported at similar incidences in the non-Caucasian and Caucasian populations.

- Safety in patients with prior exposure to bevacizumab

Among the 766 patients treated in the study, 449 (58.6%) had a prior treatment with bevacizumab.

There were no flares in incidences of anti-VEGF class events. The only TEAE that was more frequently reported in patients who had a prior exposure to bevacizumab was fatigue (23.8% vs 17.0%, all grade).

Secondary objectives:

Overall survival

At the study cut-off date, 563/766 (73.5%) patients had died at any time during the study.

Median (95% CI) overall survival in the overall population was 12.45 (11.56; 13.63) months.

Multivariate analyses were performed for subgroups of interest, including age (<65 vs ≥65), renal function status (impaired function, yes vs no), hepatic function status (impaired function, yes vs no), race (Caucasian vs non Caucasian), and prior anticancer treatments (number of lines: 1 vs ≥2 and prior bevacizumab: yes vs no).

- OS by Age:

Median (95% CI) overall survival was 12.91 (11.56; 14.88) months in patients aged ≥65 years old and 11.96 (10.97; 13.63) months in patients aged less than 65 years old.

After adjustment on prognostic factors the estimated hazard ratio (95% CI) by multivariate analysis was 0.951(0.794; 1.139).

- OS by renal function status at baseline:

Median (95% CI) overall survival was 12.52 (11.56; 15.08) months in patient with impaired renal function at baseline and 12.09 (11.17; 13.63) months in patients with normal renal function at baseline.

After adjustment on prognostic factors the estimated hazard ratio (95% CI) by multivariate analysis was 0.908 (0.749; 1.000).

- OS by hepatic function status at baseline:

Median (95% CI) overall survival was 8.739 (6.834; 10.64) in patients with hepatic impairment and 13.67 (12.12; 15.05) months in patients without hepatic impairment.

After adjustment on prognostic factors, the estimated hazard ratio by multivariate analysis (95% CI) was 1.561 (1.255, 1.941), favoring the subgroup of patients with no hepatic impairment.

There was a higher proportion of patients with liver metastasis in the subgroup of patients with impaired hepatic function by comparison to patients without impaired hepatic function (79.8% vs 64.8%) and more patients with impaired hepatic function were metastatic at diagnosis (81.4% vs 66.7%).

- OS by Race:

Median (95% CI) overall survival was 12.12 (8.805; 14.39) months in non-Caucasian patients and 12.45 (11.47; 13.73) months in Caucasian patients.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.070 (0.789; 1.450).

- OS by number of prior lines of chemotherapy:

Median (95% CI) overall survival was 12.58 (11.37; 14.59) months in patients with >1 line of anti-cancer therapy and 12.16 (11.01; 13.67) in patients with 0-1 line of prior anti-cancer therapy.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.916 (0.764; 1.097).

- OS by prior bevacizumab:

Median (95% CI) overall survival was 10.61 (9.495; 11.73) months in patients with prior bevacizumab and 16.62 (14.09; 18.17) months in patients without prior bevacizumab.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.666 (1.379; 2.013), favoring the subgroup of patients without prior use of bevacizumab.

Progression free survival

A total of 669/766 (87.3%) patients had a PFS event at the study cut-off date. Median (95% CI) PFS was 6.078 (5.552; 6.669) months.

As for the OS, multivariate analyses were performed on the subgroups of interest which results are expressed below:

- PFS by Age:

Median (95% CI) progression free survival was 6.472 (5.684; 7.228) months in patients aged ≥65 years old and 5.552 (4.895; 6.275) months in patients aged less than 65 years old.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.871 (0.737; 1.028).

- PFS by renal function status at baseline:

Median (95% CI) progression free survival was 6.275 (5.618; 7.228) months in patients with renal impairment at baseline and 5.881 (5.158; 6.669) months in patients normal renal function at baseline.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.960 (0.806; 1.144).

- PFS by hepatic function status at baseline:

Median (95% CI) progression free survival was 4.402 (3.088; 5.585) months in patients with hepatic impairment and 6.275 (5.717; 6.998) months in patients without hepatic impairment.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.424 (1.160; 1.748), favoring the subgroup of patients with no hepatic impairment.

There was a higher proportion of patients with liver metastasis in the subgroup of patients with impaired hepatic function by comparison to patients without impaired hepatic function (79.8% vs 64.8%) and more patients with impaired hepatic function were metastatic at diagnosis (81.4% vs 66.7%).

- PFS by Race:

Median (95% CI) progression free survival was 4.402 (3.483; 6.834) months in non-Caucasian patients and 6.209 (5.618; 6.735) months in Caucasian patients.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.220 (0.924; 1.611).

- PFS by number of prior lines of chemotherapy:

Median (95% CI) progression free survival was 5.782 (5.224; 6.669) months in patients with >1 line of anti-cancer therapy and 6.275 (5.388; 7.129) in patients with 0-1 line of prior anti-cancer therapy.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.096 (0.927; 1.296).

- PFS by prior bevacizumab:

Median (95% CI) progression free survival was 5.224 (4.435; 5.782) months in patients with prior bevacizumab and 7.458 (6.275; 8.411) months in patients without prior bevacizumab.

After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.585 (1.333; 1.883), favoring the subgroup of patients without prior use of bevacizumab.

Overall response rate

Of the 766 patients included, 125 patients reported objective response (CR or PR) to treatment. Overall response rate (95% CI) was 16.3% (13.77%, 19.13%). Ten (1.3%) patients reported a complete response and 115 (15.0%) patients reported a partial response.

Stable disease was reported as the best response in 264 (34.5%) patients.

Progressive disease was reported as the best response in 260 (33.9%) patients.

As for OS and PFS endpoints, analyses of objective response were performed for each subgroup of interest. ORR was analyzed using a multivariate logistic model:

- Response rate by age: responders' rate (95% CI) was 11.51% (8.52%; 15.10%) in patients <65 years and 19.18% (15.27%; 23.60%) in patients ≥65 years, showing an odds ratio (95% CI) 1.842 (1.208; 2.810) after adjustment on pre-selected prognostic factors.

- Response rate by renal function status: responders' rate (95% CI) was 13.47% (10.53%; 16.88%) in patients without renal impairment and 19.37% (14.69%; 24.78%) responders in patients with renal impairment, showing an odds ratio (95% CI) of 1.517 (0.989; 2.328) after adjustment on pre-selected prognostic factors.
- Response rate by hepatic function status: responders' rate (95% CI) was 16.96% (13.83%; 20.47%) in patients without hepatic impairment and 10.85% (6.06%; 17.54%) responders in patients with hepatic impairment, showing an odds ratio (95% CI) of 0.625 (0.333; 1.173) after adjustment on pre-selected prognostic factors.
- Response rate by race: responders' rate (95% CI) was 15.4% (12.77%; 18.33%) in Caucasian patients and 14.29% (7.07%; 24.71%) responders in non-Caucasian patients, showing an odds ratio (95% CI) of 0.307 (0.007; 2.114) after adjustment on pre-selected prognostic factors.
- Response rate by number of prior lines of chemotherapy: responders' rate (95% CI) was 16.22% (12.46%; 20.59%) in patients with 0-1 line of anti-cancer therapy and 14.39% (11.16%; 18.13%) responders in patients with >1 line of anti-cancer therapy, showing an odds ratio (95% CI) of 0.998 (0.656; 1.520) after adjustment on pre-selected prognostic factors.
- Response rate by prior bevacizumab: responders' rate (95% CI) was 20.58% (16.22%; 25.50%) in patients without previous use of bevacizumab therapy and 11.46% (8.65%; 14.79%) responders in patients with previous use of bevacizumab therapy, showing an odds ratio (95% CI) of 0.511 (0.338; 0.775) after adjustment on pre-selected prognostic factors.

Discussion and interpretation

The OZONE study has compiled a large experience on the management of patients with metastatic colorectal cancer treated with the combination of aflibercept-irinotecan and 5-FU in daily clinical practice from 11 countries, with 84.3% of the treated patients recruited in Europe, and of these 57.5% recruited in Spain and France. 15.7% of the patients were included from North America.

In this prospective observational study, all patients, who, according to the treating physician's judgement, were eligible for a treatment with irinotecan/5-FU in combination with an anti-VEGF agent were proposed, in the absence of specific contra-indication to any of the 3 agents, to participate.

The patients were treated and monitored according to the local practice; the evaluation of the effectiveness of the treatment was performed according to the local practice/guidelines and the global evaluation made by the treating oncologist/physician.

The primary objective of this PASS study was to describe the safety of ZALTRAP® + FOLFIRI in patients treated in a daily practice. In particular safety was assessed in subgroups of interest, including elderly patients, patients with impaired renal function, patients with impaired hepatic function, non-Caucasian patients, patients with prior exposure to bevacizumab and patients with more than one prior line of chemotherapy.

Effectiveness was the secondary endpoint.

The patients in the OZONE study were older than in the VELOUR study (median 64 years, 48.3% aged 65 or more, vs median 61 years, 33.5% aged 65 or more).

A total of 766 patients were included and treated, 59.5% were male, only few of the patients had an ECOG PS at baseline of 2 or 3 (4.1%). The majority of the patients (73.5%) had a colon cancer; all patients had metastatic disease at baseline, with 55.4% of them with more than one metastatic site. All patients but 17 (2.2%), had a prior exposure to oxaliplatin. About half of the patients (51.5%) had a mutated KRAS status.

Of the treated patients, 48.3% were ≥65 years old, 9.2% were non-Caucasian, 35.0% had renal impairment, and 19.6% had hepatic impairment

Disease characteristics were not fundamentally different from the VELOUR study; however, as it could be expected (VELOUR was initiated in 2007), the 2 patient populations differed with regards to prior anti-cancer treatment. The proportion of patients who had neo/adjuvant chemotherapy and who had a prior exposure to bevacizumab was higher in OZONE (45.6% vs 26.5% and 58.6% vs 27.6%, respectively). The proportion of patients who had more than one line of chemotherapy was higher as well. Of note, KRAS status was not mandated in the VELOUR study, precluding any type of comparison between the 2 studies.

On the safety standpoint, 98.3% of the patients experienced at least one TEAE and 68.3% experienced at least one TEAE of Grade ≥3.

By decreasing order of frequency, the most frequent TEAEs (≥20%, all grades, regardless of relationship to study treatment) were asthenic conditions (HLT), diarrhea, stomatitis & ulceration (HLT), infection (SOC), nausea, hemorrhage (grouped term), hypertension (grouped term), decreased appetite , GI and abdominal pains (HLT), and vomiting .

For all grade events, and by comparison to the VELOUR study, hemorrhage, decreased appetite, dysphonia, hypertension, headache, diarrhea, stomatitis and ulceration and weight decrease were reported less frequently in the OZONE study, in a range spanning from 8 to 19% less. A similar trend was observed for the severe events (grade ≥3).

Anti-VEGF class effects, such as gastrointestinal perforation, gastrointestinal fistula, non-gastrointestinal fistula, osteonecrosis, wound healing disorders, nephrotic syndrome and reversible posterior leukoencephalopathy was uncommon and remained in the range of what was reported during the VELOUR study.

With all the usual limitation when comparing studies, several hypotheses can be formulated to explain this apparent more favorable safety profile reported in the OZONE study, including a shorter exposure (median of 7 treatment cycles vs 9 treatment cycles), a better knowledge of aflibercept in combination with irinotecan and 5-FU, and a greater experience in managing/preventing side effects. Overall, the safety profile of aflibercept in combination with aflibercept and 5-FU, as reported in the OZONE study, was consistent with that reported in the VELOUR study.

Importantly, no new safety signal emerged from the OZONE study.

Safety analyses by subgroup did not reveal major differences in the safety profile across age groups, renal status groups; and hepatic status groups. Prior treatment with bevacizumab did not negatively influence the safety profile of aflibercept.

Some differences were noted for the non-Caucasian population with some events (all grades) more frequently reported in the non-Caucasian population and others reported less frequently than in the Caucasian population. However, only70 non-Caucasian patients were evaluated and no firm conclusion can be made.

For the overall population the median overall survival was 12.45 months, the median PFS was 6.078 months and the overall response rate 16.3%. These results are consistent with these reported in the VELOUR pivotal study (median OS: 13.5 months, median PFS: 6.90 months and RR: 19.8%).

Of note, the proportion of patients in the OZONE study reported with stable disease as best response, was nearly half of that in the VELOUR study (34.5% vs 65.9%). A possible explanation to this notable difference might be in relation with the frequency of imaging in the VELOUR study (every 6 weeks), allowing more patients to have stable disease as best response than when performing imaging, as in real life practice, every 8 to 12 weeks.

After adjustment on prognostic factors, multivariate analysis of overall survival by subgroups showed no clinically meaningful differences between age groups, race groups, baseline renal function groups, and number of prior lines of chemotherapy group.

Median OS was shorter in patients with hepatic impairment than in patients without hepatic impairment (8.74 vs 13.67 months). The estimated HR by multivariate analysis (95% CI) was 1.424 (1.160; 1.748). In patients with hepatic impairment, the higher proportion of patients with liver metastasis (79.8% vs 64.8%), and the higher proportion of patients diagnosed with upfront metastatic disease (81.4% vs 66.7%) may have contributed to the observed numerical differences in median OS.

Median OS was longer in patients who had no prior treatment with bevacizumab (16.62 vs 10.61 months). The estimated HR by multivariate analysis (95% CI) was 1.666 (1.379; 2.013). In the VELOUR study the median OS in the subgroup of patients who had no prior exposure to bevacizumab was 13.9 months and 12.5 months in patients with prior exposure to bevacizumab, The same pattern for a numerical difference in the control group of the VELOUR study (FOLFIRI) was noted with median OS in the subgroup of patients who had no prior exposure to bevacizumab of 12.4 months and 11.7 months in patients with prior exposure to bevacizumab. In the absence of control in the OZONE study the results are difficult to interpret. A restriction of the use of anti-EGFR treatment to the wild KRAS population was implemented after the last patient completed treatment in the VELOUR study. This landmark change in the treatment of patients with mCRC may have contributed to this favorable 16.62 month median OS in the group of patients with no prior exposure to bevacizumab by selecting wild KRAS population for this subgroup.

In conclusion, the results of the OZONE study, conducted in real life conditions, and in a less selected population, do not contradict the results of the VELOUR pivotal study, and no new safety issue was noted.

Generalizability

The OZONE study has compiled a large experience on the management of metastatic colorectal cancer patients treated with aflibercept in combination with irinotecan and 5-FU in current clinical practice from 11 participating countries, complementing the pivotal phase 3 VELOUR study. On the safety standpoint results were consistent, in a less selected population, with these reported in the Phase 3 study. In many instances crude incidences of frequently reported TEAES (such as hemorrhage, decreased appetite, dysphonia, hypertension, headache, diarrhea, stomatitis and ulceration and weight decrease) were lower than those reported in the VELOUR study, possibly reflecting a lower exposure by comparison to VELOUR and an increasing knowledge of the management of the drug by the prescribing physicians. The less-frequent, however feared, anti-VEGF class adverse drug reaction, such as GI perforation, fistula, severe hemorrhage, posterior reversible encephalopathy syndrome, nephrotic syndrome or thrombotic microangiopathy, were not reported at clinically meaningful different incidences than in the VELOUR study. Importantly, no new safety signal was noted. With respect to generalizability, limitations persist for characterizing of the safety profile in certain subgroups of patients, such as non-Caucasian (70 patients) or patient with severely impaired organ functions.

Marketing Authorization Holder(s)

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
FRANCE

Study Personnel

The Company responsible medical officer's signed approvals of the report are provided in Annex 2.

This report was prepared by:

- Marina Celanovic, Clinical Study Director (Sanofi)
- Pascaline Picard, Statistician (mandated by Ividata)
- Sharifa Fidaly, Clinical Trial Operations Manager (Sanofi)
- Jesse Johnson, Medical Writer (Sanofi)
- Juan Ramón Martínez, Medical Writer (Linical)

The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

Names and affiliations of Principal Investigators

The list of investigators is provided in Annex 2.

National coordinators

Not applicable.

2 LIST OF ABBREVIATIONS

AE:	adverse event
CR:	complete response
CRC:	colorectal cancer
eCRF:	electronic case report form
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
FOLFIRI:	irinotecan + bolus/infusion 5-fluorouracil and leucovorin
ICF:	informed consent form
MAH:	marketing authorization holder
mCRC:	metastatic colorectal cancer
NE:	not evaluable
OS:	overall survival
PASS:	post-authorisation safety study
PFS:	progression free survival
PR:	partial response
RR:	response rate
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease
UPCR:	urine protein-to-creatinine ratio
US:	United States

3 INVESTIGATORS

Participating Investigators

The Investigators performed the study in accordance with the protocol, applicable local regulations and international guidelines.

The Investigator or a person designated by the Investigator, fully informed the patient, in language and terms they were able to understand, to the fullest extent possible, about the study, objectives, constraints, duration, and patient's rights.

It was the responsibility of the Investigator's or a person designated by the Investigator to obtain written and signed informed consent from patients prior to inclusion. The patient's legal representative could also sign the written informed consent form (ICF) on behalf of the patient. A copy of the signed and dated written ICF was provided to the patient and/ or his legal representative.

The list of investigators is provided in Annex 2.

4 OTHER RESPONSIBLE PARTIES

Scientific Committee and Charter

The Steering Committee was responsible for coordinating the conduct of the study. It was involved in the preparation and approval of the protocol and its amendment(s), it assessed the progress of the study at both global and site levels and was given full authority for presentation/publication of the results. The detailed responsibilities of the Steering Committee, its relationship with the other actors responsible for the management and conduct of the study, its membership, and the purpose and timing of its meetings are described in the Steering Committee Charter. The Steering Committee Charter can be found in Annex 2

- Ian Chau, MD - Chairman

  Royal Marsden Hospital
  Department of Medicine
  Downs Road, Sutton
  Surrey SM2 5PT

  United Kingdom

- Marwan Fakid, MD - Co-Chairman

  City of Hope Comprehensive Cancer Center
  1500 E Duarte St.
  Duarte, CA 91010

  United States

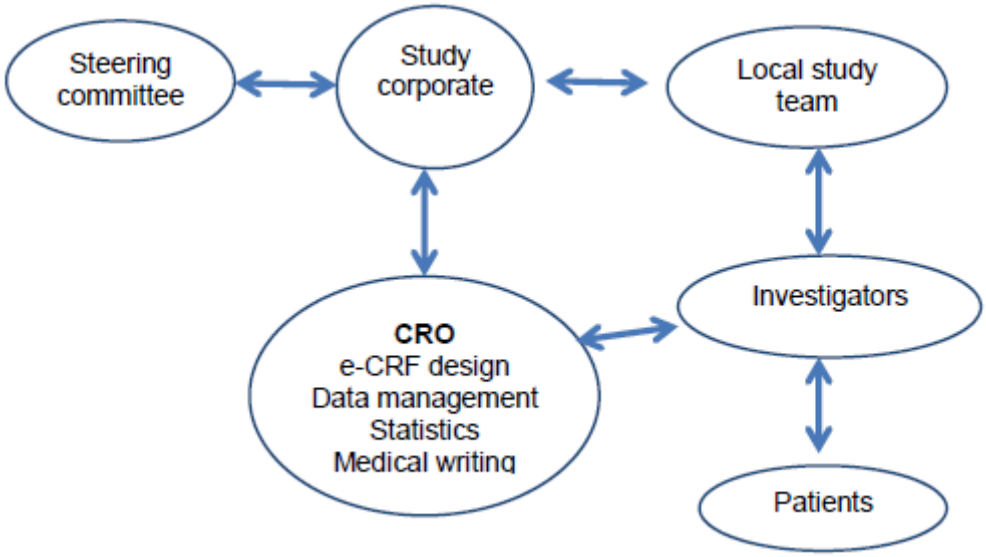
Other experts/consultants

Not applicable.

Service Provider

Data-management, statistical activities and report writing were carried out by Linical, Madrid, Spain, under the supervision of the company (see Annex 2).

Figure 1 - Service provider flowchart



Central Laboratory

Not applicable.

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	08 October 2013	08 October 2013	-
End of data collection	-	12 April 2018	-
Registration in the EU PAS register	-	23 August 2017	-
Final report of study results	11 August 2018	27 November 2018	-

6 RATIONALE AND BACKGROUND

Colorectal cancer (CRC) is a major worldwide health problem. It is the third most common cancer amongst men (behind lung and prostate cancer) accounting for 10% of the total, and the second most common cancer in women (behind breast cancer), accounting for 9.4% of the total. Incidence rates are higher in men (1.4 to 1) (1). In 2008, the incidence of CRC was over 1.2 million cases, with mortality over 600,000 worldwide (2); in the US, the incidence of CRC was over 153,000 and in Europe (including Central and Eastern Europe) the incidence was over 450,000. Approximately half of all patients develop metastasis (3). The five year survival rate in early localized stage is about 90%, decreasing to approximately 60-65% after spread to adjacent organ(s) or lymph nodes, and to less than 10% after spread to distant sites (1).

For patients with metastatic CRC (mCRC) having failed a prior oxaliplatin-based regimen for first-line treatment of mCRC, the preferred treatment is an irinotecan based regimen (most often irinotecan combined with bolus/infusional 5-fluorouracil and leucovorin: FOLFIRI).

The randomized Phase 3 pivotal study EFC10262/VELOUR study (ClinicalTrials.gov NCT00561470) in second-line mCRC comparing ZALTRAP® versus placebo in patients treated with irinotecan/FOLFIRI combination after failure of an oxaliplatin based regimen demonstrated statistically and clinically significant improvement in overall survival (OS), progression free survival (PFS) duration and a significantly higher overall response rate (ORR) in patients treated with ZALTRAP®/FOLFIRI over those treated with placebo/FOLFIRI and demonstrating for the first time an overall survival benefit of a targeted therapy in combination with FOLFIRI in second line chemotherapy (4). Therefore, ZALTRAP® provides an important new treatment option for the treatment of second-line mCRC patients in combination with FOLFIRI, and is the only agent to demonstrate an OS benefit in this setting (Table 1).

Table 1 - VELOUR, Main efficacy endpoints[a] - ITT population

	Placebo/FOLFIRI (N=614)	ZALTRAP®/FOLFIRI (N=612)
Overall survival		
Number of death events, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95.34% CI) (months)	12.06 (11.07 to 13.11)	13.50 (12.52 to 14.95)
Stratified Hazard ratio (95.34% CI)	0.817 (0.713 to 0.937)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)[b]		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (99.99% CI) (months)	4.67 (4.07 to 5.55)	6.90 (5.88 to 7.85)
Stratified Hazard ratio (99.99% CI)	0.758 (0.578 to 0.995)	
Stratified Log-Rank test p-value	0.00007	
Overall Response rate	(N=530)	(N=531)
(CR+PR)[c] (95% CI) (%)[d]	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

a Stratified on ECOG Performance Status (0 versus 1 versus 2) and Prior Bevacizumab (yes versus no)
b PFS (based on tumor assessment by the IRC): Significance threshold is set to 0.0001
c Overall objective response rate by IRC
d CR (complete response) PR (partial response)

On the basis of these study results, in August 2012, the US Food and Drug Administration (FDA) granted approval for ZALTRAP® (ziv-aflibercept) with the following indication: ZALTRAP® in combination with FOLFIRI, is indicated for patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen.

In November 2012, the European Medicines Agency's Committee for Medicinal Product for Human Use (CHMP) recommended the authorization of aflibercept (ZALTRAP®) in combination with FOLFIRI chemotherapy in the treatment of adults with mCRC that is resistant to or has progressed after an oxaliplatin containing regimen.

The recommended dose of ZALTRAP®, administered as an intravenous infusion over 1 hours, is 4 mg/Kg of body weight, followed by the FOLFIRI regimen, every 2 weeks.

For details, please consult the most recent ZALTRAP® European Union (EU) Summary of Product Characteristics (SmPC) or US Package Insert or local Product Information.

Rationale

Following the European Medicines Agency (EMA) evaluation, the Applicant was requested to conduct a PASS in real life to assess safety and effectiveness of ZALTRAP® administered in the approved indication. The sponsor proposed to conduct an observational cohort non-comparative study, of which primary objective was to better characterize the safety and effectiveness of ZALTRAP® in the real life setting, particularly in subpopulations such as elderly patients or patients with hepatic or renal impairment (within the limits of the irinotecan label) or non-Caucasian patients. This study prospectively collected safety and effectiveness data in patients treated with ZALTRAP® in clinical practice.

7 RESEARCH QUESTION AND OBJECTIVES

Primary objective

- To describe long term safety and clinical outcomes of the ZALTRAP® + FOLFIRI combination in patients treated in daily practice for a mCRC after failure of an oxaliplatin-based regimen.
- To assess safety of the ZALTRAP® + FOLFIRI combination in the following patient cohorts:
  - Elderly patients (≥65 years old);
  - Patients with renal or hepatic impairment (within the limits of irinotecan label);
  - Non Caucasian patients,
  - Number and type of prior anti-cancer therapy (eg, prior bevacizumab).

Secondary objectives

- To describe effectiveness of the ZALTRAP® + FOLFIRI combination (eg, progression free survival [PFS], overall survival [OS], response rate [RR]) in the following patient cohorts:
  - Elderly patients (≥65 years old);
  - Patients with renal or hepatic impairment (within the limits of irinotecan label);
  - Non Caucasian patients,
  - Number and type of prior anti-cancer therapy (eg, prior bevacizumab).
- To describe utilization of health resources in patients treated with the ZALTRAP® + FOLFIRI combination.

8 AMENDMENTS AND UPDATES

The final version of the protocol which includes the two amendments described below can be found in Annex 2 Supportive Documents.

Number	Date	Section of study protocol	Amendment or update	Reason
1	12 December 2013	12	1	The prolongation of the period for the reporting of non-serious adverse events to the MAH
2	01 February 2016	10.5	2	Decrease the study sample size

9 RESEARCH METHODS

9.1 STUDY DESIGN

This was a prospective, international, multicenter observational (non-interventional on the therapeutic strategy) cohort non-comparative study. It included a cohort of patients treated with ZALTRAP® + FOLFIRI in the clinical setting (not as part of an interventional clinical trial) and followed for 24 months after initiation of ZALTRAP®. The design of the study mirrored real life management of these patients. It was expected that collected data represent realistic characterization of the patient population treated with ZALTRAP® and a rational evaluation of clinical outcome measures related to effectiveness and safety as assessed by the physicians in routine clinical practice.

There was no fixed study visit schedule. The study visits occurred according to the treating physician's clinical practice and judgement. However, physicians were asked to record data for study endpoint assessments every 3 months.

9.2 SETTING

Oncologists and gastroenterologists with a recognized competency in oncology who prescribed ZALTRAP® + FOLFIRI after failure of an oxaliplatin-based regimen. The physicians were randomly selected based on physicians' lists in each participating countries. The random process was stratified on country-specific criteria in order to accurately reflect routine clinical practices within each country. Each site which declined to participate was replaced by the following one selected by the same random selection process in the same country.

Patients enrolled in the study were selected among the patients for whom the physician decided to prescribe ZALTRAP® independently from study entry. Each physician included consecutive patients until the targeted number of patient in his/her country was reached. A screening form was implemented at each site to document the consecutive enrolment in order to help to limit bias related to physician-led patient selection, and captured why an eligible patient was not included.

OZONE study was planned to involve approximately 750 patients in approximately 170 sites of 14 countries in Europe and the United States (US) during a recruitment period of 28 months.

This report includes data reported to the OZONE registry from patients included in the study between 8 October 2013 and 12 April 2018.

9.3 PATIENTS

Inclusion criteria

I 01. Patients planned to be treated with ZALTRAP® in combination with a 5FU plus irinotecan regimen (FOLFIRI) for mCRC after failure of an oxaliplatin based regimen (including bevacizumab pretreated patients). Patients for which the physician decided to prescribe ZALTRAP® independently from entry in study.

I 02. Patients' age ≥18 years old.

I 03. Patient's availability of a written informed consent.

Exclusion criteria

E 01. Patients who were concurrently participating in any clinical study.

E 02. Patients who were receiving concomitant antivascular endothelial growth factor (VEGF) agents and/or receiving ZALTRAP® through an investigational clinical study or through any compassionate use program.

E 03. Patients who received ZALTRAP® in combination with chemotherapy regimens other than FOLFIRI.

9.4 VARIABLES

- Safety
  - Treatment emergent adverse events (TEAE), related TEAE and serious TEAE, serious related TEAE, TEAE leading to premature or permanent treatment discontinuation, TEAE leading to fatal outcome and deaths.
- Effectiveness
  - OS, PFS, objective response (OR) and best overall response (BOR) as per physician
- Health resource utilization
  - Emergency Room visits, cumulated length of stay (days) and type of hospitalization.

9.5 DATA SOURCES AND MEASUREMENT

For each patient, the investigator entered the information requested by protocol in an electronic case report form (eCRF). Details on eCRF completion were explained to the investigator.

All adverse events (AEs), regardless of seriousness or relationship to ZALTRAP® and/or FOLFIRI, spanning from the signature of the informed consent form through 30 days after the last administration of ZALTRAP® + FOLFIRI, were recorded on the corresponding page(s) of the eCRF.

After this 30-day period only AEs (including serious AEs [SAEs]) considered by the physician to be caused by ZALTRAP® + FOLFIRI with a reasonable possibility were collected.

9.6 BIAS

In order to limit potential bias in patient's selection, participating physicians were randomly selected, and were asked to propose inclusion to all consecutive patients meeting the study criteria.

9.7 STUDY SIZE

The study planned to enroll approximately 750 patients in 170 centers in 14 countries; within this population, it was expected to have:

- About 40% of patients in the elderly (≥65 years old) group,
- Around 10% to 15% of patients in the non-Caucasian group,
- Around 30% of patients in renal impairment group,
- Around 18% of patients in hepatic impairment group.

A subset of 40% (300), respectively 10%-15% (75-112), 30% (225) and 18% (135) of patients in each subgroup would allow having the below precision:

For safety/health resources event rates (Table 2):

Table 2 - Sample size for various event rates

Sample size	Expected 95% CI for various event rates					
	5%	10%	20%	30%	40%	50%
300	[2.5% - 7.5%]	[6.6% - 13.4%]	[15.5% - 24.5%]	[24.8% - 35.2%]	[34.5% - 45.5%]	[44.3% - 55.7%]
75	[1.0% - 9.9%]	[3.2% - 16.8%]	[10.9% - 29.1%]	[19.6% - 40.4%]	[28.9% - 51.1%]	[38.7% - 61.3%]
112	[1.0% - 9.0%]	[4.4% - 15.6%]	[12.6% - 27.4%]	[21.5% - 38.5%]	[30.9% - 49.1%]	[40.7% - 59.3%]
225	[2.2% - 7.8%]	[6.1% - 13.9%]	[14.8% - 25.2%]	[24.0% - 36.0%]	[33.6% - 46.4%]	[43.5% - 56.5%]
135	[1.3% - 8.7%]	[4.9% - 15.1%]	[13.3% - 26.7%]	[22.3% - 37.7%]	[31.7% - 48.3%]	[41.6% - 58.4%]

For overall survival:

Assuming an exponential distribution of the OS and a median survival of 12 months, the survival rate would be 50% at 12 months, 35% at 18 months and of 25% at 24 months. The precision (Greenwood's formula) around the OS rates (Kaplan-Meier estimates) at these time points is provided in Table 3 (SAS simulations performed on 5,000 replicates - Lost to follow up were simulated using an exponential distribution, a 5% rate at 12 months was assumed.

Table 3 - Sample sizes for various survival time points

Sample size	Expected 95% CI for various survival time points		
	OS rate at 12 months	OS rate at 18 months	OS rate at 24 months
	50%	35%	25%
300	[44.1% - 55.6%]	[29.5% - 40.5%]	[20.1% - 30.2%]
75	[38.1% - 60.7%]	[24.3% - 46.0%]	[15.7% - 35.6%]
112	[40.3% - 58.9%]	[26.1% - 44.0%]	[17.2% - 33.6%]
225	[43.2% - 56.4%]	[28.6% - 41.4%]	[19.4% - 31.0%]
135	[41.1% - 58.1%]	[26.9% - 43.2%]	[17.8% - 32.8%]

9.8 DATA TRANSFORMATION

9.8.1 Laboratory variables at baseline

- Urine protein-to-creatinine ratio (UPCR) were derived based on protein and creatinine values assessed on morning spot urinalysis. UPCR was described according to the following classes: [0-1], [1-2], [2-3], >3.
- Proteinuria, the grade was based on Table 4:

Table 4 - Derivation of proteinuria grade

Grade	Spot urine protein (mg/dL)	24-hour proteinuria (g/24h)
Grade 1	30-100	<1.0
Grade 2	>100-300	1.0-3.4
Grade 3	>300	≥3.5
Grade 4	NA as per CTC v4.03	

9.8.2 Overall survival

OS was defined as the time interval from the date of 1st administration of ZALTRAP® or FOLFIRI to the date of death due to any cause.

If death was not observed during the study (time from first study treatment received till end of study), survival time was censored at the patient's last contact date (last date the patient was known to be alive).

The end of study period was defined as death or completion of 24 months observation period or withdrawal of the study before the end of 24 months observation period, whichever occurred first.

Patient's last contact was derived as the latest date of any of the following panels: Patient status (date of last contact for patient's status ticked alive) and investigational product administration.

9.8.3 Progression free survival

PFS was defined as the time from the date of the 1st administration of ZALTRAP® or FOLFIRI to the date of tumor progression or death due to any cause, whichever came first. Disease progression was based on the treating physician judgment.

If death and progression were not observed during the study (time from first study treatment received till end of study), the patient was censored at the patient's last contact date.

9.8.4 Best overall response

BOR during treatment period, as defined by the physician: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE).

9.8.5 Objective response

OR: BOR equaled to CR or PR. Patients were responders if their BOR was CR or PR.

9.8.6 Study treatment and dosing modifications

Dose reduction was derived using the definition provided in Table 5, Table 6 and Table 7 compared to the previous dose.

Table 5 - ZALTRAP® actual dose level definition

Actual dose level (mg/Kg)	Actual dose administered (mg/Kg)
Upper dose	5 ≤Dose
4	3 ≤Dose <5
2	1 ≤Dose <3
Under dose	0 <Dose <1
No dose administered	0

Table 6 - Irinotecan actual dose level definition

Actual dose level (mg/m^2)	Actual dose administered (mg/m^2)
Upper dose	195 ≤Dose
180	165 ≤Dose <195
150	135 ≤Dose <165
120	105 ≤Dose <145
Under dose	0 <Dose <105
No dose administered	0

Table 7 - 5-FU actual dose level definition (bolus + infusional)

Actual dose level (mg/m^2)	Actual dose administered (mg/m^2)
Upper dose	3080 ≤Dose
2800	2520 ≤Dose <3080
2240	1960 ≤Dose <2520
1680	1400 ≤Dose <1960
Under dose	0 <Dose <1400
No dose administered	0

9.9 STATISTICAL METHODS

9.9.1 Main summary measures

Most of the statistical analyses were descriptive using 2-sided 95% confidence intervals (CI). All analyses were performed on the all treated population.

Descriptive summary for continuous data included the number of non-missing observations (n), mean, standard deviation (SD), median 25% percentile and 75% percentile, minimum and maximum. The number of patients with missing data was displayed when relevant.

Categorical data were summarized using counts and percentages. The number of patients with missing data was displayed when relevant, but it was not included in the denominator for the calculation of percentages unless otherwise specified.

For time to event outcomes, the Kaplan-Meier estimates (including curves) were computed and the 95% CI for the median survival times / survival rates at given time points was provided.

9.9.2 Main statistical methods

For detailed statistical considerations, please refer to Annex 2 Supportive Documents - Statistical Analysis Plan (SAP).

Analyses on effectiveness and safety outcomes were conducted on the treated population: This population included all patients who had given their informed consent and who received at least part of the ZALTRAP® + FOLFIRI combination treatment.

Analyses on site questionnaires were conducted on the active site population. This population included all sites who had included at least one patient (treated or not).

Primary analysis on effectiveness endpoints

Overall survival and Progression Free Survival

The OS and PFS were estimated using the Kaplan-Meier method. The median OS and PFS, probabilities or surviving at 3, 6, 9, 12, 15, 18, 21 and 24 months, and 95% CI were computed using Kaplan-Meier estimates. Kaplan-Meier survival curves were displayed.

Best overall response

BOR as defined by the physician (CR, PR, SD, PD and NE) was summarized as count of patients and frequencies.

Objective response rate

ORR was summarized using descriptive statistics and 95% CI (computed based on the Clopper-Pearson method).

Secondary analyses on effectiveness endpoints

Secondary analyses were focused on the description of effectiveness of ZALTRAP® (eg, PFS, OS, RR) in the subgroups summarized in Table 8:

Table 8 - Subgroups

Subgroup	Description (coding)
Age	≥65 y (1) vs. <65 y (0)
Patients with renal impairment[a]	Yes (1) vs. No (0)
Patients with hepatic impairment[b]	Yes (1) vs. No (0)
Race	Non Caucasian (1) vs. Caucasian (0)
Nb of Prior anti-cancer therapy[c]	≥2 lines (1) vs. 0-1 line (0)
Prior bevacizumab	Yes (1) vs. No (0)

a Renal impairment patients defined as: patients with at baseline creatinine clearance ≤80 mL/min

b Hepatic impairment patients defined as: patients with at baseline either total bilirubin >UNL or transaminases >1.5 UNL

c For advanced disease or any type of anti-cancer treatment

- Univariate analyses:

  Median for OS and PFS (or % for ORR) at its 95% CI within each selected subgroup as well as the selected subgroup effect hazard ratio and its 95% CI were computed using univariate Cox model for the OS and PFS and using univariate logistic regression for the ORR.

- Multivariate analyses:

  Potential prognostic factors are defined in Table 9.

Table 9 - Potential prognostic factors

Prognostic factor	Description (coding)
ECOG PS	2 vs. 0, 1 vs. 0
Prior bevacizumab	Yes (1) vs. No (0)
Gender	Female (1) vs. Male (0)
Location of primary tumor	Colon vs. Rectum, Recto sigmoid vs. Rectum, Other vs. Rectum
Number of distinct organs with metastasis	>1 (1) vs. 1 (0)
Liver metastasis	Yes (1) vs. No (0)
Prior hypertension	Yes (1) vs. No (0)
Geographical region	Europe (1) vs. USA (0)
Age	≥65 y (1) vs. <65 y (0)
Patients with renal impairment	Yes (1) vs. No (0)
Patients with hepatic impairment	Yes (1) vs. No (0)
Race	Non Caucasian (1) vs. Caucasian (0)
Nb of Prior anti-cancer therapy:	≥2 lines (1) vs. 0-1 line (0)

- As a first step, each prognostic factor was assessed individually for prognostic value ($p < 0.20$) using a univariate Cox model for the OS and PFS and using logistic regression for ORR.
- Secondly, for each couple of prognostic factors selected in the first step, a chi-square test for independence (or Fisher's Exact test) was performed. If the p-value of such association test was <0.05, only the factor with the lower p-value from the previous step was included in the following step.
- For each selected subgroup (Table 8) a multivariate Cox model for the OS and PFS and a multivariate logistic model for ORR were performed including the prognostic factors selected in the previous step as covariate together with the corresponding interactions with the subgroups of interest. Then, a stepwise selection process forcing the selected subgroup effect was used to identify the final set of prognostic factors, using the stepwise procedure with a variable entry of 5% level and a variable removal at each step of 10% level. In this stepwise, procedure was selected by the option HIERARCHY=NONE.
- Hazard ratios and their associated / Odds ratio (for logistic model) 95% CI were computed using the final selected model.

Additionally, Kaplan-Meier survival curves for OS (summarizing patients at risk and median) were displayed for each subgroup.

Safety analyses

Summary of safety results (treatment emergent adverse events) was presented overall and by cycle on all safety population, and by selected subgroup (Table 8).

9.9.3 Missing values

As general rules, no imputation was planned for missing data. The following conventions for handling missing data were applied but no imputation was done at the data level.

For categorical variables, patients with missing data were not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data was presented.

Continuous data: the analyses and summaries for variables with continuous scales were based on observed data only. However, the number of patients with missing observations was provided.

Handling of missing data for adverse events

AE: missing data were not imputed. When any information (start date of AE, first study treatment administration date, Cycle 1 date) was missing, the TEAE was determined by the following conservative principle: an AE was considered a TEAE if it could not be confirmed that the event was not a TEAE due to missing data

To extend the AEs to the cycles, for incomplete AE end date (day missing), the last day of the month was imputed, as it was the worst case.

Handling of missing assessment of relationship of adverse events to study treatment

If the assessment of the relationship to study treatment was missing, then the relationship to study treatment was assumed and the AE considered as such was included in the frequency tables of possibly related AEs, but no imputation was done at the data level.

Handling of missing grades of adverse events

If the grade was missing for 1 of the treatment-emergent episodes of an AE, the maximal severity on the remaining episodes was considered. If the severity was missing for all the episodes, a "missing" category was added in the summary table.

For determination of concomitance of hematuria (reported as AE) with proteinuria or with UPCR, no imputation was performed in case of incomplete date of AE. Events were considered concomitant if they occurred in the same cycle.

Handling of partial date of histological diagnosis

Partial date of diagnosis of mCRC was imputed to calculate the time from initial histological diagnosis till study entry.

- If the month was present the 15 of the month was used (day was not collected).
- If year was present and month was missing then 1st July was used.

Handling of medication missing/partial dates

No imputation of medication start/end dates was performed. If a medication date was missing or partially missing, so it could not be determined whether it was taken prior or concomitantly, it was considered as a prior, concomitant medication and post treatment.

Incomplete date of first further therapy: if the day of first further therapy date was missing, the date was imputed to the first day of the month or the day after last study treatment administration, whichever came last.

Incomplete date of death

If the day of death date was missing, it was imputed to the first day of the month, except if the date of patient's last contact was the same month as death date. In this case, the death date was imputed to the date of last contact + 1 day.

If the day and month of death date were missing, date of death was imputed to 1st January of the year, except if date of patient's last contact was the same year as death date. In this case, the death date was imputed to the date of last contact + 1 day.

Handling of missing data for hospitalization

No replacement of missing data was done. If date of discharge was missing and the death occurred within a 3 days after hospital admission date, then the date of death was considered to be the date of discharge.

No replacement was done in listings.

9.9.4 Sensitivity analyses

A sensitivity analysis of PFS was performed as defined below in Table 10:

- Censoring for new anti-tumor therapies in patients alive who did not have a PD documented before start of further anticancer therapies.

Table 10 - Description of analysis of PFS

Situation	Date of progression or censoring	Outcome
Progression	Date of the first Progression Disease (PD)	Event
Death	Date of death	Event
New anticancer treatment started*	Date of last status update with no progression and no death before the start date of new anticancer treatment (considering concomitant and post surgeries, radiation therapies and systemic treatments)	Censored
No progression and no death at the completed 24 months FU	Date of the completed 24 months FU	Censored
Lost to FU	Date of the last status update with no progression and no death	Censored

*Sensitivity analysis

9.9.5 Amendments to the statistical analysis plan

Table 11 - Statistical modifications made in the statistical analysis plan

SAP version number	Date approved	Rationale	Description of statistical changes
Final 2.0	09 May 2018	Elderly patients' groups: ≥75 and baseline creatinine clearance categories defined as well to cover a data gap for those subgroup categories	New subgroups of interest definition • baseline creatinine clearance categories (>80, [50-80], <50) for additional safety analysis • patients ≥75 years old for additional analysis (with ages categories defined as <65, [65-75], ≥75)

9.10 QUALITY CONTROL

Data quality control (QC) was performed on active sites (which enrolled at least one patient). QC was performed by qualified designated personnel in each country.

The methodology of data QC and appropriate consecutive corrective actions were detailed in the study guidebook.

The computerized handling of the data by the Company after receipt of the CRFs could generate additional requests to which the participating physician was obliged to respond by confirming or modifying the data questioned.

Data collection and validation procedures were detailed in appropriate operational documents.

The database was locked on 22 June 2018.

10 RESULTS

10.1 PARTICIPANTS

10.1.1 Overall participation status

Out of the 861 candidates, corresponding to the patients for whom the treating physician decided that aflibercept would be a valid treatment option, 69 were not enrolled in the study; ie, refused to participate. Reasons for not enrolling are provided in Table 1.1.1-1b. After further review of inclusion/exclusion criteria, 9 patients among the 792 enrolled patients, were not included. Among the 783 patients included in the study, 766 patients were treated and considered in safety and effectiveness analyses (17 patients were not treated with the IMP). Patient 840-028-002 was only treated with ZALTRAP® (Table 12).

A summary of candidate patients in the study is provided in Table 1.1.1-2. Summaries for number of patients by country, site and treatment received, and subgroups of interest are provided in Table 1.1.1-2, Table 1.1.1-2a, Table 1.1.1-2b, Table 1.1.1-2c, Table 1.1.1-2d, Table 1.1.1-2e and Table 1.1.1-2f, respectively.

Table 12 - Summary of patients included in the study

Candidate patients	N	861
Enrolled	n/N(%)	792/861 (92.0%)
Not Enrolled	n/N(%)	69/861 (8.0%)
Enrolled Population	N	792
Included	n/N(%)	783/792 (98.9%)
Not included	n/N(%)	9/792 (1.1%)
Included population	N	783
Analysis Populations		
Treated population	n/N(%)	766/783 (97.8%)
- Receiving FOLFIRI	n/N(%)	765/783 (97.7%)
Not Treated population	n/N(%)	17/783 (2.2%)
- Receiving FOLFIRI	n/N(%)	4/783 (0.5%)

Enrolled population: all patients who signed ICF
Included patients: all patients who answer to "Will the patient be included in the study" as Yes
Treated population: all patients who took at least one dose of ZALTRAP
Not Treated population: all patients who took no dose of ZALTRAP (or receiving Folfiri only)
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10.1.2 Discontinued patients

A total of 760 (99.2%) treated patients permanently discontinued treatment as of the cutoff date for analysis. The most frequent reasons for study treatment discontinuation were disease progression (484 patients, 63.7%) and adverse events (116 patients, 15.3%). In addition, 154 patients (20.1%) prematurely discontinued one component of the treatment (either ZALTRAP® or FOLFIRI); in most cases (102/154 patients, 66.2%) consecutive to an adverse event (Table 13). Few patients were lost to follow-up (1.7%). A listing for the reasons of permanent and premature discontinuation classified as other are provided in Listing 1.1.1-3a and Listing 1.1.1-3b, respectively.

Table 13 - Summary of reason for permanent and premature discontinuation of one component of the treatment - All treated population

		ZALTRAP / FOLFIRI N=766
Patients having permanently treatment discontinued	n/N(%)	760/766 (99.2%)
Reason for permanent discontinuation	N	760
Disease Progression	n/N(%)	484/760 (63.7%)
Adverse Event	n/N(%)	116/760 (15.3%)
Lost To Follow Up	n/N(%)	13/760 (1.7%)
Investigator Decision	n/N(%)	68/760 (8.9%)
Patient´s Decision	n/N(%)	47/760 (6.2%)
Other	n/N(%)	32/760 (4.2%)
Patients having prematurely discontinued one component of the study treatment	n/N(%)	154/766 (20.1%)
Reason for premature discontinuation	N	154
Adverse Event	n/N(%)	102/154 (66.2%)
Other	n/N(%)	52/154 (33.8%)

Patient 276-004-002 with TEAE leading to permanent treatment discontinuation but reason for permanent discontinuation as 'Investigator Decision'. Patient's reason reclassified as 'Adverse Event'.
Patient 380-006-001 with TEAE leading to premature treatment discontinuation but reason for premature discontinuation as 'Other: Other adverse event and clinical condition'. Patient's reason reclassified as 'Adverse Event'.
6 patients (3 are still on Th>24mos and 3 had <24mos) without treatment permanently discontinued:
250-008-002;250-039-005;724-005-009;724-006-021;826-002-009;840-059-002
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10.1.3 Protocol deviations

A total of 25 (3.3%) of the 766 treated patients reported a protocol deviation. Of them, 18 patients did not meet inclusion criteria (17 patients [2.2%] were not previously treated on an oxaliplatin based regimen, and patient 250-007-009 had a prior cancer therapy which intent was advanced/metastatic therapy but diagnosis actually could not be confirmed but just assumed).

During the treatment phase, 8 patients (1.0%) were administered other anticancer therapies than ZALTRAP® + FOLFIRI. Additional details can be found in Table 1.1.1-4, and a listing of patients with deviations is provided in Listing 1.1.1-4a.

10.1.4 End of study status

A total of 601 (78.5%) patients did not complete the 24 months follow-up. The main reason for not completing the 24 months follow-up was earlier death reported in 558 (92.9%) patients (Table 14). Only 34 (5.66%) patients were lost to follow-up. A listing of patients who were on treatment after having completed the 24 months follow-up is provided in Listing 1.1.1-5a, and listing with the main reason if the patient did not complete the study, classified as other is provided in Listing 1.1.1-5b.

Table 14 - End of study status - All treated population

	Aflibercept/FOLFIRI (N=766)
Patients having completed the End of study visit	766
Patients having completed the 24 months follow-up	
No	601/766 (78.46%)
Yes	165/766 (21.54%)
Patients still on treatment after having completed the 24 months follow-up	4/165 (2.42%)
Main reason if patient has not completed the 24 months follow-up	
death	558/601 (92.85%)
lost to follow-up	34/601 (5.66%)
other	9/601 (1.50%)

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10.2 DESCRIPTIVE DATA

10.2.1 Demographic and Baseline characteristics

A total of 766 patients constituted the treated population (Table 15). They had a median age of 64 years, with 59.5% being male patients. Of the 766 treated patients, 48.3% were ≥65 years old, 9.2% of 762 patients were non-Caucasian, 35.0% of 738 patients had renal impairment, 19.6% of 657 patients had hepatic impairment, matching the protocol assumptions. There were 94.8% of 746 patients who had ECOG PS 0 or 1, and 646 (84.3%) patients were included in Europe and 120 (15.7%) patients were included in North America (United States and Puerto Rico). Of these patients, 35.0% had more than one prior line of chemotherapy for advanced disease.

Table 15 - Demographic and Baseline characteristics - All treated population

		ZALTRAP / FOLFIRI N=766
Gender		
	N	766
Male	n (%)	456/766 (59.5%)
Female	n (%)	310/766 (40.5%)
Missing	n	0
Race		
	N	762
Caucasian/White	n (%)	692/762 (90.8%)
Black	n (%)	33/762 (4.3%)
Asian/Oriental	n (%)	18/762 (2.4%)
Other	n (%)	19/762 (2.5%)
Missing	n	4
Age years (subgroup)		
	N	766
<65	n (%)	396/766 (51.7%)
>=65	n (%)	370/766 (48.3%)
Missing	n	0
Age (years)		
	N	766
	Mean (SD)	62.9 (10.5)
	Median (Q1 ; Q3)	64.0 (56.0 ; 71.0)
	Min ; Max	26 ; 88
	Missing	0
ECOG Performance Status		
	N	746
0	n (%)	370/746 (49.6%)
1	n (%)	337/746 (45.2%)
2	n (%)	36/746 (4.8%)
3	n (%)	3/746 (0.4%)
Missing	n	20
Renal impairment		
	N	738
Yes	n (%)	258/738 (35.0%)
No	n (%)	480/738 (65.0%)
Missing	n	28
Hepatic impairment		
	N	657
Yes	n (%)	129/657 (19.6%)
No	n (%)	528/657 (80.4%)
Missing	n	109
Nb of prior anti cancer therapy		
	N	766
0-1 line	n (%)	343/766 (44.8%)
> 1 lines	n (%)	423/766 (55.2%)
Missing	n	0
Nb of advance prior anti cancer therapy		
	N	766
0-1 line	n (%)	498/766 (65.0%)
> 1 lines	n (%)	268/766 (35.0%)
Missing	n	0

		ZALTRAP / FOLFIRI N=766
Prior bevacizumab		
	N	766
Yes	n (%)	449/766 (58.6%)
No	n (%)	317/766 (41.4%)
Missing	n	0
Geographical Region		
	N	766
Europe	n (%)	646/766 (84.3%)
North America	n (%)	120/766 (15.7%)
Missing	n	0
Prior EGFR		
	N	766
Yes	n (%)	147/766 (19.2%)
No	n (%)	619/766 (80.8%)
Missing	n	0
Creatinine Clearance		
	N	738
<50	n (%)	43/738 (5.8%)
[50-80]	n (%)	213/738 (28.9%)
>80	n (%)	482/738 (65.3%)
Missing	n	28

Hepatic impairment: Defined as either Total bilirubin>UNL or AST or ALT >1.5 UNL
Renal impairment: Defined as Creatinine clearance <=80 mL/min
North America = United States + Puerto Rico
Prior eGFR used (Yes/No) defined as Yes for patients who took Cetuximab and/or Panitumumab as previous anti-cancer therapy
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10.2.2 Prior medical and surgical history

A total of 68.0% (521) patients reported a previous history of thrombovascular events and/or presence of cardiovascular risk factors.

The most frequent thrombovascular events and/or presence of cardiovascular risk factors were those referred to:

- hypertension (grouped term) with a proportion of 49.6% (380 patients),
- other factors (grouped term) with a proportion of 29.0% (222 patients),
- dyslipidaemia (grouped term) with a proportion of 20.6% (158 patients).

Additional details on all thrombovascular events and/or presence of cardiovascular risk factors are provided in Table 1.1.2-3.

Summary table on prior relevant medical and surgical history reported by patients is provided in Table 1.1.2-2.

10.2.3 Disease characteristics

Up to 73.5% (563 patients) were treated in the study with colon adenocarcinoma and 25.6% (196 patients) with rectum adenocarcinoma. Most patients had multiple organs invaded at baseline (55.5%); most frequent metastatic sites were liver in 67.5% of the patients and lung in 51.4% of the patients; 51.5% of the patients had mutated KRAS status (Table 16).

Table 16 - Disease characteristics (Cancer history) - All treated population

		ZALTRAP / FOLFIRI N=766
Location of primary tumor		
	N	766
Colon	n (%)	563/766 (73.5%)
Rectum	n (%)	196/766 (25.6%)
Other	n (%)	7/766 (0.9%)
Missing	n (%)	0
Histology type		
	N	766
Adenocarcinoma	n (%)	766/766 (100.0%)
Missing	n (%)	0
Stage at initial diagnosis		
	N	766
Metastatic	n (%)	536/766 (70.0%)
No Metastatic	n (%)	230/766 (30.0%)
Missing	n (%)	0
Metastases site(s)		
Liver	n (%)	517/766 (67.5%)
Lung	n (%)	394/766 (51.4%)
Lymph Nodes	n (%)	172/766 (22.5%)
Peritoneum	n (%)	163/766 (21.3%)
Other	n (%)	161/766 (21.0%)
Organs with metastases at baseline		
1	n (%)	341/766 (44.52%)
> 1	n (%)	425/766 (55.48%)
Kras Status		
	N	765
Wild Type	n (%)	270/765 (35.3%)
Mutated	n (%)	394/765 (51.5%)
Unknown	n (%)	28/765 (3.7%)
Not Done	n (%)	73/765 (9.5%)
Missing	n (%)	1
BRAF Status		
	N	766
Wild Type	n (%)	172/766 (22.5%)
Mutated	n (%)	21/766 (2.7%)
Unknown	n (%)	128/766 (16.7%)
Not Done	n (%)	445/766 (58.1%)
Missing	n (%)	0

Patient: 276-001-002 with Location of primary tumor= Other (Coecum) that couldn't be corrected at time of DBL
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10.2.4 Prior anti-cancer therapies

All patients were administered previous chemotherapy. Of them, 22.8% were administered neoadjuvant/adjuvant therapy only, 54.3% advanced therapy only, and 22.8% neoadjuvant/adjuvant and advanced therapy. 97.8% of the patients had a prior exposure to oxaliplatin. The mean (SD) cumulative duration of prior oxaliplatin-based regimen was 7.5 (6.4) months. Prior exposure to bevacizumab was noted in 58.6% of the patients (Table 17).

Table 17 - Prior anti-cancer therapies - All treated population

		ZALTRAP /FOLFIRI N=766
Prior chemotherapy *		
	N	766
Yes	n (%)	766/766 (100.0%)
Neoadjuvant/Adjuvant only	n (%)	175/766 (22.8%)
Advanced only	n (%)	416/766 (54.3%)
Neoadjuvant/Adjuvant+Advanced	n (%)	175/766 (22.8%)
Patients entering the study directly from neoadjuvant/adjuvant [a]		
	N	175
No oxaliplatin	n (%)	5/175 (2.9%)
Oxaliplatin-based neoadjuvant/adjuvant chemotherapy @	n (%)	170/175 (97.1%)
Oxaliplatin only	n (%)	1/175 (0.6%)
Oxaliplatin + Fluoropyrimidine	n (%)	95/175 (54.3%)
Oxaliplatin + Fluoropyrimidine +Biologic agent	n (%)	72/175 (41.1%)
With Bevacizumab	n (%)	62/175 (35.4%)
Patients with advanced chemotherapy only [a]		
	N	416
No oxaliplatin	n (%)	8/416 (1.9%)
Oxaliplatin-based chemotherapy @	n (%)	408/416 (98.1%)
Oxaliplatin only	n (%)	1/416 (0.2%)
Oxaliplatin + Fluoropyrimidine	n (%)	75/416 (18.0%)
Oxaliplatin + Fluoropyrimidine +Biologic agent	n (%)	330/416 (79.3%)
With Bevacizumab	n (%)	277/416 (66.6%)
Maintenance therapy with Bevacizumab only	n (%)	10/416 (2.4%)
Patients with neoadjuvant/adjuvant followed by advanced chemotherapy [a]		
	N	175
Neoadjuvant/adjuvant chemotherapy	N	175
-No oxaliplatin	n (%)	50/175 (28.6%)
-Oxaliplatin-based neoadjuvant/adjuvant chemotherapy	n (%)	125/175 (71.4%)
Advanced chemotherapy	N	175
-No oxaliplatin	n (%)	54/175 (30.9%)
-Oxaliplatin-based chemotherapy	n (%)	121/175 (69.1%)
-Oxaliplatin only	n (%)	1/175 (0.6%)
-Oxaliplatin + Fluoropyrimidine	n (%)	24/175 (13.7%)
-Oxaliplatin + Fluoropyrimidine +Biologic agent	n (%)	95/175 (54.3%)
-With Bevacizumab	n (%)	101/175 (57.7%)
With Bevacizumab [c]	n (%)	110/175 (62.9%)
Maintenance therapy with Bevacizumab only	n (%)	8/175 (4.6%)

		ZALTRAP /FOLFIRI N=766
Cumulative duration of oxaliplatin-based regimens (months)		
	N	748
	Mean (SD)	7.5 (6.4)
	Median (Q1 ; Q3)	5.7 (4.0 ; 9.2)
	Min ; Max [d]	0 ; 75
	Missing	0
Time from end of advanced chemotherapy to inclusion (months) [d]		
	N	591
	Mean (SD)	3.0 (4.8)
	Median (Q1 ; Q3)	1.0 (0.6 ; 3.2)
	Min ; Max [d]	-1 ; 42
	Missing	0
Time from end of neoadjuvant/adjuvant treatment to inclusion (months) [b] [d]		
	N	175
	Mean (SD)	7.5 (9.8)
	Median (Q1 ; Q3)	4.4 (1.1 ; 10.2)
	Min ; Max [d]	-0 ; 71
	Missing	0
Prior eGFR used (Prior Cetuximab and/or Panitumumab)		
	N	766
Yes	n (%)	147/766 (19.2%)
No	n (%)	619/766 (80.8%)

@: Patients 840-031-010, 840-076-002, 724-018-008 and 840-032-002 with Oxaliplatin and Bevacizumab so they are not included in the categories: Oxaliplatin only, Oxaliplatin + Fluoropyrimidine and Oxaliplatin + Fluoropyrimidine +Biologic agent
*: One patient with missing data is considered as No prior chemotherapy
[a] Denominator used for following percentages; [b] Displayed for patients included directly after adjuvant treatment only
[c] Whatever if in neoadjuvant/adjuvant or in advanced
[d] 0 corresponds to a time between 1 and 31 days. Negative values correspond to those patients who were still receiving previous anti-cancer therapy at the ICF date but before to first treatment administration
Fluoropyrimidine : 5-fluorouracil, capecitabine and/or TS-1; Biologic agent : bevacizumab, cetuximab, panitumumab and/or re
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Prior surgeries and prior radiations are provided in Table 1.1.2-6 and Table 1.1.2-7, respectively.

10.2.5 Prior and concomitant medications (other than anticancer therapy)

Prior medications not related to anticancer therapy taken within one week prior to first study treatment are provided in Table 1.1.3-1. Summaries of prior anticoagulant medications for patients with and without thrombovascular events and prior antihypertensive medications for patients with and without history of hypertension are provided in Table 1.1.3-2 and Table 1.1.3-3, respectively. Concomitant medications not related to anticancer therapy are provided in Table 1.1.3-4.

Regarding granulocyte-colony stimulating factor (G-CSF) a total of 56 (7.3%) patients were administered G-CSF medication at Cycle 1 and 104 patients (13.6%) were administered G-CSF medication at any cycle (except Cycle 1) with a prophylactic intent. Data on granulocyte-colony stimulating factor (G-CSF) administration at Cycle 1 and at any cycle (except Cycle 1) with a prophylactic intent is provided in Table 1.1.3-7.

10.2.6 Study treatment exposure

Medan duration of exposure to the study treatment was 16.4 weeks, ranging from 2 to 108 weeks. Median number of cycles administered was 7 cycles, ranging from 1 to 46 cycles (Table 18). Full details of the number of patients by cycle and overall treatment exposure are provided in Table 1.1.4-1.

Table 18 - Number of patients by cycle and overall treatment exposure - All treated population

		ZALTRAP / FOLFIRI N=766
Duration of dosing (weeks)		
	N	766
	Mean (SD)	22.6 (19.2)
	Median (Q1 ; Q3)	16.4 (9.6 ; 30.0)
	Min ; Max	2 ; 108
	Missing	0
Total number of cycles administered by patient [n(%)]		
	N	766
1	n/N(%)	53/766 (6.9%)
2	n/N(%)	48/766 (6.3%)
3	n/N(%)	56/766 (7.3%)
4	n/N(%)	70/766 (9.1%)
5	n/N(%)	57/766 (7.4%)
6	n/N(%)	89/766 (11.6%)
7	n/N(%)	48/766 (6.3%)
8	n/N(%)	28/766 (3.7%)
9	n/N(%)	18/766 (2.3%)
10	n/N(%)	26/766 (3.4%)
11	n/N(%)	38/766 (5.0%)
12	n/N(%)	66/766 (8.6%)
> 12	n/N(%)	161/766 (21.0%)
Total number of cycles administered per patient		
	N	766
	Mean (SD)	9.2 (7.5)
	Median (Q1 ; Q3)	7.0 (4.0 ; 12.0)
	Min ; Max	1 ; 46
	Missing	0
	Sum	7027

A theoretical cycle is a 2-week period (14 days).
Duration of dosing = (Day 1 last cycle - Day 1 cycle 1 + 14) / 7
Number of cycles received: number of cycles with at least one dose intake of ZALTRAP and /or FOLFIRI
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Summary table for the number of patients by cycle and overall treatments exposure according to age group is provided in Table 1.1.4-1a.

The median number of cycles with ZALTRAP® per patient was 6 cycles, ranging from 1 to 44 cycles. This translated into a median duration of exposure of 14.8 weeks, ranging from 2 to 108 weeks. The median relative dose intensity was 79.0% (Table 19). Full details of the number of patients by cycle and ZALTRAP® treatment exposure are provided in Table 1.1.4-2.

Table 19 - ZALTRAP® treatment exposure, cumulative dose and dose intensity - All treated population

		ZALTRAP / FOLFIRI N=766
Total number of cycles administered per patient		
	N	766
	Mean (SD)	8.0 (6.9)
	Median (Q1 ; Q3)	6.0 (3.0 ; 11.0)
	Min ; Max	1 ; 44
	Missing	0
	Sum	6135
Total number of cycles administered by patient [n(%)]		
	N	766
1	n/N(%)	69/766 (9.0%)
2	n/N(%)	64/766 (8.4%)
3	n/N(%)	69/766 (9.0%)
4	n/N(%)	74/766 (9.7%)
5	n/N(%)	69/766 (9.0%)
6	n/N(%)	82/766 (10.7%)
7	n/N(%)	49/766 (6.4%)
8	n/N(%)	26/766 (3.4%)
9	n/N(%)	23/766 (3.0%)
10	n/N(%)	30/766 (3.9%)
11	n/N(%)	41/766 (5.4%)
12	n/N(%)	37/766 (4.8%)
> 12	n/N(%)	133/766 (17.4%)
Duration of dosing (weeks)		
	N	766
	Mean (SD)	20.5 (18.5)
	Median (Q1 ; Q3)	14.8 (8.0 ; 28.0)
	Min ; Max	2 ; 108
	Missing	0
Total cumulative dose (mg/kg)		
	N	763
	Mean (SD)	30.82 (26.82)
	Median (Q1 ; Q3)	23.31 (12.00 ; 42.24)
	Min ; Max	3.0 ; 184.3
	Missing	3
Actual dose intensity (mg/kg/week)		
	N	763
	Mean (SD)	1.49 (0.45)
	Median (Q1 ; Q3)	1.55 (1.22 ; 1.84)
	Min ; Max	0.1 ; 2.6
	Missing	3
Relative dose intensity (%)		
	N	763
	Mean (SD)	75.5 (22.0)
	Median (Q1 ; Q3)	79.0 (63.8 ; 92.6)
	Min ; Max	4 ; 129

A theoretical cycle is a 2-week period (14 days).
Number of cycles received: number of cycles with at least one dose intake of ZALTRAP.
Duration of exposition to the drug = (Day 1 last cycle with ZALTRAP -Day 1 cycle 1 with ZALTRAP + 14) /7
Actual and relative dose intensity are calculated using the overall treatment duration starting from first administration of study treatment, either ZALTRAP or FOLFIRI, to last study treatment administration exposure.
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Summary table for the ZALTRAP® treatment exposure, cumulative dose and dose intensity according to age is provided in Table 1.1.4-2a.

The median number of cycles with 5-FU per patient was 6 cycles, ranging from 0 to 46 cycles. This translated into a median duration of exposure of 16.0 weeks, ranging from 0 to 108 weeks. The median relative dose intensity was 82.9% (Table 20). Full details of the number of patients by cycle and 5-FU treatment exposure are provided in Table 1.1.4-3.

Table 20 - 5-FU treatment exposure, cumulative dose and dose intensity - All treated population

		ZALTRAP / FOLFIRI N=766
Total number of cycles administered per patient		
	N	766
	Mean (SD)	8.8 (7.0)
	Median (Q1 ; Q3)	6.0 (4.0 ; 12.0)
	Min ; Max	0 ; 46
	Missing	0
	Sum	6722
Total number of cycles administered by patient [n(%)]		
	N	766
0	n/N(%)	3/766 (0.4%)
1	n/N(%)	54/766 (7.0%)
2	n/N(%)	52/766 (6.8%)
3	n/N(%)	54/766 (7.0%)
4	n/N(%)	72/766 (9.4%)
5	n/N(%)	60/766 (7.8%)
6	n/N(%)	90/766 (11.7%)
7	n/N(%)	48/766 (6.3%)
8	n/N(%)	26/766 (3.4%)
9	n/N(%)	17/766 (2.2%)
10	n/N(%)	29/766 (3.8%)
11	n/N(%)	40/766 (5.2%)
12	n/N(%)	66/766 (8.6%)
> 12	n/(N%)	155/766 (20.2%)
Duration of dosing (weeks)		
	N	766
	Mean (SD)	21.7 (18.3)
	Median (Q1 ; Q3)	16.0 (9.1 ; 29.0)
	Min ; Max	0 ; 108
	Missing	0
Total cumulative dose (mg/m²)		
	N	766
	Mean (SD)	20583.32 (17056.84)
	Median (Q1 ; Q3)	16289.14 (8632.73 ; 28804.58)
	Min ; Max	0.0 ; 118820.0
	Missing	0
Actual dose intensity (mg/m²/week)		
	N	766
	Mean (SD)	978.19 (307.36)
	Median (Q1 ; Q3)	1003.46 (791.89 ; 1193.91)
	Min ; Max	0.0 ; 1705.2
	Missing	0

		ZALTRAP / FOLFIRI N=766
Relative dose intensity (%)		
	N	766
	Mean (SD)	80.9 (21.2)
	Median (Q1 ; Q3)	82.9 (70.4 ; 94.5)
	Min ; Max	0 ; 175
	Missing	0

A theoretical cycle is a 2-week period (14 days).
Number of cycles received: number of cycles with at least one dose intake of 5-FU.
Duration of exposition to the drug = (Day 1 last cycle with 5-FU -Day 1 cycle 1 with 5-FU +14)/7
Actual and relative dose intensity are calculated using the overall treatment duration (starting from first administration of study treatment, either ZALTRAP or FOLFIRI, to last study treatment administration
Relative dose intensity (%): missing includes patients for which planned dose is missing due to country dose banding guideline exposure.
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The median number of cycles with irinotecan per patient was 6 cycles, ranging from 0 to 46 cycles. This translated into a median duration of exposure of 15.1 weeks, ranging from 0 to 108 weeks. The median relative dose intensity was 81.4% (Table 21). Full details of the number of patients by cycle and irinotecan treatment exposure are provided in Table 1.1.4-4.

Table 21 - Irinotecan treatment exposure, cumulative dose and dose intensity - All treated population

		ZALTRAP / FOLFIRI N=766
Total number of cycles administered per patient		
	N	766
	Mean (SD)	8.4 (6.7)
	Median (Q1 ; Q3)	6.0 (4.0 ; 12.0)
	Min ; Max	0 ; 46
	Missing	0
	Sum	6437
Total number of cycles administered by patient [n(%)]		
	N	766
0	n/N(%)	1/766 (0.1%)
1	n/N(%)	56/766 (7.3%)
2	n/N(%)	52/766 (6.8%)
3	n/N(%)	57/766 (7.4%)
4	n/N(%)	74/766 (9.7%)
5	n/N(%)	64/766 (8.4%)
6	n/N(%)	99/766 (12.9%)
7	n/N(%)	47/766 (6.1%)
8	n/N(%)	25/766 (3.3%)
9	n/N(%)	21/766 (2.7%)
10	n/N(%)	28/766 (3.7%)
11	n/N(%)	40/766 (5.2%)
12	n/N(%)	71/766 (9.3%)
> 12	n/N(%)	130/766 (17.0%)

		ZALTRAP / FOLFIRI N=766
Duration of dosing (weeks)		
	N	766
	Mean (SD)	21.0 (18.1)
	Median (Q1 ; Q3)	15.1 (9.0 ; 27.4)
	Min ; Max	0 ; 108
	Missing	0
Total cumulative dose (mg/m²)		
	N	766
	Mean (SD)	1322.38 (1107.45)
	Median (Q1 ; Q3)	1039.64 (580.62 ; 1799.46)
	Min ; Max	0.0 ; 7841.6
	Missing	0
Actual dose intensity (mg/m²/week)		
	N	766
	Mean (SD)	63.90 (19.73)
	Median (Q1 ; Q3)	66.17 (52.23 ; 78.05)
	Min ; Max	0.0 ; 110.3
	Missing	0
Relative dose intensity (%)		
	N	766
	Mean (SD)	78.5 (21.7)
	Median (Q1 ; Q3)	81.4 (67.6 ; 93.8)
	Min ; Max	0 ; 175
	Missing	0

A theoretical cycle is a 2-week period (14 days).
Number of cycles received: number of cycles with at least one dose intake of irinotecan.
Duration of exposition to the drug = (Day 1 last cycle with irinotecan -Day 1 cycle 1 with irinotecan +14)/7
Actual and relative dose intensity are calculated using the overall treatment duration (starting from first administration of study treatment, either ZALTRAP or FOLFIRI, to last study treatment administration
Relative dose intensity (%): missing includes patients for which planned dose is missing due to country dose banding guideline exposure.
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A total of 277 (36.2%) patients had at least one dose modification of ZALTRAP® during the study. The most frequently dose modification reported with ZALTRAP® was dose omission reported in 223 (29.1%) patients and only dose reduction reported in 32 (4.2%) patients.

A total of 513 (67.0%) patients had at least one dose modification of 5-FU during the study. The most frequently dose modification reported with 5-FU was dose reduction reported in 272 (35.5%) patients.

Finally, a total of 393 (51.3%) patients had at least one dose modification of irinotecan during the study. The most frequently dose modification reported with irinotecan was dose reduction in 255 (33.3%) patients.

In 46 (6.0%) patients ZALTRAP® was not given as per protocol at Cycle 1. Of them, 29 patients started Cycle 1 only with FOLFIRI. Among them, 23 patients started ZALTRAP® on Cycle 2 and 3 patients on Cycle 3. Six patients started with a dose higher than 4 mg/kg on Cycle 1 and 11 with a dose lower than 4 mg/kg.

A total of 584 (76.2%) patients reported to have a delay in at least one cycle (Table 22).

Table 22 - Summary of patients with cycle delay and/or dose modification (by study drug) - All treated population

		ZALTRAP / FOLFIRI N=766
Patients with at least one dose modification[a] of ZALTRAP	n/N(%)	277/766 (36.2%)
Patients with ZALTRAP dose reduction only	n/N(%)	32/766 (4.2%)
Patients with ZALTRAP dose omission only	n/N(%)	223/766 (29.1%)
Patients with ZALTRAP dose reduction followed by dose omission	n/N(%)	9/766 (1.2%)
Patients with ZALTRAP dose omission followed by dose reduction	n/N(%)	2/766 (0.3%)
Patients with ZALTRAP dose not given as per protocol at cycle 1 [b]	n/N(%)	46/766 (6.0%)
Patients with at least one dose modification[a] of 5-FU	n/N(%)	513/766 (67.0%)
Patients with 5-FU dose reduction only	n/N(%)	272/766 (35.5%)
Patients with 5-FU dose omission only	n/N(%)	57/766 (7.4%)
Patients with 5-FU dose reduction followed by dose omission	n/N(%)	27/766 (3.5%)
Patients with 5-FU dose omission followed by dose reduction	n/N(%)	7/766 (0.9%)
Patients with 5-FU lower dose at cycle 1 [c]	n/N(%)	260/766 (33.9%)
Patients with at least one dose modification[a] of Irinotecan	n/N(%)	393/766 (51.3%)
Patients with irinotecan dose reduction only	n/N(%)	255/766 (33.3%)
Patients with irinotecan dose omission only	n/N(%)	62/766 (8.1%)
Patients with irinotecan dose reduction followed by dose omission	n/N(%)	51/766 (6.7%)
Patients with irinotecan dose omission followed by dose reduction	n/N(%)	5/766 (0.7%)
Patients with irinotecan lower dose at cycle 1 [c]	n/N(%)	36/766 (4.7%)
Patients with at least one cycle delayed [n(%)]	n/N(%)	584/766 (76.2%)
Between 3 and 7 days [n(%)]	n/N(%)	426/766 (55.6%)
More than 7 days [n(%)]	n/N(%)	431/766 (56.3%)
Patients with at least one cycle delayed of ZALTRAP [n(%)]	n/N(%)	520/766 (67.9%)
Between 3 and 7 days [n(%)]	n/N(%)	376/766 (49.1%)
More than 7 days [n(%)]	n/N(%)	369/766 (48.2%)
Number of cycles of ZALTRAP® omitted and total number of cycles of ZALTRAP®	n/N(%)	867/6135 (14.13%)
Number of cycles of ZALTRAP® reduced and not omitted and, total number of cycles of ZALTRAP®	n/N(%)	43/6135 (0.70%)
V DOSE REDUCTION	n/N(%)	42/6135 (0.68%)
V PROTOCOL DOSE	n/N(%)	1/6135 (0.02%)

A cycle is delayed if duration of previous cycle is greater than 14 + 2 days
[a] dose modification = (cycle 2 or more) dose reduction or (cycle 2 or more) dose omission or cycle 1 lower dose
[b] Protocol does not allow cycle 1 ZALTRAP dose modification
[c] Protocol allows 5-FU / Irinotecan dose lowering at cycle 1
A patient can be counted in cycle 1 dose modification and in a further cycle dose reduction/omission.
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Kaplan-Meier curve from time to first administration to permanent treatment discontinuation in months is provided Figure 1.

10.3 OUTCOME DATA

Not applicable.

10.4 MAIN RESULTS

10.4.1 Overall survival

At the study cut-off date, 563/766 (73.5%) patients had died at any time during the study.

Median (95% confidence interval [CI]) OS was 12.45 (11.56; 13.63) months (Table 23).

In this analysis, 203 (26.5%) patients were censored (either alive [n=170] or lost to follow-up [n=31]), including 88 patients with a follow-up ≤24 months. The median (Q1; Q3) time from last contact to study cut-off date for the patients with a follow-up ≤24 months was 0.7 (0.1; 15.2) months. Additional details on the censored patients are provided in Table 1.2.1-2.

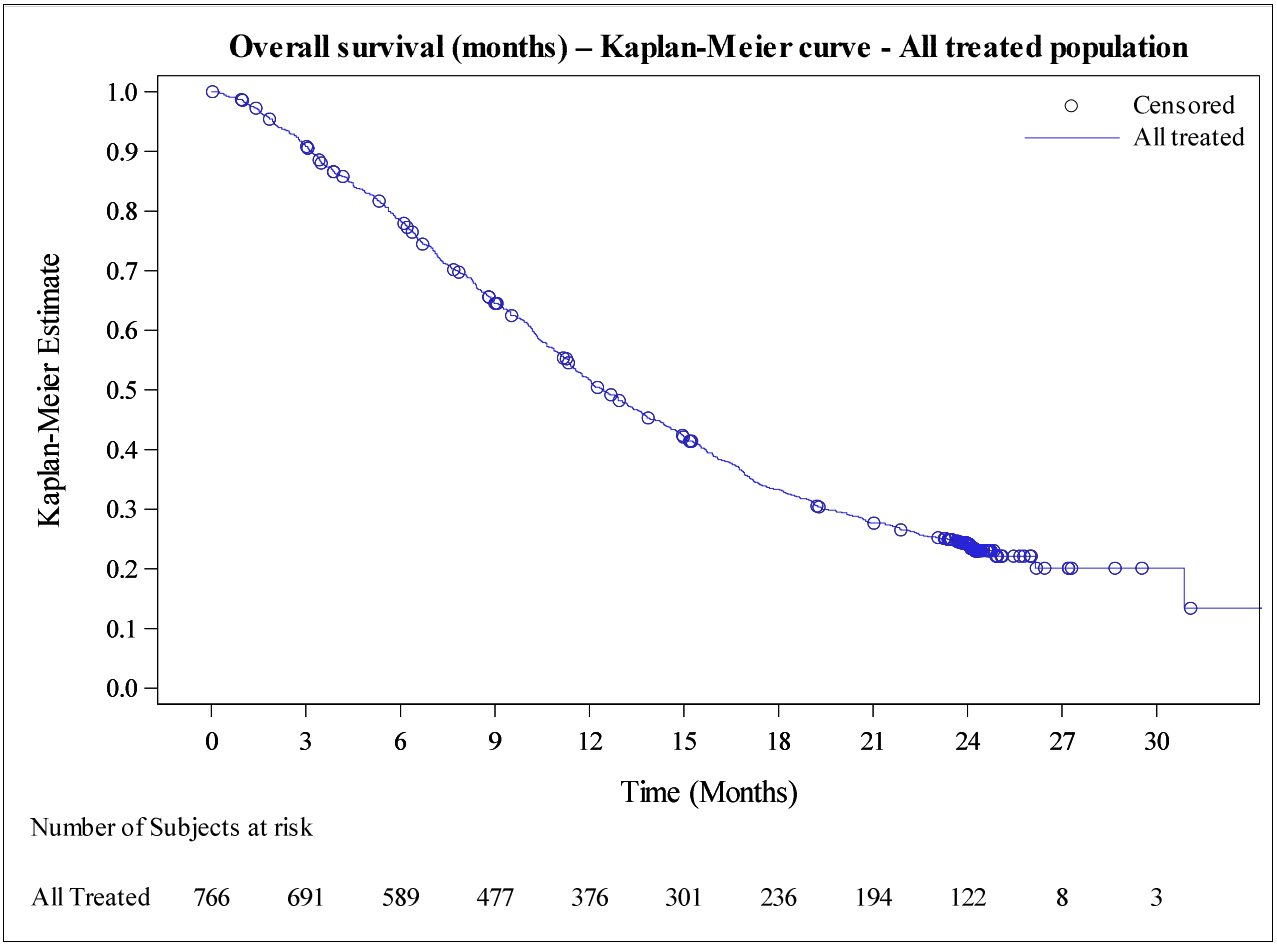
Table 23 - Overall survival (months) - Kaplan-Meier survival estimates - Primary analysis - All treated population

Time to event or censoring	All N=766
Overall [a]	766
Number of death events, n/N(%) [a]	563/ 766 (73.50 %)
25% quantile follow-up duration (95% CI) (months)	6.637 (6.111, 7.261)
Median follow-up duration (95% CI) (months)	12.45 (11.56, 13.63)
75% quantile follow-up duration (95% CI) (months)	23.36 (20.70, 30.88)
Number of patients at risk	766
3 Months	691
6 Months	589
9 Months	477
12 Months	376
15 Months	301
18 Months	236
21 Months	194
24 Months	122
Survival probability (95% CI)	
3 Months	0.908 (0.888, 0.929)
6 Months	0.785 (0.755, 0.814)
9 Months	0.645 (0.611, 0.679)
12 Months	0.517 (0.481, 0.553)
15 Months	0.421 (0.385, 0.457)
18 Months	0.334 (0.299, 0.368)
21 Months	0.277 (0.244, 0.309)
24 Months	0.241 (0.210, 0.273)

NA: Due to the structure of the events and censoring this data can not be calculated
Follow-up duration: time from 1st treatment administration to date of study withdrawal
[a] 5 patients with date of death or date of last contact imputed according to SAP:
Patients with date of death imputed: 276-006-001; 276-006-003 and 380-013-002
Patients censored with date of last contact imputed: 300-004-001 and 840-031-006

The Figure 2 shows overall survival:

Figure 2 - Overall survival (months) - Kaplan-Meier curve - All treated population



Multivariate analyses were performed for subgroups of interest, including age (<65 vs. ≥65), renal function status (impaired function, yes vs no), hepatic function status (impaired function, yes vs no), race (Caucasian vs non-Caucasian), and prior anticancer treatments (number of lines: 1 vs ≥2 and prior bevacizumab: yes vs no).

Analysis of overall survival for each subgroup was also performed using a multivariate Cox model. For each subgroup, prognostic factors to be used as covariates in the multivariate analyses were selected using prior univariate analyses.

Among all potential prognostic factors and subgroups, the univariate analysis identified the following factors that may have an impact on the overall survival outcome: ECOG PS, number of organs involved, liver metastasis, prior hypertension, geographical region, hepatic impairment and prior anti-cancer therapy (number of lines and prior bevacizumab) (Table 1.2.1-3). These factors were further tested for multicollinearity, for final selection, for each of the subgroup multivariate analyses (Table 1.2.1-4).

Overall survival by age:

Median (95% CI) overall survival was 12.91 (11.56; 14.88) months in patients aged ≥65 years old and 11.96 (10.97; 13.63) months in patients aged less than 65 years old.

Adjustment on prognostic factors, including ECOG PS, hepatic impairment and prior treatment with bevacizumab, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 0.951 (0.794; 1.139) (Table 1.2.1-5).

Overall survival by renal impairment status at baseline:

Median (95% CI) overall survival was 12.52 (11.56; 15.08) months in patients with renal impairment at baseline and 12.09 (11.17; 13.63) months in patients without renal impairment at baseline.

Adjustment on prognostic factors, including ECOG PS, hepatic impairment and prior treatment with bevacizumab, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 0.908 (0.749; 1.100) (Table 1.2.1-5).

Overall survival by hepatic impairment status at baseline:

Median (95% CI) overall survival was 8.739 (6.834; 10.64) months in patients with hepatic impairment and 13.67 (12.12; 15.05) months in patients without hepatic impairment. There was no overlap in CI.

Adjustment on prognostic factors, including ECOG PS; prior treatment with bevacizumab, interaction between hepatic impairment and ECOG PS, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.561 (1.255; 1.941), favoring the subgroup of patients with no hepatic impairment.

A retrospective analysis of disease characteristics (see Table 1.1.2-4a) showed a higher proportion of patients with liver metastasis in the subgroup of patients with impaired hepatic function by comparison to patients without impaired hepatic function (79.8% vs 64.8%). Also more patients with impaired hepatic function were metastatic at diagnosis (81.4% vs 66.7%). (Table 1.2.1-5).

Overall survival by race:

Median (95% CI) overall survival was 12.12 (8.805; 14.39) months in non-Caucasian patients and 12.45 (11.47; 13.73) months in Caucasian patients.

Adjustment on prognostic factors, including race, ECOG PS, hepatic impairment and prior treatment with bevacizumab, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.070 (0.789; 1.450) (Table 1.2.1-5).

Overall survival by prior anti-cancer treatment (number of lines):

Median (95% CI) overall survival was 12.58 (11.37; 14.59) months in patients with >1 line of anti-cancer therapy and 12.16 (11.01; 13.67) in patients with 0-1 line of prior anti-cancer therapy.

Adjustment on prognostic factors, including ECOG PS, hepatic impairment, interactions between prior anti-cancer therapy (number of line) with ECOG PS and with geographical region, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 0.916 (0.764; 1.097). (Table 1.2.1-5).

Overall survival by prior anti-cancer treatment (bevacizumab):

Median (95% CI) overall survival was 10.61 (9.495; 11.73) months in patients with prior bevacizumab and 16.62 (14.09; 18.17) months in patients without prior bevacizumab. There was no overlap in CI.

Adjustment on prognostic factors, including prior bevacizumab, ECOG PS, interaction with patients with hepatic impairment, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.666 (1.379; 2.013), favoring the subgroup of patients without prior use of bevacizumab. (Table 1.2.1-5).

10.4.2 Progression free survival

A total of 669 (87.3%) patients had disease progression or died prior to progression during the study.

Median (95% confidence interval [CI]) PFS was 6.078 (5.552; 6.669) months (Table 24).

A total of 97 patients were censored (77 patients were alive after completing the 24 months follow-up and 18 were lost to follow up, for 2 patients no information was available). Progression was reported in 554 (82.8%) of the 669 patients and death without disease progression was reported in 115 (17.2%) of the 669 patients. Additional details on the summary of patients with event or patients censored are provided in Table 1.2.2-2.

Table 24 - Progression free survival (months) - Kaplan-Meier survival estimates - All treated population

Time to event or censoring	All N=766
Number assessed [a]	766
Number of progression events, n/N(%) [a]	669/ 766 (87.34 %)
25% quantile PFS (95% CI) (months)	2.957 (2.793, 3.187)
Median PFS (95% CI) (months)	6.078 (5.552, 6.669)
75% quantile PFS (95% CI) (months)	11.10 (9.988, 12.19)
Number of patients at risk	766
3 Months	565
6 Months	379
9 Months	244
12 Months	167
15 Months	126
18 Months	98
21 Months	85
24 Months	56
Survival probability (95% CI)	
3 Months	0.743 (0.712, 0.774)
6 Months	0.503 (0.467, 0.539)
9 Months	0.329 (0.296, 0.363)
12 Months	0.226 (0.196, 0.256)
15 Months	0.177 (0.150, 0.204)
18 Months	0.140 (0.115, 0.165)
21 Months	0.123 (0.099, 0.147)
24 Months	0.106 (0.084, 0.129)

[a] 3 patients with date of death or date of last contact imputed according to SAP:
Patient with date of death imputed: 276-006-003
Patients censored with date of last contact imputed: 300-004-001 and 840-031-006
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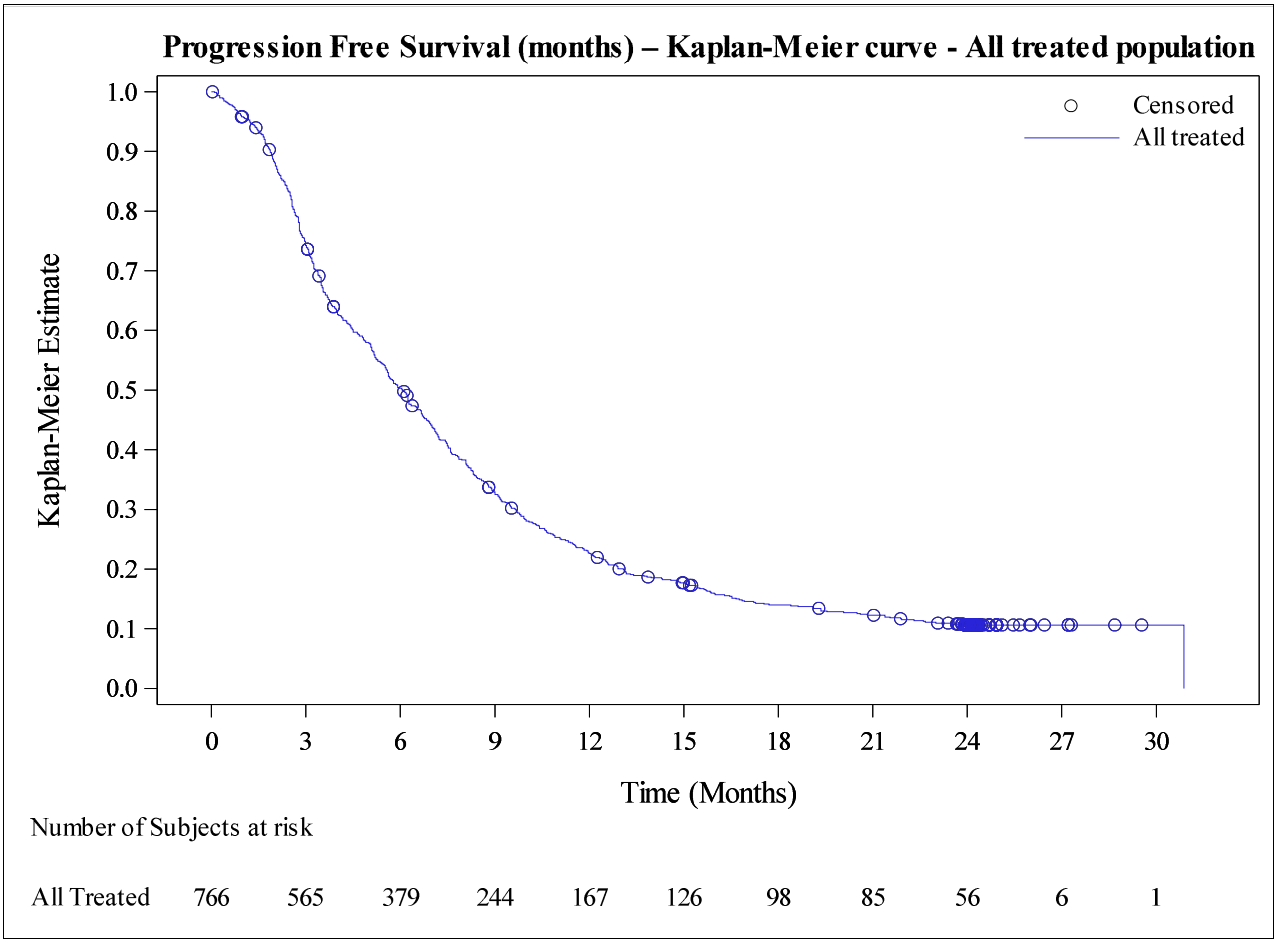
Figure 3 shows the progression free survival:

Figure 3 - Progression free survival (months) - Kaplan-Meier curve - All treated population



Multivariate analyses were performed for subgroups of interest, including age (<65 vs. ≥65), renal function status (impaired function, yes vs no), hepatic function status (impaired function, yes vs no), race (Caucasian vs non-Caucasian), and prior anticancer treatments (number of lines: 1 vs ≥2 and prior bevacizumab: yes vs no).

Analysis of progression free survival for each subgroup was performed using a multivariate Cox model. For each subgroup, prognostic factors to be used as covariates in the multivariate analyses were selected using prior univariate analyses (Table 1.2.2-3). These factors were further tested for multicollinearity, for final selection, for each of the subgroup multivariate analyses (Table 1.2.2-4).

Progression free survival by age:

Median (95% CI) progression free survival was 6.472 (5.684; 7.228) months in patients aged ≥65 years old and 5.552 (4.895; 6.275) months in patients aged less than 65 years old.

Adjustment on prognostic factors, including age, ECOG PS, prior treatment with bevacizumab and interaction between age and baseline hepatic impairment status, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 0.871 (0.737; 1.028) (Table 1.2.2-5).

Progression free survival by renal impairment status at baseline:

Median (95% CI) progression free survival was 6.275 (5.618; 7.228) months in patients with renal impairment at baseline and 5.881 (5.158; 6.669) months in patients without renal impairment at baseline.

Adjustment on prognostic factors, including ECOG PS, hepatic impairment and prior treatment with bevacizumab, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 0.960 (0.806; 1.144) (Table 1.2.2-5).

Progression free survival by hepatic impairment status at baseline:

Median (95% CI) progression free survival was 4.402 (3.088; 5.585) months in patients with hepatic impairment and 6.275 (5.717; 6.998) months in patients without hepatic impairment. There was no overlap in CI.

Adjustment on prognostic factors, including ECOG PS and prior treatment with bevacizumab, was made for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.424 (1.160; 1.748), favoring the subgroup of patients with no hepatic impairment.

A retrospective analysis of disease characteristics (see Table 1.1.2-4a) showed a higher proportion of patients with liver metastasis in the subgroup of patients with impaired hepatic function by comparison to patients without impaired hepatic function (79.8% vs 64.8%). Also more patients with impaired hepatic function were metastatic at diagnosis (81.4% vs 66.7%) (Table 1.2.2-5).

Progression free survival by race:

Median (95% CI) progression free survival was 4.402 (3.483; 6.834) months in non-Caucasian patients and 6.209 (5.618; 6.735) months in Caucasian patients.

Adjustment on prognostic factors, including number of organs involved and hepatic impairment, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.220 (0.924; 1.611) (Table 1.2.2-5).

Progression free survival by prior anti-cancer treatment (number of lines):

Median (95% CI) progression free survival was 5.782 (5.224; 6.669) months in patients with >1 line of anti-cancer therapy and 6.275 (5.388; 7.129) in patients with 0-1 line of prior anti-cancer therapy.

Adjustment on prognostic factors, including ECOG PS, hepatic impairment, prior bevacizumab therapy and interaction between number of line of prior anti-cancer therapy and ECOG, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.096 (0.927; 1.296). (Table 1.2.2-5).

Progression free survival by prior anti-cancer treatment (bevacizumab):

Median (95% CI) progression free survival was 5.224 (4.435; 5.782) months in patients with prior bevacizumab and 7.458 (6.275; 8.411) months in patients without prior bevacizumab. There was no overlap in CI.

Adjustment on prognostic factors, including ECOG PS and hepatic impairment, was used for the multivariate analysis, and the estimated hazard ratio (95% CI) was 1.585 (1.333; 1.883), favoring the subgroup of patients without prior use of bevacizumab (Table 1.2.2-5).

10.4.3 Overall response rate

Of the 766 patients included, 125 patients reported objective response (CR or PR) to treatment. Overall response rate (95% CI) was 16.3% [13.77; 19.13] (Table 25). Ten (1.3%) patients reported complete response and 115 (15.0%) patients reported partial response.

Stable disease was reported as best response in 264 (34.5%) patients.

Progressive disease was reported as the best response in 260 (33.9%) patients.

Table 25 - Summary of overall response rate - All treated population

		ZALTRAP / FOLFIRI N=766
Best Overall Response		
	N	766
Complete response	N	10/766 (1.3%)
Partial Response	N	115/766 (15.0%)
Stable Disease	N	264/766 (34.5%)
Progressive Disease	N	260/766 (33.9%)
Not Evaluable	N	68/766 (8.9%)
Unknown	N	49/766 (6.4%)
Objective Response		
	N	766
Responders [a] (complete response or partial response)	N	125/766 (16.3%)
95% CI [b]	N	[13.77 , 19.13]

[a] Patients are responders if their BOR is Complete response or Partial response and are no responders otherwise.
[b] 95% CI Clopper-Pearson exact
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Among all the potential prognostic factors tested, the univariate analysis identified the following factors that may have an impact on the overall response rate outcome: ECOG PS, location of primary tumor, number of organs involved, liver metastasis, geographical region, age, renal impairment, hepatic impairment and prior treatment with bevacizumab (Table 1.2.3-2).

As for overall survival and progression free survival endpoints, analysis of objective response was performed for each subgroup of interest. Overall response rate was analyzed using a multivariate logistic model:

- Response rate by age: responders' rate (95% CI) was 11.51% (8.52%; 15.10%) in patients <65 years and 19.18% (15.27%; 23.60%) in patients ≥65 years, showing an odds ratio (95% CI) 1.842 (1.208; 2.810) after adjustment on pre-selected prognostic factors: ECOG PS and prior bevacizumab.
- Response rate by renal function status: responders' rate (95% CI) was 13.47% (10.53%; 16.88%) in patients without renal impairment and 19.37% (14.69%; 24.78%) responders in patients with renal impairment, showing an odds ratio (95% CI) 1.517 (0.989; 2.328) after adjustment on pre-selected prognostic factors: ECOG PS and prior bevacizumab.
- Response rate by hepatic function status: responders' rate (95% CI) was 16.96% (13.83%; 20.47%) in patients without hepatic impairment and 10.85% (6.06%; 17.54%) responders in patients with hepatic impairment, showing an odds ratio (95% CI) 0.625 (0.333; 1.173) after adjustment on pre-selected prognostic factors: ECOG PS and prior bevacizumab.
- Response rate by race: responders' rate (95% CI) was 15.4% (12.77%; 18.33%) in Caucasian patients and 14.29% (7.07%; 24.71%) responders in non-Caucasian patients, showing an odds ratio (95% CI) 0.307 (0.007; 2.114) after adjustment on pre-selected prognostic factors: ECOG PS, age and prior bevacizumab.
- Response rate by number of prior lines of chemotherapy: responders' rate (95% CI) was 16.22% (12.46%; 20.59%)in patients with 0-1 line of anti-cancer therapy and 14.39% (11.16%; 18.13%) responders in patients with >1 line of anti-cancer therapy, showing an odds ratio (95% CI) 0.998 (0.656; 1.520) after adjustment on pre-selected prognostic factors: ECOG PS, age and prior bevacizumab.
- Response rate by prior bevacizumab: responders' rate (95% CI) was 20.58% (16.22%; 25.50%) in patients without previous use of bevacizumab therapy and 11.46% (8.65%; 14.79%) responders in patients with previous use of bevacizumab therapy, showing an odds ratio (95% CI) 0.511 (0.338; 0.775) after adjustment on pre-selected prognostic factors: ECOG PS and age.

10.5 OTHER ANALYSES

Not applicable.

10.6 ADVERSE EVENTS/ADVERSE REACTIONS

10.6.1 Brief summary of adverse events

All adverse events were coded using the MedDRA dictionary version 21.0 and graded using NCI CTC Version 4.03.

During the study, overall 753 (98.3%) out of the 766 treated patients experienced at least one treatment emergent adverse event (TEAE), and 523 patients (68.3%) experienced at least on TEAE of Grade ≥3. A total of 60 patients (7.8%) experienced a TEAE leading to death, including those in the context of disease progression. TEAEs possibly related to the study medication were reported in 692 patients (90.3%). Serious TEAEs were reported in 334 patients (43.6%), being reported as possibly related in 185 patients (24.2%).

A total 115 patients (15.0%) experienced a TEAE leading to permanent study treatment discontinuation and 102 (13.3%) patients reported a TEAE leading to the premature discontinuation either of ZALTRAP® or FOLFIRI (Table 26).

Table 26 - Overview of adverse events: Number (%) of patients - All Treated Population

	ZALTRAP /FOLFIRI N=766	95% CI(Proportion)
Number of patients with		
Any TEAE	753/766 (98.3%)	[97.1 %,99.1 %]
Any Possible related TEAE	692/766 (90.3%)	[88.0 %,92.3 %]
Any Grade 5 TEAE	59/766 (7.7%)	[5.9 %, 9.8 %]
Any Grade [3-4] TEAE	508/766 (66.3%)	[62.9 %,69.7 %]
Any Grade >=3 TEAE	523/766 (68.3%)	[64.9 %,71.6 %]
Any Grade [3-4] related TEAE	384/766 (50.1%)	[46.5 %,53.7 %]
Any Serious TEAE	334/766 (43.6%)	[40.1 %,47.2 %]
Any Serious related TEAE	185/766 (24.2%)	[21.2 %,27.3 %]
Any TEAE leading to death	60/766 (7.8%)	[6.0 %,10.0 %]
Any TEAE leading to permanent treatment discontinuation	115/766 (15.0%)	[12.6 %,17.7 %]
Any TEAE leading to premature treatment discontinuation	102/766 (13.3%)	[11.0 %,15.9 %]

n (%) = number and percentage of patients with at least one adverse event.
TEAE: Treatment-emergent adverse event.
TEAE leading to permanent treatment discontinuation: TEAE leading to stop of the combination of ZALTRAP and FOLFIRI or any of the still ongoing treatment if prior premature discontinuation
TEAE leading to premature treatment discontinuation: TEAE leading to stop of ZALTRAP with FOLFIRI continued, or to stop of FOLFIRI (last component of FOLFIRI) with ZALTRAP continued
Patient 380-019-005 with Post-Treatment leading to permanent treatment discontinuation not displayed in this table.
Grade 3-4 TEAE is defined as any TEAE grade 3-4 regardless patients did experienced or not a grade 5 TEAE.
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Data on overview of adverse events per cycle is provided in Table 1.3.1-2.

10.6.2 Display of adverse events

The summary of TEAE(s) presented by Primary System Organ Class (SOC), High Level Grouped Term (HLGT), High level term (HLT) and Preferred Term (PT) and worst National Cancer Institute (NCI) Grade is provided in Table 1.3.1-3, and by SOC and PT in Table 1.3.1-4. Summary of adverse events per cycle is provided in Table 1.3.1-5.

Table 27 shows the summary of the number of patients with TEAEs reported by Primary SOC and worst NCI Grade.

At the SOC level, the most frequently reported TEAEs were Gastrointestinal disorders (85.6%) and General disorders and administration site conditions (68.4%). Hematological events are not generally mentioned in the text, as there was no systematic collection of laboratory results.

The most frequently reported Gastrointestinal disorders (all grades) were diarrhea (56.3%), nausea (34.3%), stomatitis and ulceration (HLT) (39.3%), vomiting (21.5%) and abdominal pain (21.7%). In the General disorders SOC, the most frequently reported TEAEs (all grades) were asthenic conditions (HLT) (58.4%).

By decreasing order of frequency, the most frequent TEAEs (≥20%, all grades, regardless of relationship to study treatment) were diarrhea, asthenic conditions (HLT), stomatitis and ulceration (HLT), infections (SOC), nausea, hypertension (HLGT), gastrointestinal and abdominal pains (HLT), decreased appetite and vomiting.

Grade ≥3 events were reported in 68.3% of the patients.

By decreasing order of frequency, the most frequent Grade ≥3 TEAEs (≥5%, regardless of relationship to study treatment) were asthenic conditions (HLT), hypertension (HLGT), diarrhea, infection (SOC) and stomatitis and ulceration (HLT).

The adverse events reported with the highest percentage of administered cycles (>10% of cycles, all grades) were: diarrhea (28.1%), asthenia (25.4%), hypertension (18.4%), stomatitis (18.1%), fatigue (12.4%) and nausea (12.0%).

Grade ≥3 TEAEs reported in the highest percentage of cycles (>2%) were: hypertension (4.0%), neutropenia (3.1%) and diarrhea (2.4%).

Table 27 - Summary of TEAEs by Primary SOC and Worst NCI Grade - Number of patients - All treated population

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)					
	All Grades	Grades >=3	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	753 (98.3%)	523 (68.3%)	464 (60.6%)	361 (47.1%)	103 (13.4%)	59 (7.7%)
INFECTIONS AND INFESTATIONS	269 (35.1%)	69 (9.0%)	63 (8.2%)	49 (6.4%)	14 (1.8%)	6 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	14 (1.8%)	4 (0.5%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	277 (36.2%)	142 (18.5%)	141 (18.4%)	99 (12.9%)	42 (5.5%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	6 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	4 (0.5%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	249 (32.5%)	48 (6.3%)	48 (6.3%)	40 (5.2%)	8 (1.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	82 (10.7%)	11 (1.4%)	10 (1.3%)	6 (0.8%)	4 (0.5%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	258 (33.7%)	32 (4.2%)	28 (3.7%)	24 (3.1%)	4 (0.5%)	4 (0.5%)
EYE DISORDERS	37 (4.8%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	19 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	40 (5.2%)	13 (1.7%)	13 (1.7%)	9 (1.2%)	4 (0.5%)	0 (0.0%)
VASCULAR DISORDERS	256 (33.4%)	91 (11.9%)	91 (11.9%)	83 (10.8%)	8 (1.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	335 (43.7%)	48 (6.3%)	45 (5.9%)	40 (5.2%)	5 (0.7%)	3 (0.4%)
GASTROINTESTINAL DISORDERS	656 (85.6%)	213 (27.8%)	206 (26.9%)	176 (23.0%)	30 (3.9%)	7 (0.9%)
HEPATOBILIARY DISORDERS	48 (6.3%)	13 (1.7%)	12 (1.6%)	11 (1.4%)	1 (0.1%)	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	213 (27.8%)	11 (1.4%)	11 (1.4%)	11 (1.4%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	177 (23.1%)	20 (2.6%)	20 (2.6%)	19 (2.5%)	1 (0.1%)	0 (0.0%)
RENAL AND URINARY DISORDERS	164 (21.4%)	31 (4.0%)	31 (4.0%)	29 (3.8%)	2 (0.3%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	26 (3.4%)	5 (0.7%)	5 (0.7%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	524 (68.4%)	157 (20.5%)	120 (15.7%)	112 (14.6%)	8 (1.0%)	37 (4.8%)
INVESTIGATIONS	178 (23.2%)	40 (5.2%)	40 (5.2%)	29 (3.8%)	11 (1.4%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	43 (5.6%)	11 (1.4%)	11 (1.4%)	9 (1.2%)	2 (0.3%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	12 (1.6%)	4 (0.5%)	4 (0.5%)	3 (0.4%)	1 (0.1%)	0 (0.0%)
PRODUCT ISSUES	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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10.6.2.1 Display of adverse events by subgroups of interest

Subgroups of interest (elderly, renal impairment, hepatic impairment, non-Caucasian, prior anti-cancer therapies and prior use of bevacizumab) were selected for analysis. The following tables show the summary of the number of patients with TEAEs reported by Primary SOC and worst NCI Grade per subgroup.

Among the 766 patients, 370 (48.3%) were aged 65 or more (Table 28). At the SOC level, there was no SOC with an excess in incidence of "any TEAE", all grades, of more than 5% in the elderly population when compared to the less than 65 years old population.

Grades ≥3 events in the General disorders and administration site condition SOC were more frequent in the elderly population when compared to the patients aged less than 65 (25.4% vs. 15.9%). At the SOC level, no difference of more than 2% excess in the elderly population was reported for any of the other SOCs. Data on all the TEAEs reported by PT by age group is provided in Table 1.3.1-4.1.

Table 28 - Summary of TEAEs by Primary SOC and Worst NCI Grade by age group (<65 / ≥65 years) - Number of patients - All treated population

PRIMARY SYSTEM ORGAN CLASS	Age < 65 (N=396)					Age >= 65 (N=370)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	389 (98.2%)	237 (59.8%)	178 (44.9%)	59 (14.9%)	29 (7.3%)	364 (98.4%)	227 (61.4%)	183 (49.5%)	44 (11.9%)	30 (8.1%)
INFECTIONS AND INFESTATIONS	157 (39.6%)	39 (9.8%)	33 (8.3%)	6 (1.5%)	3 (0.8%)	112 (30.3%)	24 (6.5%)	16 (4.3%)	8 (2.2%)	3 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	13 (3.3%)	3 (0.8%)	2 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	145 (36.6%)	75 (18.9%)	53 (13.4%)	22 (5.6%)	1 (0.3%)	132 (35.7%)	66 (17.8%)	46 (12.4%)	20 (5.4%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	4 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	2 (0.5%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDER	122 (30.8%)	25 (6.3%)	21 (5.3%)	4 (1.0%)	0 (0.0%)	127 (34.3%)	23 (6.2%)	19 (5.1%)	4 (1.1%)	0 (0.0%)
PSYCHIATRIC DISORDERS	47 (11.9%)	5 (1.3%)	3 (0.8%)	2 (0.5%)	0 (0.0%)	35 (9.5%)	5 (1.4%)	3 (0.8%)	2 (0.5%)	1 (0.3%)
NERVOUS SYSTEM DISORDERS	148 (37.4%)	14 (3.5%)	11 (2.8%)	3 (0.8%)	4 (1.0%)	110 (29.7%)	14 (3.8%)	13 (3.5%)	1 (0.3%)	0 (0.0%)
EYE DISORDERS	13 (3.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	24 (6.5%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	12 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	20 (5.1%)	6 (1.5%)	5 (1.3%)	1 (0.3%)	0 (0.0%)	20 (5.4%)	7 (1.9%)	4 (1.1%)	3 (0.8%)	0 (0.0%)
VASCULAR DISORDERS	141 (35.6%)	51 (12.9%)	48 (12.1%)	3 (0.8%)	0 (0.0%)	115 (31.1%)	40 (10.8%)	35 (9.5%)	5 (1.4%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	172 (43.4%)	20 (5.1%)	17 (4.3%)	3 (0.8%)	2 (0.5%)	163 (44.1%)	25 (6.8%)	23 (6.2%)	2 (0.5%)	1 (0.3%)
GASTROINTESTINAL DISORDERS	346 (87.4%)	109 (27.5%)	94 (23.7%)	15 (3.8%)	5 (1.3%)	310 (83.8%)	97 (26.2%)	82 (22.2%)	15 (4.1%)	2 (0.5%)
HEPATOBILIARY DISORDERS	32 (8.1%)	7 (1.8%)	6 (1.5%)	1 (0.3%)	1 (0.3%)	16 (4.3%)	5 (1.4%)	5 (1.4%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	110 (27.8%)	8 (2.0%)	8 (2.0%)	0 (0.0%)	0 (0.0%)	103 (27.8%)	3 (0.8%)	3 (0.8%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	114 (28.8%)	10 (2.5%)	10 (2.5%)	0 (0.0%)	0 (0.0%)	63 (17.0%)	10 (2.7%)	9 (2.4%)	1 (0.3%)	0 (0.0%)
RENAL AND URINARY DISORDERS	77 (19.4%)	15 (3.8%)	14 (3.5%)	1 (0.3%)	0 (0.0%)	87 (23.5%)	16 (4.3%)	15 (4.1%)	1 (0.3%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	18 (4.5%)	2 (0.5%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	8 (2.2%)	3 (0.8%)	3 (0.8%)	0 (0.0%)	0 (0.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	265 (66.9%)	49 (12.4%)	42 (10.6%)	7 (1.8%)	14 (3.5%)	259 (70.0%)	71 (19.2%)	70 (18.9%)	1 (0.3%)	23 (6.2%)
INVESTIGATIONS	104 (26.3%)	30 (7.6%)	20 (5.1%)	10 (2.5%)	0 (0.0%)	74 (20.0%)	10 (2.7%)	9 (2.4%)	1 (0.3%)	0 (0.0%)

PRIMARY SYSTEM ORGAN CLASS	Age < 65 (N=396)					Age >= 65 (N=370)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19 (4.8%)	6 (1.5%)	4 (1.0%)	2 (0.5%)	0 (0.0%)	24 (6.5%)	5 (1.4%)	5 (1.4%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	5 (1.3%)	4 (1.0%)	3 (0.8%)	1 (0.3%)	0 (0.0%)	7 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PRODUCT ISSUES	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Among the 738 patients with renal status documented at baseline, 258 (34.9%) were reported with creatinine clearance ≤80 mL/min (Table 29). At the SOC level, there was no SOC with an excess of incidence of "any TEAE", all grades, of more than 5% in the patient with impaired renal function when compared to these with normal renal function. No difference of more than 2% excess, in any Grade ≥3 events, in the population with impaired renal function was reported at the SOC level.

Data on all the TEAEs reported by PT by renal impairment group is provided in Table 1.3.1-4.2.

Table 29 - Summary of TEAEs by Primary SOC and Worst NCI Grade by renal impairment (Yes / No) - Number of patients - All treated population

PRIMARY SYSTEM ORGAN CLASS	Renal Impairment=No (N=480)					Renal Impairment=Yes (N=258)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	472 (98.3%)	288 (60.0%)	216 (45.0%)	72 (15.0%)	37 (7.7%)	253 (98.1%)	160 (62.0%)	131 (50.8%)	29 (11.2%)	18 (7.0%)
INFECTIONS AND INFESTATIONS	181 (37.7%)	48 (10.0%)	40 (8.3%)	8 (1.7%)	3 (0.6%)	77 (29.8%)	13 (5.0%)	8 (3.1%)	5 (1.9%)	2 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	9 (1.9%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	5 (1.9%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	178 (37.1%)	92 (19.2%)	67 (14.0%)	25 (5.2%)	0 (0.0%)	86 (33.3%)	44 (17.1%)	28 (10.9%)	16 (6.2%)	1 (0.4%)
IMMUNE SYSTEM DISORDERS	5 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	3 (0.6%)	2 (0.4%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	153 (31.9%)	28 (5.8%)	24 (5.0%)	4 (0.8%)	0 (0.0%)	88 (34.1%)	19 (7.4%)	15 (5.8%)	4 (1.6%)	0 (0.0%)
PSYCHIATRIC DISORDERS	59 (12.3%)	8 (1.7%)	4 (0.8%)	4 (0.8%)	1 (0.2%)	17 (6.6%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	166 (34.6%)	15 (3.1%)	11 (2.3%)	4 (0.8%)	2 (0.4%)	83 (32.2%)	13 (5.0%)	13 (5.0%)	0 (0.0%)	2 (0.8%)
EYE DISORDERS	20 (4.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	16 (6.2%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	13 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	22 (4.6%)	6 (1.3%)	4 (0.8%)	2 (0.4%)	0 (0.0%)	17 (6.6%)	6 (2.3%)	4 (1.6%)	2 (0.8%)	0 (0.0%)
VASCULAR DISORDERS	172 (35.8%)	61 (12.7%)	55 (11.5%)	6 (1.3%)	0 (0.0%)	76 (29.5%)	28 (10.9%)	26 (10.1%)	2 (0.8%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	218 (45.4%)	28 (5.8%)	25 (5.2%)	3 (0.6%)	2 (0.4%)	106 (41.1%)	14 (5.4%)	12 (4.7%)	2 (0.8%)	1 (0.4%)
GASTROINTESTINAL DISORDERS	414 (86.3%)	137 (28.5%)	115 (24.0%)	22 (4.6%)	4 (0.8%)	215 (83.3%)	61 (23.6%)	54 (20.9%)	7 (2.7%)	2 (0.8%)
HEPATOBILIARY DISORDERS	37 (7.7%)	6 (1.3%)	5 (1.0%)	1 (0.2%)	1 (0.2%)	11 (4.3%)	6 (2.3%)	6 (2.3%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	131 (27.3%)	6 (1.3%)	6 (1.3%)	0 (0.0%)	0 (0.0%)	71 (27.5%)	5 (1.9%)	5 (1.9%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	122 (25.4%)	15 (3.1%)	15 (3.1%)	0 (0.0%)	0 (0.0%)	49 (19.0%)	5 (1.9%)	4 (1.6%)	1 (0.4%)	0 (0.0%)
RENAL AND URINARY DISORDERS	100 (20.8%)	18 (3.8%)	16 (3.3%)	2 (0.4%)	0 (0.0%)	61 (23.6%)	13 (5.0%)	13 (5.0%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	16 (3.3%)	2 (0.4%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	10 (3.9%)	3 (1.2%)	3 (1.2%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	330 (68.8%)	69 (14.4%)	62 (12.9%)	7 (1.5%)	25 (5.2%)	172 (66.7%)	45 (17.4%)	44 (17.1%)	1 (0.4%)	10 (3.9%)
INVESTIGATIONS	110 (22.9%)	29 (6.0%)	20 (4.2%)	9 (1.9%)	0 (0.0%)	61 (23.6%)	10 (3.9%)	8 (3.1%)	2 (0.8%)	0 (0.0%)

PRIMARY SYSTEM ORGAN CLASS	Renal Impairment=No (N=480)					Renal Impairment=Yes (N=258)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	25 (5.2%)	6 (1.3%)	5 (1.0%)	1 (0.2%)	0 (0.0%)	17 (6.6%)	4 (1.6%)	3 (1.2%)	1 (0.4%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	4 (0.8%)	3 (0.6%)	2 (0.4%)	1 (0.2%)	0 (0.0%)	8 (3.1%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
PRODUCT ISSUES	3 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Renal impairment: Defined as Creatinine clearance <=80 mL/min
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Among the 657 patients with liver function documented at baseline, 129 (19.6%) had an impaired liver function (total bilirubin >ULN or AST or ALT >1.5 ULN) (Table 30). At the SOC level, there was an excess in incidence of "any TEAE", all grades, of more than 5% in the patients with an impaired liver function for the Hepatobiliary disorders SOC, by comparison to the patients with normal liver function (11.6% vs. 6.1%). Grade ≥3 events in the Nervous system disorders SOC and in the Gastrointestinal disorders SOC were reported in an excess of more than 2% in the patients with impaired liver function when compared to these with normal liver function (9.4% vs. 3.6%, and 29.5% vs. 27.3%, respectively).

Data on all the TEAEs reported by PT by hepatic impairment group is provided in Table 1.3.1-4.3.

Table 30 - Summary of TEAEs by Primary SOC and Worst NCI Grade by hepatic impairment (Yes / No) - Number of patients - All Treated Population

PRIMARY SYSTEM ORGAN CLASS	Hepatic Impairment=No (N=528)					Hepatic Impairment=Yes (N=129)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	518 (98.1%)	319 (60.4%)	249 (47.2%)	70 (13.3%)	31 (5.9%)	127 (98.4%)	78 (60.5%)	59 (45.7%)	19 (14.7%)	19 (14.7%)
INFECTIONS AND INFESTATIONS	184 (34.8%)	45 (8.5%)	37 (7.0%)	8 (1.5%)	2 (0.4%)	42 (32.6%)	11 (8.5%)	9 (7.0%)	2 (1.6%)	1 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	8 (1.5%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	2 (1.6%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	186 (35.2%)	90 (17.0%)	63 (11.9%)	27 (5.1%)	1 (0.2%)	50 (38.8%)	23 (17.8%)	14 (10.9%)	9 (7.0%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	6 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	3 (0.6%)	2 (0.4%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	181 (34.3%)	35 (6.6%)	31 (5.9%)	4 (0.8%)	0 (0.0%)	47 (36.4%)	9 (7.0%)	6 (4.7%)	3 (2.3%)	0 (0.0%)
PSYCHIATRIC DISORDERS	60 (11.4%)	7 (1.3%)	5 (0.9%)	2 (0.4%)	1 (0.2%)	14 (10.9%)	2 (1.6%)	0 (0.0%)	2 (1.6%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	179 (33.9%)	18 (3.4%)	16 (3.0%)	2 (0.4%)	1 (0.2%)	39 (30.2%)	10 (7.8%)	8 (6.2%)	2 (1.6%)	2 (1.6%)
EYE DISORDERS	26 (4.9%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	12 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	34 (6.4%)	11 (2.1%)	7 (1.3%)	4 (0.8%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	185 (35.0%)	65 (12.3%)	57 (10.8%)	8 (1.5%)	0 (0.0%)	33 (25.6%)	15 (11.6%)	15 (11.6%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	232 (43.9%)	32 (6.1%)	28 (5.3%)	4 (0.8%)	3 (0.6%)	63 (48.8%)	9 (7.0%)	8 (6.2%)	1 (0.8%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	450 (85.2%)	140 (26.5%)	124 (23.5%)	16 (3.0%)	4 (0.8%)	109 (84.5%)	36 (27.9%)	30 (23.3%)	6 (4.7%)	2 (1.6%)
HEPATOBILIARY DISORDERS	32 (6.1%)	11 (2.1%)	11 (2.1%)	0 (0.0%)	0 (0.0%)	15 (11.6%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	1 (0.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	147 (27.8%)	8 (1.5%)	8 (1.5%)	0 (0.0%)	0 (0.0%)	34 (26.4%)	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	127 (24.1%)	17 (3.2%)	16 (3.0%)	1 (0.2%)	0 (0.0%)	26 (20.2%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	129 (24.4%)	22 (4.2%)	20 (3.8%)	2 (0.4%)	0 (0.0%)	15 (11.6%)	2 (1.6%)	2 (1.6%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	20 (3.8%)	5 (0.9%)	5 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	358 (67.8%)	89 (16.9%)	83 (15.7%)	6 (1.1%)	20 (3.8%)	85 (65.9%)	18 (14.0%)	17 (13.2%)	1 (0.8%)	13 (10.1%)
INVESTIGATIONS	123 (23.3%)	28 (5.3%)	19 (3.6%)	9 (1.7%)	0 (0.0%)	29 (22.5%)	10 (7.8%)	8 (6.2%)	2 (1.6%)	0 (0.0%)

PRIMARY SYSTEM ORGAN CLASS	Hepatic Impairment=No (N=528)					Hepatic Impairment=Yes (N=129)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	32 (6.1%)	10 (1.9%)	8 (1.5%)	2 (0.4%)	0 (0.0%)	7 (5.4%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	9 (1.7%)	3 (0.6%)	3 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PRODUCT ISSUES	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Hepatic impairment: Defined as either Total bilirubin>UNL or AST or ALT >1.5 UNL
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Among the 762 patients with race documented at baseline, 70 (9.2%) were non-Caucasian (Table 31). At the SOC level, there was an excess in incidence of "any TEAE", all grades, of more than 5% in the non-Caucasian population for Musculoskeletal and connective tissue disorders SOC, by comparison to the Caucasian population (35.7% vs. 21.7%). Conversely, also by a threshold of 5%, "any TEAE", all grades, were less frequent in the non-Caucasian population than in the Caucasian population for the Vascular disorders SOC and for Respiratory, thoracic and mediastinal disorders SOC (20.0% vs. 34.8%, and 35.7% vs. 44.5%, respectively). Grades ≥3 events were reported by an excess in incidence of at least 2% in the non-Caucasian population in the Infections and infestations disorders SOC (12.9% vs. 8.7%), Musculoskeletal and connective tissue disorders SOC (5.7% vs. 2.3%). Conversely, also by a threshold of 2%, "any TEAE", Grades ≥3, were less frequent in the non-Caucasian population in the Vascular disorders SOC and Respiratory, thoracic and mediastinal disorders SOC (10.0% vs. 12.1%, and 4.3% vs. 6.5%, respectively).

Data on all the TEAEs reported by PT by race group is provided in Table 1.3.1-4.4.

Table 31 - Summary of TEAEs by Primary SOC and Worst NCI Grade by race (non-Caucasian / Caucasian) - Number of patients - All treated population

PRIMARY SYSTEM ORGAN CLASS	Race=Non Caucasian (N=70)					Race=Caucasian (N=692)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	68 (97.1%)	43 (61.4%)	36 (51.4%)	7 (10.0%)	1 (1.4%)	681 (98.4%)	418 (60.4%)	322 (46.5%)	96 (13.9%)	58 (8.4%)
INFECTIONS AND INFESTATIONS	24 (34.3%)	9 (12.9%)	8 (11.4%)	1 (1.4%)	0 (0.0%)	245 (35.4%)	54 (7.8%)	41 (5.9%)	13 (1.9%)	6 (0.9%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (2.0%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	23 (32.9%)	15 (21.4%)	11 (15.7%)	4 (5.7%)	0 (0.0%)	254 (36.7%)	126 (18.2%)	88 (12.7%)	38 (5.5%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	22 (31.4%)	5 (7.1%)	5 (7.1%)	0 (0.0%)	0 (0.0%)	227 (32.8%)	43 (6.2%)	35 (5.1%)	8 (1.2%)	0 (0.0%)
PSYCHIATRIC DISORDERS	9 (12.9%)	2 (2.9%)	2 (2.9%)	0 (0.0%)	0 (0.0%)	72 (10.4%)	8 (1.2%)	4 (0.6%)	4 (0.6%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	25 (35.7%)	3 (4.3%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	233 (33.7%)	25 (3.6%)	21 (3.0%)	4 (0.6%)	4 (0.6%)
EYE DISORDERS	4 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	33 (4.8%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	4 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	38 (5.5%)	13 (1.9%)	9 (1.3%)	4 (0.6%)	0 (0.0%)
VASCULAR DISORDERS	14 (20.0%)	7 (10.0%)	7 (10.0%)	0 (0.0%)	0 (0.0%)	241 (34.8%)	84 (12.1%)	76 (11.0%)	8 (1.2%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	25 (35.7%)	3 (4.3%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	308 (44.5%)	42 (6.1%)	37 (5.3%)	5 (0.7%)	3 (0.4%)
GASTROINTESTINAL DISORDERS	62 (88.6%)	18 (25.7%)	18 (25.7%)	0 (0.0%)	0 (0.0%)	590 (85.3%)	185 (26.7%)	155 (22.4%)	30 (4.3%)	7 (1.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	21 (30.0%)	3 (4.3%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	190 (27.5%)	8 (1.2%)	8 (1.2%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	25 (35.7%)	4 (5.7%)	4 (5.7%)	0 (0.0%)	0 (0.0%)	151 (21.8%)	16 (2.3%)	15 (2.2%)	1 (0.1%)	0 (0.0%)
RENAL AND URINARY DISORDERS	16 (22.9%)	2 (2.9%)	2 (2.9%)	0 (0.0%)	0 (0.0%)	147 (21.2%)	28 (4.0%)	26 (3.8%)	2 (0.3%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3 (4.3%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	23 (3.3%)	4 (0.6%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND	49 (70.0%)	13 (18.6%)	13 (18.6%)	0 (0.0%)	1 (1.4%)	471 (68.1%)	106 (15.3%)	98 (14.2%)	8 (1.2%)	36 (5.2%)

PRIMARY SYSTEM ORGAN CLASS	Race=Non Caucasian (N=70)					Race=Caucasian (N=692)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
ADMINISTRATION SITE CONDITIONS										
INVESTIGATIONS	13 (18.6%)	3 (4.3%)	2 (2.9%)	1 (1.4%)	0 (0.0%)	165 (23.8%)	37 (5.3%)	27 (3.9%)	10 (1.4%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (2.9%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	41 (5.9%)	10 (1.4%)	9 (1.3%)	1 (0.1%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	11 (1.6%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0 (0.0%)
PRODUCT ISSUES	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Among the 766 patients, 449 (58.6%) had a prior treatment with bevacizumab (Table 32). At the SOC level, there was no SOC with an excess in incidence of “any TEAE”, all grades, of more than 5% in the patients who had a prior treatment with bevacizumab when compared to the patients who had no prior exposure to an anti-VEGF therapy. No difference of more than 2% excess in any Grades ≥3, in the patients who had prior treatment with bevacizumab was reported at the SOC level.

Data on all the TEAEs reported by PT by prior use of bevacizumab group is provided in Table 1.3.1-4.6.

Table 32 - Summary of TEAEs by Primary SOC and Worst NCI Grade by prior use of bevacizumab (Yes / No) - Number of patients - All treated population

PRIMARY SYSTEM ORGAN CLASS	Without Prior Bevacizumab (N=317)					With Prior Bevacizumab (N=449)				
	Grades					Grades				
	All Grades	[3-4]	Grades 3	Grades 4	Grades 5	All Grades	[3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	315 (99.4%)	204 (64.4%)	153 (48.3%)	51 (16.1%)	18 (5.7%)	438 (97.6%)	260 (57.9%)	208 (46.3%)	52 (11.6%)	41 (9.1%)
INFECTIONS AND INFESTATIONS	108 (34.1%)	24 (7.6%)	17 (5.4%)	7 (2.2%)	2 (0.6%)	161 (35.9%)	39 (8.7%)	32 (7.1%)	7 (1.6%)	4 (0.9%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (2.2%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	7 (1.6%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	120 (37.9%)	64 (20.2%)	47 (14.8%)	17 (5.4%)	0 (0.0%)	157 (35.0%)	77 (17.1%)	52 (11.6%)	25 (5.6%)	1 (0.2%)
IMMUNE SYSTEM DISORDERS	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)	2 (0.4%)	2 (0.4%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	95 (30.0%)	17 (5.4%)	12 (3.8%)	5 (1.6%)	0 (0.0%)	154 (34.3%)	31 (6.9%)	28 (6.2%)	3 (0.7%)	0 (0.0%)
PSYCHIATRIC DISORDERS	35 (11.0%)	4 (1.3%)	3 (0.9%)	1 (0.3%)	0 (0.0%)	47 (10.5%)	6 (1.3%)	3 (0.7%)	3 (0.7%)	1 (0.2%)
NERVOUS SYSTEM DISORDERS	119 (37.5%)	12 (3.8%)	11 (3.5%)	1 (0.3%)	0 (0.0%)	139 (31.0%)	16 (3.6%)	13 (2.9%)	3 (0.7%)	4 (0.9%)
EYE DISORDERS	24 (7.6%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	13 (2.9%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	10 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	20 (6.3%)	6 (1.9%)	4 (1.3%)	2 (0.6%)	0 (0.0%)	20 (4.5%)	7 (1.6%)	5 (1.1%)	2 (0.4%)	0 (0.0%)
VASCULAR DISORDERS	130 (41.0%)	54 (17.0%)	49 (15.5%)	5 (1.6%)	0 (0.0%)	126 (28.1%)	37 (8.2%)	34 (7.6%)	3 (0.7%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	157 (49.5%)	22 (6.9%)	18 (5.7%)	4 (1.3%)	0 (0.0%)	178 (39.6%)	23 (5.1%)	22 (4.9%)	1 (0.2%)	3 (0.7%)
GASTROINTESTINAL DISORDERS	277 (87.4%)	89 (28.1%)	73 (23.0%)	16 (5.0%)	2 (0.6%)	379 (84.4%)	117 (26.1%)	103 (22.9%)	14 (3.1%)	5 (1.1%)
HEPATOBILIARY DISORDERS	19 (6.0%)	5 (1.6%)	5 (1.6%)	0 (0.0%)	1 (0.3%)	29 (6.5%)	7 (1.6%)	6 (1.3%)	1 (0.2%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	90 (28.4%)	2 (0.6%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	123 (27.4%)	9 (2.0%)	9 (2.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	69 (21.8%)	5 (1.6%)	5 (1.6%)	0 (0.0%)	0 (0.0%)	108 (24.1%)	15 (3.3%)	14 (3.1%)	1 (0.2%)	0 (0.0%)
RENAL AND URINARY DISORDERS	73 (23.0%)	11 (3.5%)	9 (2.8%)	2 (0.6%)	0 (0.0%)	91 (20.3%)	20 (4.5%)	20 (4.5%)	0 (0.0%)	0 (0.0%)

PRIMARY SYSTEM ORGAN CLASS	Without Prior Bevacizumab (N=317)					With Prior Bevacizumab (N=449)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	12 (3.8%)	2 (0.6%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	14 (3.1%)	3 (0.7%)	3 (0.7%)	0 (0.0%)	0 (0.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	217 (68.5%)	49 (15.5%)	44 (13.9%)	5 (1.6%)	13 (4.1%)	307 (68.4%)	71 (15.8%)	68 (15.1%)	3 (0.7%)	24 (5.3%)
INVESTIGATIONS	77 (24.3%)	17 (5.4%)	15 (4.7%)	2 (0.6%)	0 (0.0%)	101 (22.5%)	23 (5.1%)	14 (3.1%)	9 (2.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	17 (5.4%)	5 (1.6%)	4 (1.3%)	1 (0.3%)	0 (0.0%)	26 (5.8%)	6 (1.3%)	5 (1.1%)	1 (0.2%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	4 (1.3%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	8 (1.8%)	2 (0.4%)	2 (0.4%)	0 (0.0%)	0 (0.0%)
PRODUCT ISSUES	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Summary of the number of patients with possibly related TEAEs reported by Primary SOC, PT and worst NCI Grade is provided in Table 1.3.1-7. Summary of number of patients with possibly related TEAEs reported by Primary SOC, PT and worst NCI Grade for each subgroup of interest is provided in Table 1.3.1-7.1 to Table 1.3.1-7.6.

10.6.3 Analysis of adverse events

10.6.3.1 Analysis of adverse events by individual SOCs

10.6.3.1.1 Gastrointestinal disorders

Gastrointestinal disorders were reported by 656 patients (85.6%), representing the most frequent TEAEs in patients treated with aflibercept in combination with FOLFIRI in this study.

The most frequently (≥10%, all grades) reported TEAEs in this SOC were, diarrhea (56.3%), stomatitis (37.9%), nausea (33.4%), abdominal pain (21.7%), vomiting (21.5%) and constipation (16.6%).

Corresponding Grade ≥3 events were reported in less than 10% of the patients: diarrhea (9.5%), stomatitis (5.2%), nausea (1.3%), abdominal pain (3.8%), vomiting (1.8%) and constipation (0.1%).

There were no increases (by at least 5%) in incidences of these most frequent TEAEs (all grades) in the elderly population (n=370) when compared to the patients ages <65 years old (n=396). Severe events of diarrhea, which are associated with dehydration, were reported in 11.1% of the elderly population and in 8.1% of the patients aged less than 65 years old.

There were no increases (by at least 5%) in incidences of these most frequent TEAEs (all grades) in patients with creatinine clearance ≤80 mL/min (n = 258) when compared to the patients with normal renal function (n=480).

In patients with impaired liver function (total bilirubin >ULN or AST or ALT >1.5 ULN) at baseline, constipation (all grades) was more frequently reported than in the patients with normal liver function (23.3% vs 14.0%).

In the non-Caucasian population (n=70), all grades nausea, vomiting and abdominal pain (all grades) were more frequently reported than in the Caucasian population (n=692) (41.4% vs. 32.7%, 31.4% vs. 20.7%, and 27.1% vs. 21.2%, respectively).

Nausea (all grades) was more frequently reported in patients with more than 1 prior line of systemic chemotherapy (n=423) than in patients who only had one prior line of prior chemotherapy (37.1% vs. 28.9%). There were no flares in gastrointestinal toxicities in patients who had a prior exposure to bevacizumab.

10.6.3.1.2 General disorders and administration site conditions

General disorders were reported by 524 patients (68.4%), representing the second most frequent TEAEs in patients treated with aflibercept in combination with FOLFIRI in this study.

The most frequently (≥10%, all grades) reported TEAEs in this SOC were, asthenia (39.6%) and fatigue (21.0%). Collectively (HLT) asthenic conditions were reported in 58.4% of the patients.

Corresponding Grade ≥3 events were reported in 9.1% and 3.5% of the patients for asthenia and fatigue, respectively. Grade ≥3 events of asthenic conditions (HLT) were reported in 12.7% of the patients.

In the elderly population, all grades asthenia were more frequently reported than in patients aged less than 65 years old (43.5% vs. 35.9%). Severe events of asthenia were reported in 11.9% of the elderly population and in 6.6% of the patients aged less than 65 years old.

General physical health deterioration was also more frequent in the elderly population by comparison to patients aged less than 65 years old (all grades: 8.4% vs. 2.8%, grade ≥3: 6.3% vs. 1.3%). However, among the 31 elderly patients reporting TEAEs of general physical health deterioration, the event was in relation with progressive disease (according to investigator) in 10 cases or emerged within 1 month prior to diagnosis of disease progression in 6 other cases.

There were no increases (by at least 5%) in incidences of asthenia and of fatigue (all grades) in patients with baseline creatinine clearance ≤80 mL/min when compared to the patients with normal renal function.

Similarly, there were no increases (by at least 5%) in incidences of asthenia and of fatigue (all grades) in patients with baseline impaired liver function when compared to the patients with normal liver function.

In the non-Caucasian population, all grades fatigue was more frequently reported than in the Caucasian population (31.4% vs. 20.1%) and the opposite for all grades asthenia which was more frequently reported in the Caucasian population (40.6% vs. 25.7%). Subgroup analysis by HLT is not available.

Events leading to death in the General disorders SOC were reported in 37 patients (4.8%).

10.6.3.1.3 Respiratory, thoracic and mediastinal disorders

Respiratory, thoracic and mediastinal disorders were reported by 335 patients (43.7%), representing the third most frequent TEAEs in patients treated with aflibercept in combination with FOLFIRI in this study.

The most frequently (≥10%, all grades) reported TEAEs in this SOC were, epistaxis (18.7%), and dysphonia (16.2%).

Corresponding Grade ≥3 events were reported in 0.1% and 0.6% of the patients for epistaxis and dysphonia, respectively.

There were no increases (by at least 5%) in incidences of these two most frequent TEAEs (all grades) in the elderly population when compared to the patients aged <65 years old, in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver function at baseline when compared to patients with normal liver function at baseline and in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line.

Epistaxis and dysphonia were more frequent in bevacizumab naïve patients than in patients with prior exposure to bevacizumab (24.3% vs 14.7% and 20.2% vs 13.1%, respectively).

Epistaxis and dysphonia were less frequent in the non-Caucasian population when compared to the Caucasian population (14.4% vs 19.1% and 7.1% vs 16.8%, respectively).

10.6.3.1.4 Infections and infestations

Infections were reported by 269 patients (35.1%), representing the fourth most frequent TEAEs in patients treated with aflibercept in combination with FOLFIRI in this study. Grade ≥3 events were reported in 69 patients (9.0%). Five patients (0.7%) died in the context of an infection (see Section 10.6.9).

The most frequent type of infections was urinary tract infections reported in 6.5% of the patients.

There were no increases (by at least 5%) of infections (all grades) in the elderly population when compared to the patients aged <65 years old, in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver function at baseline when compared to patients with normal liver function at baseline, in the non-Caucasian population when compared to the Caucasian population, in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line, and in patients who had a prior exposure to bevacizumab when compared to these naïve of prior bevacizumab exposure.

10.6.3.1.5 Vascular disorders

Vascular disorders were reported by 256 patients (33.4%), with Grade ≥3 events reported in 91 patients (11.9%). The vast majority of the TEAEs in this SOC were TEAEs of hypertension (PT) reported in 28.5% of the patients. Analysis of hypertension, as grouped term, can be found in Section 10.6.9.4, including analysis of pre-specified subgroups.

10.6.3.1.6 Nervous system disorders

Nervous system disorders were reported by 258 patients (33.7%), Grade ≥3 events reported in 32 patients (4.2%). Headache was the only TEAE reported in more than 10% of the patients (10.4%), in this SOC.

There were no increases (by at least 5%) in incidences of headache in the elderly population when compared to the patients aged <65 years old, in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver

function at baseline when compared to patients with normal liver function at baseline, in the non-Caucasian population when compared to the Caucasian population, in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line, and in patients who had a prior exposure to bevacizumab when compared to these naïve of prior bevacizumab exposure.

Three patients (0.4%) experienced a posterior reversible encephalopathy syndrome.

10.6.3.1.7 Metabolism and nutrition disorders

Metabolism and nutrition disorders were reported by 249 patients (32.5%), with Grade ≥3 events reported in 48 patients (6.3%). Decreased appetite was the only TEAE reported in more than 10% of the patients (22.7%) in this SOC, with Grade ≥3 events reported in 2.7% of the patients.

Decreased appetite was more frequent in the elderly population when compared to patients aged less than 65 years (25.4% vs. 20.2%); however Grade ≥3 events were reported at similar incidences (3.0% vs. 2.5%).

There were no increases (by at least 5%) in incidences of decreased appetite in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver function at baseline when compared to patients with normal liver function at baseline, in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line, and in patients who had a prior exposure to bevacizumab when compared to these naïve of prior bevacizumab exposure.

TEAEs of dehydration were not reported at an increased incidence in the elderly population when compared to patients aged less than 65 years (4.9% vs. 5.8%). Of note, TEAEs of dehydration were reported in 14.3% of the patients in the non-Caucasian population and in 4.3% of the patients in the Caucasian population.

10.6.3.1.8 Skin and subcutaneous tissue disorders

Skin and subcutaneous tissue disorders were reported by 213 patients (27.8%). Grade ≥3 events were reported in 11 patients (1.4%). Alopecia was the only TEAE reported in more than 10% of the patients (12.1%) in this SOC.

There were no increases (by at least 5%) in incidences of alopecia in the elderly population when compared to the patients aged <65 years old, in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver function at baseline when compared to patients with normal liver function at baseline, in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line and in patients who had a prior exposure to bevacizumab when compared to these naïve of prior bevacizumab exposure.

Palmar-plantar erythrodysaesthesia syndrome which was reported in less than 10% of the patients (7.2%) overall, was more frequently reported in the non-Caucasian population (15.7%) than in the Caucasian population (6.1%).

10.6.3.1.9 Investigations

TEAEs in the Investigations SOC were reported by 178 patients (23.2%) with Grade ≥3 events reported in 40 patients (5.2%). Weight decrease was the only TEAE reported in more than 10% of the patients (11.7%) in this SOC.

There were no increases (by at least 5%) of infections (all grades) in incidences of weight decrease the elderly population when compared to the patients aged <65 years old, in patients with impaired renal function at baseline when compared to patients with normal renal function at baseline, in patients with impaired liver function at baseline when compared to patients with normal liver function at baseline, in the non-Caucasian population when compared to the Caucasian population, in patients who had more than one line of prior systemic chemotherapy when compared to patients with only one prior line, and in patients who had a prior exposure to bevacizumab when compared to these naïve of prior bevacizumab exposure.

10.6.3.1.10 Musculoskeletal and connective tissue disorders

Musculoskeletal and connective tissue disorders were reported by 177 patients (23.1%), with Grade ≥3 events reported in 20 patients (2.6%). No particular event was reported at an incidence of at least 10%. The most frequently reported TEAE was back pain (7.8%).

At the SOC level events were more frequent in the non-Caucasian population than in the Caucasian population (35.7% vs. 21.8%).

10.6.3.1.11 Other SOCs of interest

Renal and urinary disorders and cardiac disorders are addressed in Section 10.6.8.9 and Section 10.6.8.2, respectively.

10.6.3.2 Analysis of adverse events by population of interest

10.6.3.2.1 Patients aged ≥65

Among the 766 patients, 370 (48.3%) were aged 65 or more. All grades TEAEs were reported in 98.4% of the patients aged 65 or more and in 98.2% of the patients aged less than 65; with severe events (Grade ≥3) reported in 69.5% and 67.1% of the patients, respectively.

At the SOC level, there was no SOC with an excess in incidence of "any TEAE", all grades, by more than 5% in the elderly population when compared to the less than 65 years old population. Grade ≥3 events in the General disorders and administration site condition SOC were more frequent in the elderly population when compared to the patients aged less than 65 (25.4% vs. 15.9%). For severe events, no difference of more than 2% excess in the elderly population was reported for any of the other SOCs.

At the PT level asthenia, general physical health deterioration and decreased appetite were more frequently (by ≥5%) reported in the elderly population (asthenia, all grades: 43.5% vs. 35.9%;

Grades ≥3: 11.9% vs. 6.6% - general physical health deterioration, all grades: 8.4% vs. 2.8%; Grades ≥3: 6.3% vs. 1.3% - decreased appetite, all grades: 25.4% vs. 20.2%; Grades ≥3: 3.0% vs. 2.5%).

Among the 31 elderly patients reporting TEAEs of general physical health deterioration, the event was in relation with progressive disease (according to investigator) in 10 cases or emerged within 1 month prior to diagnosis of disease progression in 6 other cases.

Of importance for the elderly population, no increases by at least 5% in incidence were noted for diarrhea, dehydration, hemorrhages (grouped term), hypertension (grouped term) and renal failure events (grouped term).

10.6.3.2.2 Patients with impaired renal function at baseline

Among the 738 patients with renal status documented at baseline, 258 (34.9%) were reported with creatinine clearance ≤80 mL/min.

At the SOC level, there was no SOC with an excess in incidence of "any TEAE", all grades, of more than 5% in the patients with impaired renal function when compared to these with normal renal function. Similarly, there was no SOC with an excess in incidence of more than 2% in "any Grades ≥3 TEAEs, in the population with impaired renal function when compared to the population with normal renal function at baseline.

In the Renal and urinary disorder SOC, all grade TEAEs were reported in 23.6% of the patients with baseline creatinine clearance ≤80 mL/min and in 20.8% of the patients with baseline creatinine clearance >80 mL/min. TEAEs Grades ≥3 were reported in 5.0% and in 3.8% of the patients, respectively.

At the PT level renal failure, as a grouped term (from Renal and urinary disorder SOC and from Investigations SOC) was more frequently reported in the patients with baseline creatinine clearance ≤80 mL/min (7.0% vs. 2.9%), however not reaching the 5% threshold in difference. Incidence of severe events was not different between the 2 baseline categories (0.4% vs. 0.2%).

Proteinuria was reported in 13.2% of the patients with baseline creatinine clearance ≤80 mL/min and in 11.5% of the patients with baseline creatinine clearance >80 mL/mon. Events of Grade ≥3 were reported in 3.5% and 2.5% of the patients, respectively.

Among the 738 patients with renal status documented at baseline, 43 (5.8%) were reported with creatinine clearance <50 mL/min.

In the Renal and urinary disorder SOC, all grade TEAEs were reported in 32.6% of these patients. TEAEs Grades ≥3 were reported in 9.3% patients.

Proteinuria was reported in 11.6% of the patients with baseline creatinine clearance <50 mL/min. Events Grades ≥3 were reported in 7.0% of the patients.

Aside from the analysis initially planned in the protocol (CrCl ≤80 mL/min [213 patients] vs >80 mL/min [482 patients]) further analysis was performed to look at the patients with more severe renal impairment (CrCL ≤50 mL/min (43 patients]). The safety summary for these patients can be found in Table 1.3.1-4.8.

In the group of patients with baseline creatinine clearance <50 mL/min, TEAEs from the Renal and Urinary disorders and from Metabolism and Nutrition disorders SOCs were reported with higher incidences tham in the other groups.

In the Renal and Urinary disorders SOC, events were reported more frequently in the <50 mL/min creatinine clearance group than in the 2 other categories (32.6% vs 21.6% and 21.0% in the <50 mL/min, ≥50-80 mL/min and >80 mL/min creatinine groups, respectively). Events of renal failure and hematuria were more frequent in the <50 mL/min creatinine clearance group than in the 2 other categories (renal failure: 7.0% vs 2.3% and 1.2%; hematuria: 7.0% vs 0.5% and 0%).

Proteinuria was reported at similar incidences across categories (11.6% vs 13.6% and 11.4%), however severe events were more frequent in the <50 mL/min creatinine clearance group than in the 2 other categories (7.0% vs 2.8% and 2.5%).

In the Metabolism and Nutrition disorders SOC events were reported in 46.5% vs 31.5% and 32.0% of the patients in the <50 mL/min, ≥50-80] mL/min and >80 mL/min creatinine categories, respectively. Decreased appetite, the most frequent TEAE within this SOC, was reported more frequently in the creatinine clearance <50 mL/min category than in the other categories (32.6% vs 22.1% and 22.2%), however no increase in incidence of severe events was noted (2.3% vs 2.8% and 2.9%). Hypokalemia was also reported more frequently in the creatinine clearance <50 mL/min group (11.6% vs 1.9% and 4.0%), however these data should not be over-interpreted in the absence of systemic collection of laboratory abnormalities in this study.

In the Nervous System disorders SOC, all grades of dysgeusia and peripheral neuropathy were more frequent in the creatinine clearance <50 mL/min group than in the other groups (dysgeusia: 16.3% vs 3.8% and 4.6%; peripheral sensory neuropathy: 9.3% vs 4.7% and 4.8%). No severe events were reported in the creatinine clearance <50 mL/min group.

Of note, the incidence of hypertension was lower in the creatinine clearance <50 mL/min group than in the two other renal categories (11.6% vs 28.2% and 30.5%).

10.6.3.2.3 Patients with impaired liver function at baseline

Among the 657 patients with liver function documented at baseline, 129 (19.6%) had an impaired liver function (defined as, total bilirubin >ULN or AST or ALT >1.5 ULN).

At the SOC level, there was an excess in incidence of “any TEAE”, all grades, of more than 5% in the patients with an impaired liver function for the Hepatobiliary disorders SOC, by comparison to the patients with normal liver function (11.6% vs. 6.1%). Any Grades ≥3 events in the Nervous system disorders SOC and in the Gastrointestinal disorders SOC were reported in an excess of more than 2% in the patients with impaired liver function when compared to these with normal liver function (9.4% vs. 3.6% and 29.5% vs. 27.3%, respectively).

The difference in incidence of all grade TEAEs for the Hepatobiliary disorders SOC and of any Grades ≥3 events in the Nervous system disorders SOC and in the Gastrointestinal disorders SOC were not driven by any particular type of events.

At the PT level all grade constipation was more frequent in patients with impaired liver function (23.3% vs. 14.2%). Although not reaching the 5% level threshold, all grade dyspnea were more frequent in patients with impaired liver function (13.2% vs. 8.9%).

Hemorrhage, as a grouped term, were reported in more patients with impaired liver function population (all grades: 37.2% vs. 30.1%; Grades ≥3: 5.5% vs. 2.1%), the most frequent events being epistaxis (23.3% vs. 18.9%) and hemorrhage of gastrointestinal origin (16.3% vs. 12.1%).

10.6.3.2.4 Safety in the non-Caucasian population

Among the 762 patients with race documented at baseline, only 70 (9.2%) were non-Caucasian.

At the SOC level, there was an excess in incidence of "any TEAE", all grades, of more than 5% in the non-Caucasian population for Musculoskeletal and connective tissue disorders SOC, by comparison to the Caucasian population (35.7% vs. 21.8%). Conversely, also by a threshold of 5%, "any TEAE", all grades, were less frequent in the non-Caucasian population than in the Caucasian population for the Vascular disorders SOC and for Respiratory, thoracic and mediastinal disorders SOC (20.0% vs. 34.8% and 35.7% vs. 44.5%, respectively).

Grades ≥3 events (any) were reported by an excess in incidence of at least 2% in the non-Caucasian population in the Infections and infestations disorders SOC (12.9% vs. 8.7%), Musculoskeletal and connective tissue disorders SOC (5.7% vs. 2.3%). Conversely, also by a threshold of 2%, Grades ≥3 events (any) were less frequent in the non-Caucasian population in the Vascular disorders SOC and Respiratory, thoracic and mediastinal disorders SOC (10.0% vs. 12.1%, and 4.3% vs. 6.5%, respectively).

At PT level, and by decreasing order of incidence, the following events were reported more frequently (≥5%) in the non-Caucasian population by comparison to the Caucasian population: nausea (41.4% vs. 32.7%), vomiting (31.4% vs. 20.7%), fatigue (31.4% vs. 20.1%), abdominal pain (27.1% vs. 21.2%), palmar-plantar erythrodysaesthesia syndrome (15.7% vs. 6.1%), dehydration (14.3% vs. 4.5%), cough (14.3% vs. 5.8%), dizziness (11.4% vs. 4.2%), and edema peripheral (11.4% vs. 3.2%).

Of note hemorrhages, as grouped term, and hypertension, as grouped term, were reported less frequently in the non-Caucasian population (20.0% vs. 30.2%, and 15.7% vs. 30.5%, respectively). Renal failure (as grouped term) and proteinuria (as grouped term) were reported at similar incidences in the non-Caucasian and Caucasian populations.

10.6.3.2.5 Safety in patients with prior exposure to bevacizumab

Among the 766 patients treated in the study, 449 (58.6%) had a prior treatment with bevacizumab. At the SOC level, there was no SOC with an excess in incidence of "any TEAE", all grades, of more than 5% in the patients who had a prior exposure to bevacizumab when compared to the

patients who had no prior exposure to an anti-VEGF therapy. No difference of more than 2% excess in any Grades ≥3, in the patients who had a prior treatment with bevacizumab was reported at the SOC level.

At the PT level there were no flares in incidences of anti-VEGF class events. The only TEAE that was more frequently reported in patients who had a prior exposure to bevacizumab was fatigue (23.8% vs. 17.0%, all grades).

TEAEs frequently associated with aflibercept were less frequently reported in patients who had a prior exposure to bevacizumab, likely reflecting patient selection, such as hypertension (grouped term) (23.4% vs. 37.2%), and hemorrhages (grouped term) (24.3% vs. 36.9%).

Renal failure events (grouped term) and proteinuria (grouped term) were equally reported in patients with and without prior exposure to bevacizumab.

10.6.4 Serious adverse events

Number of patients who experienced serious TEAE(s) presented by Primary SOC, HLGT, HLT and PT and worst NCI Grade is provided in Table 1.3.1-8.

Table 33 shows the summary of the number of patients with serious TEAEs reported by Primary SOC and worst NCI Grade. A summary of all serious TEAEs reported by SOC and PT is provided in Table 1.3.1-9.

Table 33 - All treatment-emergent serious adverse events by Primary SOC and Worst NCE grade - All treated population

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TESAE	334 (43.6%)	223 (29.1%)	158 (20.6%)	65 (8.5%)	59 (7.7%)
INFECTIONS AND INFESTATIONS	66 (8.6%)	51 (6.7%)	38 (5.0%)	13 (1.7%)	6 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5 (0.7%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	37 (4.8%)	33 (4.3%)	16 (2.1%)	17 (2.2%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ENDOCRINE DISORDERS	2 (0.3%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	21 (2.7%)	18 (2.3%)	15 (2.0%)	3 (0.4%)	0 (0.0%)
PSYCHIATRIC DISORDERS	8 (1.0%)	7 (0.9%)	3 (0.4%)	4 (0.5%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	24 (3.1%)	14 (1.8%)	12 (1.6%)	2 (0.3%)	4 (0.5%)
EYE DISORDERS	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	13 (1.7%)	9 (1.2%)	5 (0.7%)	4 (0.5%)	0 (0.0%)
VASCULAR DISORDERS	21 (2.7%)	14 (1.8%)	7 (0.9%)	7 (0.9%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	28 (3.7%)	22 (2.9%)	19 (2.5%)	3 (0.4%)	3 (0.4%)
GASTROINTESTINAL DISORDERS	134 (17.5%)	104 (13.6%)	76 (9.9%)	28 (3.7%)	7 (0.9%)
HEPATOBILIARY DISORDERS	15 (2.0%)	10 (1.3%)	9 (1.2%)	1 (0.1%)	1 (0.1%)

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (0.9%)	6 (0.8%)	6 (0.8%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	15 (2.0%)	7 (0.9%)	7 (0.9%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4 (0.5%)	3 (0.4%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	87 (11.4%)	35 (4.6%)	28 (3.7%)	7 (0.9%)	37 (4.8%)
INVESTIGATIONS	9 (1.2%)	6 (0.8%)	3 (0.4%)	3 (0.4%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	10 (1.3%)	9 (1.2%)	7 (0.9%)	2 (0.3%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	4 (0.5%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Summary tables for the number of patients with serious TEAEs reported by Primary SOC and worst NCI Grade per populations of interest are provided in Table 1.3.1-9.1, Table 1.3.1-9.2, Table 1.3.1-9.3, Table 1.3.1-9.4, Table 1.3.1-9.5 and Table 1.3.1-9.6.

There were a total of 334 patients (43.6%) of the 766 treated who experienced at least one serious TEAE during the study. Of them, 158 patients (20.6%) experienced at least one Grade 3 serious TEAE, 65 patients (8.5%) at least one Grade 4 serious TEAE and 59 patients (7.7%) experienced Grade 5 serious TEAE.

The most frequent serious TEAEs reported in ≥2.0% of the patients were: diarrhea experienced by 35 patients (4.6%), disease progression experienced by 28 patients (3.7%), general physical health deterioration experienced by 25 patients (3.3%), abdominal pain experienced by 22 patients (2.9%), intestinal obstruction experienced by 19 patients (2.5%), and febrile neutropenia and pyrexia experienced both by 17 patients (2.2%). Supportive data on all serious TEAEs reported during the study is provided in Table 1.3.1-9.

By populations of interest, the rates in the percentage of patients with serious TEAEs were:

- Age subgroup (<65 years and ≥65 years): 42.4% and 44.9%, respectively.
- Renal status subgroup (patients without renal impairment and patients with renal impairment at baseline): 43.3% and 43.4%, respectively.
- Hepatic impairment subgroup (patients without hepatic impairment and patients with hepatic impairment at baseline): 43.6% and 48.8%, respectively.
- Race subgroup (non-Caucasian and Caucasian patients): 41.4% and 43.9%, respectively.
- Prior anti-cancer therapy (patients with 0-1 line prior anti-cancer therapy and patients with >1 lines of prior anti-cancer therapy): 41.7% and 45.2%, respectively.
- Prior bevacizumab administration subgroup (patients without prior bevacizumab and patients with prior bevacizumab): 45.1% and 45.2%, respectively.

Summary table for the number of patients with possibly related serious TEAEs reported by Primary SOC, PT and worst NCI Grade is provided in Table 1.3.1-10.

Regarding possibly related serious TEAEs, there were a total of 185 patients (24.2%) who experienced at least one possibly related serious TEAE during the study.

The most frequent possibly related serious TEAEs reported were diarrhea experienced by 33 patients (4.3%), febrile neutropenia experienced by 14 patients (1.8%) and neutropenia experienced by 12 patients (1.6%).

Similar rates of the most frequent possibly related serious TEAEs were reported in the populations of interest. Data on all possibly related serious TEAEs reported by subgroup are provided in Table 1.3.1-10.1, Table 1.3.1-10.2, Table 1.3.1-10.3, Table 1.3.1-10.4, Table 1.3.1-10.5 and Table 1.3.1-10.6.

10.6.5 Adverse events leading to treatment discontinuation

Number of patients who experienced TEAE(s) leading to permanent treatment discontinuation presented by Primary SOC, HLGT, HLT and PT and worst NCI Grade is provided in Table 1.3.1-12.

Table 34 shows the summary of the number of patients with TEAEs leading to permanent treatment discontinuation reported by Primary SOC and worst NCI Grade. A summary of TEAEs by SOC and PT and worst NCI grade is provided in Table 1.3.1-13.

Table 34 - All treatment-emergent adverse events leading to permanent discontinuation by primary SOC and Worst NCE grade - All treated population

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	115 (15.0%)	68 (8.9%)	57 (7.4%)	11 (1.4%)	15 (2.0%)
INFECTIONS AND INFESTATIONS	14 (1.8%)	9 (1.2%)	8 (1.0%)	1 (0.1%)	5 (0.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (1.2%)	5 (0.7%)	5 (0.7%)	0 (0.0%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	3 (0.4%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
PSYCHIATRIC DISORDERS	3 (0.4%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	10 (1.3%)	4 (0.5%)	4 (0.5%)	0 (0.0%)	3 (0.4%)
CARDIAC DISORDERS	5 (0.7%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0 (0.0%)
VASCULAR DISORDERS	7 (0.9%)	6 (0.8%)	3 (0.4%)	3 (0.4%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (1.6%)	5 (0.7%)	4 (0.5%)	1 (0.1%)	3 (0.4%)
GASTROINTESTINAL DISORDERS	36 (4.7%)	25 (3.3%)	21 (2.7%)	4 (0.5%)	1 (0.1%)
HEPATOBILIARY DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND	4 (0.5%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
CONNECTIVE TISSUE DISORDERS					
RENAL AND URINARY DISORDERS	11 (1.4%)	5 (0.7%)	4 (0.5%)	1 (0.1%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21 (2.7%)	12 (1.6%)	12 (1.6%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	4 (0.5%)	3 (0.4%)	1 (0.1%)	2 (0.3%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.3%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
Patient 380-019-005 with Post-Treatment leading to permanent treatment discontinuation not displayed in this table.
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Summary tables for all TEAEs leading to permanent treatment discontinuation by primary SOC and PT and worst NCI grade by age group, renal impairment group, hepatic impairment group, race group, prior anticancer therapies group, and prior use of bevacizumab group are provided in Table 1.3.1-13.1, Table 1.3.1-13.2, Table 1.3.1-13.3, Table 1.3.1-13.4, Table 1.1.3-13.5 and Table 1.1.3-13.6.

There were 115 patients (15.0%) experiencing TEAE that led to permanent discontinuation of study treatment (Table 34). The events were distributed over a variety of SOCs, however close to one third of these events (31.3%) were from the gastrointestinal SOC. The most frequent TEAEs leading to permanent treatment discontinuation were asthenic conditions (HLT) (2.1%), infections (SOC) (1.8%) and diarrhea (1.8%). Data on all the TEAEs leading to permanent treatment discontinuation reported by PT is provided in Table 1.3.1-13.

Table 35 shows the summary of the number of patients with TEAEs leading to premature treatment discontinuation reported by Primary SOC and worst NCI Grade. Data on all the TEAEs leading to premature treatment discontinuation reported by PT is provided in Table 1.3.1-13.

Table 35 - All treatment-emergent adverse events leading to premature discontinuation by primary SOC and Worst NCE grade - All treated population

PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
Any TEAE	102 (13.3%)	43 (5.6%)	39 (5.1%)	4 (0.5%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	2 (0.3%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.3%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	5 (0.7%)	2 (0.3%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
EYE DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	22 (2.9%)	7 (0.9%)	7 (0.9%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.4%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	26 (3.4%)	8 (1.0%)	8 (1.0%)	0 (0.0%)	0 (0.0%)
HEPATOBILIARY DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.3%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	21 (2.7%)	12 (1.6%)	12 (1.6%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (0.3%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9 (1.2%)	7 (0.9%)	7 (0.9%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.5%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0 (0.0%)

Patient 380-006-001 with TEAE leading to premature treatment discontinuation but reason for premature discontinuation as 'Other: Other adverse event and clinical condition'. Patient's reason reclassified as 'Adverse Event'.
Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
Only events as declared in the CRF pages are presented.
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Summary tables for all TEAEs leading to premature treatment discontinuation by primary SOC and PT and worst NCI grade by age group, renal impairment group, hepatic impairment group, race group, prior anticancer therapies group, and prior use of bevacizumab group are provided in Table 1.3.1-14.1, Table 1.3.1-14.2, Table 1.3.1-14.3, Table 1.3.1-14.4, Table 1.1.3-14.5 and Table 1.1.3-14.6, respectively.

During this study, 102 patients (13.3%) experienced a TEAE that led to the premature discontinuation of aflibercept or the FOLFIRI regimen prior to permanent study treatment discontinuation. The events were distributed over a variety of SOCs. The most frequent causes of early treatment discontinuation were from TEAEs of the Vascular disorders SOC (22 patients), Gastrointestinal SOC (26 patients) and Renal and urinary disorders SOC (21 patients) (Table 35).

The most frequently reported TEAEs leading to premature discontinuation were proteinuria (2.3%), hypertension (2.0%) and diarrhea (1.2%).

Data on all the TEAEs leading to premature treatment discontinuation reported by PT is provided in Table 1.3.1-14.

10.6.6 Adverse events leading to dose modification

Summary tables of the number of patients with TEAEs leading to dose delay and dose reduction reported by Primary SOC, PT and worst NCI Grade are provided in Table 1.3.1-15, Table 1.3.1-15a and Table 1.3.1-15b.

Summary tables for all TEAEs leading to dose delay or dose reduction by primary SOC and PT and worst NCI grade by age group, renal impairment group, hepatic impairment group, race group, prior anticancer therapies group, and prior use of bevacizumab group are provided in Table 1.3.1-15.1, Table 1.3.1-15.2, Table 1.3.1-15.3, Table 1.3.1-15.4, Table 1.1.3-15.5 and Table 1.1.3-15.6.

Summary tables of the number of patients with TEAEs leading to drug interruption reported by Primary SOC, PT and worst NCI Grade are provided in Table 1.3.1-16.

Summary tables for all TEAEs leading to drug interruption by primary SOC and PT and worst NCI grade by age group, renal impairment group, hepatic impairment group, race group, prior anticancer therapies group, and prior use of bevacizumab group are provided in Table 1.3.1-16.1, Table 1.3.1-16.2, Table 1.3.1-16.3, Table 1.3.1-16.4, Table 1.1.3-16.5 and Table 1.1.3-16.6.

10.6.7 Adverse events of specific interest

Table 36 shows the summary of the number of patients with TEAEs of specific interest reported by grouped term, Primary SOC and worst NCI Grade. Data on all the TEAEs reported by PT is provided in Table 1.3.1-17.

Table 36 - All treatment-emergent adverse events of specific interest by grouped term, primary SOC and Worst NCE grade - All treated population

GROUPED TERM PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
ACUTE DRUG REACTION	11 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC DYSFUNCTION	7 (0.9%)	4 (0.5%)	3 (0.4%)	1 (0.1%)	0 (0.0%)
CARDIAC DISORDERS	6 (0.8%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
FISTULA FROM GASTROINTESTINAL ORIGIN	9 (1.2%)	4 (0.5%)	2 (0.3%)	2 (0.3%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	9 (1.2%)	4 (0.5%)	2 (0.3%)	2 (0.3%)	0 (0.0%)
FISTULA FROM OTHER ORIGIN THAN GASTROINTESTINAL	6 (0.8%)	3 (0.4%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4 (0.5%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL PERFORATION	7 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	3 (0.4%)
GASTROINTESTINAL DISORDERS	7 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	3 (0.4%)
HAEMORRHAGE	226 (29.5%)	19 (2.5%)	17 (2.2%)	2 (0.3%)	2 (0.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	146 (19.1%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	91 (11.9%)	12 (1.6%)	11 (1.4%)	1 (0.1%)	1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14 (1.8%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EYE DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
RENAL AND URINARY DISORDERS	9 (1.2%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
HYPERTENSION	223 (29.1%)	79 (10.3%)	76 (9.9%)	3 (0.4%)	0 (0.0%)
VASCULAR DISORDERS	221 (28.9%)	79 (10.3%)	76 (9.9%)	3 (0.4%)	0 (0.0%)
INVESTIGATIONS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OSTEONECROSIS	3 (0.4%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.4%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
PARODONTOPATHY	70 (9.1%)	7 (0.9%)	7 (0.9%)	0 (0.0%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	40 (5.2%)	5 (0.7%)	5 (0.7%)	0 (0.0%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (0.7%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	28 (3.7%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
SURGICAL AND MEDICAL PROCEDURES	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PROTEINURIA	91 (11.9%)	21 (2.7%)	20 (2.6%)	1 (0.1%)	0 (0.0%)
RENAL AND URINARY DISORDERS	91 (11.9%)	21 (2.7%)	20 (2.6%)	1 (0.1%)	0 (0.0%)

GROUPED TERM PRIMARY SYSTEM ORGAN CLASS	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
RENAL FAILURE	32 (4.2%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
RENAL AND URINARY DISORDERS	18 (2.3%)	2 (0.3%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	15 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
TEAE: Treatment emergent adverse event.
Grouped terms are based on AE page only
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Tables for all TEAEs of specific interest by grouped terms, primary SOC and PT and worst NCI grade by age group, renal impairment group, hepatic impairment group, race group, prior anticancer therapies group, and prior use of bevacizumab group are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.1.3-17.5 and Table 1.1.3-17.6, respectively.

10.6.8 Analysis of adverse events of specific interest

10.6.8.1 Acute drug reaction

A total of 11 patients (1.4%) of the 766 treated reported at least one acute drug reaction. All acute drug reactions reported were of Grade 1-2. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-18.

Analyses by subgroup are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

10.6.8.2 Cardiac dysfunction

A total of 7 patients (0.9%) of the 766 treated reported at least one event of cardiac dysfunction during the study treatment period. Of them, 1 patient reported a Grade 4 event (cardiac failure), and 3 patients reported a Grade 3 (2 events of cardiac failure, 1 event of pulmonary edema). The patient with Grade 4 cardiac failure had a history of congestive cardiomyopathy (known for 13 years prior to starting the study), and the event was considered not related to study treatment. For two patients, the events were leading to the premature or permanent treatment discontinuation. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-19.

Analyses by subgroup are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

10.6.8.3 Hemorrhage

A total of 226 patients (29.5%) reported at least one hemorrhage episode during the study treatment period. Severe (grade ≥3) events were reported in 2.8% of the patients, including 2 fatal events. The most frequent TEAEs were epistaxis (143 patients [18.7%], no severe event) and hemorrhages of gastrointestinal origin (grouped term, 91 patients [11.9% all grade, 1.7% grade ≥3]). The most frequent hemorrhage from the gastrointestinal tract was rectal hemorrhage (6.7%). The fatal events were 1 case of rectal hemorrhage in the context of disease progression and 1 case of intracranial hemorrhage. Hemorrhage episodes led to the premature or permanent treatment discontinuation in 23 patients (10.2%). Additional details are provided in Table 1.3.1-17 and Table 1.3.1-20.

By population of interest, there were no increases in the incidence of hemorrhages (grouped term) in the elderly population (28.1%), in the patients with renal impairment (29.1%), in the non-Caucasian population (20.0%), or in the patients with more than 1 line of prior chemotherapy (29.3%). Additional details are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.4 and Table 1.3.1-17.5.

Hemorrhages (grouped term) were more frequent in patients with impaired liver function than in patients with normal liver function (37.2% vs. 30.1%). A similar pattern was reported for Grade ≥3 events, with 5.5% of the patients with impaired liver function and in 2.1% of the patients with normal liver function, reporting severe events. Additional details are provided in Table 1.3.1-17.3.

Of note, hemorrhages (grouped term) were less frequent in patients who had a prior treatment with bevacizumab than in those free of prior exposure to bevacizumab (24.3% vs. 36.9%), likely resulting from patient selection. Additional details are provided in Table 1.3.1-17.6.

10.6.8.4 Hypertension

A total of 223 patients (29.1%) of the 766 treated reported at least one hypertension episode (grouped term) during the study treatment period, including 79 patients (10.3%) reporting Grade ≥3 events, 3 patients (0.4%) reported a Grade 4 hypertension episode. Hypertension episodes led to the premature or permanent treatment discontinuation in 18 (8.1%) of 223 patients. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-21.

By population of interest, there was no increase in the incidence of hypertension (grouped term) in the elderly population (27.3%), in the patients with renal impairment (26.7%), in the patients with impaired liver function (23.3%), in the non-Caucasian population (15.7%), and in patients with more than 1 line of prior chemotherapy (28.8%). Additional details are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4 and Table 1.3.1-17.5.

Of note, hypertension (grouped term) was less frequent in patients who had a prior treatment with bevacizumab than in those free of prior exposure to bevacizumab (23.4% vs. 37.2%), likely resulting from patient population. Additional details are provided in Table 1.3.1-17.6.

10.6.8.5 Fistula from gastrointestinal or other origin

A total of 9 patients (1.2%) reported a fistula from gastrointestinal origin. Events were severe (Grade ≥3) in 4 patients. Additional details are provided in Table 1.3.1-23.

A total of 6 patients (0.8%) reported a fistula from other origin than gastrointestinal . Events were severe (Grade ≥3) in 3 patients. Four out of the 6 events were from the female genital tract.

Analyses by subgroup are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

10.6.8.6 Gastrointestinal perforation

A total of 7 patients (0.9%) of the 766 treated reported gastrointestinal perforation. Grade ≥3 events were reported in 6 patients, including 3 fatal events. Gastrointestinal perforation led to the premature or permanent discontinuation in 3 of the 7 patients. Additional details are provided in Table 1.3.1-22.

By population of interest, only one out the seven cases of gastrointestinal perforation was reported in the elderly population, and 4/7 in the population of patients who had prior treatment with bevacizumab. Additional details are provided in Table 1.3.1-17.1, Table 1.3.1-17.2, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

10.6.8.7 Osteonecrosis

A total of 3 patients (0.4%) of the 766 treated reported at least one osteonecrosis episode. All osteonecrosis episodes reported were of Grade 1-2 in severity. Additional details are provided in Table 1.3.1-24.

10.6.8.8 Wound healing complications

No patients reported wound healing complications during the study.

10.6.8.9 Renal failure events

A total of 32 patients (4.2%) of the 766 treated reported at least one episode of renal failure (grouped term, including PTs from renal and urinary disorders SOC and from investigations SOC). Two (0.3%) patients reported a Grade 3 event. The most frequently reported TEAEs related to renal failure were blood creatinine increased in 15 (2.0%) patients and renal failure in 14 (1.8%) patients. Renal failure episodes led to the premature or permanent treatment discontinuation in 3 (9.4%) of the 32 patients. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-26.

By population of interest, there was no higher incidence of renal failure (grouped term) in the elderly population (5.1%), in the patients with impaired liver function at baseline (1.6%), in the non-Caucasian population (4.3%), in patients with more than 1 line of prior chemotherapy (4.3%),

and in patients who had a prior exposure to bevacizumab (4.2%). Additional details are provided in Table 1.3.1-17.1, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

In patients with impaired renal function at baseline (creatinine clearance <80 mL/min), events of renal failure (grouped term), as it could be expected, were more frequent than in patients with normal renal function (7.0% vs. 2.9%). Grade ≥3 events were reported in one patient in each of the baseline renal function categories. Additional details are provided in Table 1.3.1-17.2.

10.6.8.10 Proteinuria including nephrotic syndrome

A total of 91 patients (11.9%) of the 766 treated reported at least one proteinuria (TEAEs, grouped term) episode during the study treatment period. Grade ≥3 events were reported in 21 patients (2.7%). Proteinuria episodes led to the premature or permanent treatment discontinuation in 23 (25.3%) of the 91 patients. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-27.

Nephrotic syndrome was reported in one patient and no case of thrombotic microangiopathy was reported.

By population of interest, there was no higher incidence of proteinuria in the elderly population (13.0%), in the patients with renal impairment (13.2%), with impaired liver function (7.0%), in the non-Caucasian population (12.9%), in patients with more than 1 line of prior chemotherapy (9.9%) and in patients who had a prior exposure to bevacizumab (10.5%). The same pattern was observed for Grade ≥3 events, with no difference in incidence reported of each of the comparison. Additional details are provided in Table 1.3.1-17.1, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

Of note, these analyses of proteinuria are from the TEAE panel, ie, corresponding to events that led to dosing adjustment (delay, omission, reduction, premature or permanent study treatment discontinuation) or which were reported as SAEs, and do not correspond to results of a systematic, by cycle, dipstick/ UPCR evaluation of proteinuria.

10.6.8.11 Parodontopathy

A total of 70 patients (9.1%) of the 766 treated reported at least one episode of parodontopathy (grouped term). Grade ≥3 events were reported in 7 (0.9%) patients. The most frequent TEAEs related to parodontopathy were toothache (12 (1.6%) patients) and gingivitis (10 (1.3%) patients). Parodontopathy episodes led to the premature or permanent treatment discontinuation in 1 (1.4%) of 70 patients. Additional details are provided in Table 1.3.1-17 and Table 1.3.1-28.

Analyses by subgroup are provided in Table 1.3.1-17.1, Table 1.3.1-17.3, Table 1.3.1-17.4, Table 1.3.1-17.5 and Table 1.3.1-17.6.

10.6.9 Deaths

Deaths during the treatment period (ie, from start of treatment up to 30 days after last dose), or during the follow-up period (ie, death >30 days after last dose) are summarized in Table 37.

Overall, 13 patients experienced fatal AEs within 30 days of study treatment in other context than disease progression (Table 37). One other patient died after 30 days post last dose, consecutive to an AE that developed during the on treatment period.

Of these 14 patients, 5 died in the context of an infection and one additional in the context of a febrile neutropenia.

Three other patients died in relation with a digestive tract perforation.

Among these 14 patients, 7 patients reported 7 TEAEs that were considered to be related to study treatment as per investigator's opinion. These 7 patients are briefly described below:

- Patient 250-015-005: female, 63 years old, patient diagnosed with rectum adenocarcinoma in June 2011, presenting, at study entry, with metastases in liver and lung, who started treatment with the study medication on 10 February 2015. On Cycle 6 Day 17 (87 days after the first IMP administration) she experienced cerebrovascular accident. No corrective measures were reported and the patient died 24 days after the last IMP administration. It is unknown whether an autopsy was performed.
- Patient 380-010-009: female, 65 years old, patient diagnosed with metastatic colon adenocarcinoma (including recto-sigmoid) in September 2009, presenting, at study entry, with metastases in liver, lung, lymph nodes and brain, who started treatment with the study medication on 23 Mach 2016. On Cycle 1 Day 12, she experienced febrile neutropenia. Laboratory tests showed low platelet counts and hemocultures were positive to Gram-positive cocci. No corrective measures were reported and the patient died on the same day. An autopsy was performed and cause of death was febrile neutropenia.
- Patient 724-003-013: male, 81 years old, patient diagnosed with metastatic colon adenocarcinoma (including recto-sigmoid) in November 2014, presenting, at study entry, with metastases in the liver, who started treatment with the study medication on 15 December 2015. On Cycle 1 Day 2, he experienced intestinal perforation. He complained of abdominal pain and diarrhea. No corrective measures were reported and the patient died 35 days after the last IMP administration. An autopsy was not performed.
- Patient 724-005-002: female, 68 years old, patient diagnosed with metastatic colon adenocarcinoma (including recto-sigmoid) in November 2012, presenting, at study entry, with metastases in the liver, lung, lymph nodes and peritoneum, who started treatment with the study medication on 11 June 2014. On Cycle 3 Day 12 (45 days after the first IMP administration), she experienced sepsis. Corrective measures included antibiotics and the patient died 13 days after the last IMP administration. It is unknown whether an autopsy was performed.

- Patient 724-005-003: male, 68 years old, patient diagnosed with colon adenocarcinoma (including recto-sigmoid) in August 1997, presenting, at study entry, with metastases in liver, lung and bones, who started treatment with the study medication on 02 September 2014. On Cycle 3 Day 11 (68 days after the first IMP administration), he experienced septic shock. No corrective measures were reported and the patient died on the same day. It is unknown whether an autopsy was performed.
- Patient 724-014-021: male, 50 years old, patient diagnosed with metastatic colon adenocarcinoma (including recto-sigmoid) in July 2014, presenting, at study entry, with metastases in the liver. On Cycle 6 Day 6 (76 days after the first IMP administration), he experienced small intestinal perforation. Corrective measures included antibiotics and the patient died 14 days after the last IMP administration. It is unknown whether an autopsy was performed.
- Patient 840-026-008: female, 58 years old, patient diagnosed with colon adenocarcinoma in July 2012, presenting, at study entry, with lung metastases, who started treatment with the study medication on 04 May 2015. On Cycle 1 Day 21, she experienced hemorrhage intracranial. She was admitted to the emergency room with aphasia and a computed tomography revealed acute intraparenchymal hematomas and subarachnoid hemorrhage. Corrective measures included dexamethasone, levetiracetam, nicardipine and mannitol. The patient died one day later (22 days after the last IMP administration). An autopsy was not performed.

Table 37 - Summary of deaths and cause of deaths - All treated population

		ZALTRAP/ FOLFIRI N=766
Total number of deaths	n/N(%)	563/766 (73.5%)
Cause of death		
Adverse Event	n/N(%)	14/766 (1.8%)
Disease Progression	n/N(%)	530/766 (69.2%)
Other reason	n/N(%)	19/766 (2.5%)
Missing	n/N(%)	0
Number of deaths within 30 days from last dose	n/N(%)	45/766 (5.9%)
Cause of death		
Adverse Event	n/N(%)	13/766 (1.7%)
Disease Progression	n/N(%)	32/766 (4.2%)
Other reason	n/N(%)	0
Missing	n/N(%)	0
Deaths more than 30 days from last dose due to adverse event	n/N(%)	1/766 (0.1%)
Number of deaths within 60 days from first dose	n/N(%)	40/766 (5.2%)
Cause of death		
Adverse Event	n/N(%)	5/766 (0.7%)
Disease Progression	n/N(%)	35/766 (4.6%)
Other reason	n/N(%)	0
Missing	n/N(%)	0

Patient 250-007-002 is displayed in this table with death in context of disease progression within 30 days from last dose but the start date of such AE was Pre-Treatment
Patient 724-003-013 is displayed in this table as having death with more than 30 days from last dose due to adverse event but had a Fatal TEAE leading to death in other context of disease progression

Data on all TEAEs leading to death is provided in Table 1.3.2-2.

Tables for all TEAEs leading to death by subgroups of interest are provided in Table 1.3.2-2.1, Table 1.3.2-2.2, Table 1.3.2-2.3, Table 1.3.2-2.4, Table 1.3.2-2.5 and Table 1.3.2-2.6, respectively.

Table for TEAEs leading to death during the on-treatment period in the context of disease progression is provided in Table 1.3.2-3. Summaries by subgroups of interest are provided in Table 1.3.2-3.1, Table 1.3.2-3.2, Table 1.3.2-3.3, Table 1.3.2-3.4, Table 1.3.2-3.5 and Table 1.3.2-3.6, respectively.

Table 38 shows the TEAEs leading to death in other context of disease than disease progression by primary SOC and PT and worst NCI grade.

Table 38 - Treatment-emergent adverse events leading to death in other context of disease progression by Primary SOC and PT and Worst NCI Grade - All treated population

PRIMARY SYSTEM ORGAN CLASS Preferred Term	ZALTRAP / FOLFIRI (N=766)				
	All Grades	Grades [3-4]	Grades 3	Grades 4	Grades 5
TEAE leading to death in other context of disease progression (a)	14 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (1.7%)
INFECTIONS AND INFESTATIONS	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.7%)
Pneumonia	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Sepsis	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Septic Shock	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Febrile Neutropenia	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
PSYCHIATRIC DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Completed Suicide	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
NERVOUS SYSTEM DISORDERS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Cerebrovascular Accident	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Haemorrhage Intracranial	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Pulmonary Embolism	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
GASTROINTESTINAL DISORDERS	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Intestinal Perforation	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Small Intestinal Perforation	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

Patient 724-003-013 is displayed in this table having a Fatal TEAE leading to death in other context of disease progression but the death happened more than 30 days from last dose due to adverse event
Note: Adverse Events are reported using MedDRA version 21.0 and graded using NCI CTC Version 4.03.
(a) Deaths within 30 days with cause of death different from disease progression , or death more than 30 days with cause of death equal to AE
Events are sorted by System Organ Class internationally agreed order and decreasing frequency of Preferred Term within the SOC in the All Grades group.
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Tables for TEAEs leading to death during the on-treatment period in other context of disease progression by subgroups of interest are provided in Table 1.3.2-4.1, Table 1.3.2-4.2, Table 1.3.2-4.3, Table 1.3.2-4.4, Table 1.3.2-4.5 and Table 1.3.2-4.6, respectively.

Table for possibly related TEAEs leading to death during the on-treatment period in the other context of disease progression is provided in Table 1.3.2-5. Summaries by subgroups of interest are provided in Table 1.3.2-5.1, Table 1.3.2-5.2, Table 1.3.2-5.3, Table 1.3.2-5.4, Table 1.3.2-5.5 and Table 1.3.2-5.6, respectively.

10.6.10 Pre- and post-treatment adverse events

A listing of pre- and post-treatment adverse events is provided in Listing 1.3.1-1 and Listing 1.3.1-2, respectively.

10.6.11 Other safety data

10.6.11.1 Hospitalizations

A total of 339 patients (44.3%) reported hospitalizations. Of them, hospitalizations reported in 204 patients (26.6%) took place in oncology departments, followed by hospitalizations reported in 114 patients (14.9%) in standard wards, and hospitalizations reported in 55 patients (7.2%) took place in the emergency room. The main reasons for hospitalizations were cancer-related complication reported in 125 patients (16.3%), followed by related SAE to study medication and other reasons reported 117 patients (15.3%), respectively.

Table 39 shows the hospitalizations reported during the study:

Table 39 - Hospitalizations - All treated population

	ZALTRAP / FOLFIRI (N=766)	95% CI
Emergency room visits in context other than hospitalization	463 / 271 (35.38%)	(31.99,38.76)
At least one hospitalization* [a]	4250 / 339 (44.26%)	(40.74,47.77)
Emergency room	274 / 55 (7.18%)	(5.35,9.01)
Intensive Care Unit	131 / 20 (2.61%)	(1.48,3.74)
Standar wards	1019 / 114 (14.88%)	(12.36,17.40)
Oncology	2475 / 204 (26.63%)	(23.50,29.76)
Palliative Care Unit	85 / 8 (1.04%)	(0.32,1.76)
Other	264 / 29 (3.79%)	(2.43,5.14)
Main reason for hospitalization*	339 (44.26%)	(40.74,47.77)
Chemotherapy administration	43 (5.61%)	(3.98,7.24)
Cancer-related complication	125 (16.32%)	(13.70,18.94)
ZALTRAP®/FOLFIRI related SAE	117 (15.27%)	(12.73,17.82)
Patient convenience - Logistic reasons	3 (0.39%)	(0.00,0.83)
Other	117 (15.27%)	(12.73,17.82)

* A patient can be counted in several categories
[a] nn / xx (%) = Total number of nights (or visits for ER in context other than hospitalization) / patients with at least one hospitalization (%)

	ZALTRAP / FOLFIRI (N=766)
Emergency room	
Number	55
Missing	0
Mean (SD)	4.98 (8.84)
CI 95%	(2.59,7.37)
Median	1.00
Range (Min, Max)	(1.00,49.00)
(Q1, Q3)	(1.00,4.00)
Total number of nights	274
Intensive Care Unit	
Number	20
Missing	0
Mean (SD)	6.55 (4.38)
CI 95%	(4.50,8.60)
Median	6.50
Range (Min, Max)	(1.00,15.00)
(Q1, Q3)	(2.00,10.00)
Total number of nights	131
Standard wards	
Number	114
Missing	0
Mean (SD)	8.94 (8.72)
CI 95%	(7.32,10.56)
Median	6.50
Range (Min, Max)	(1.00,58.00)
(Q1, Q3)	(3.00,12.00)
Total number of nights	1019
Oncology	
Number	204
Missing	0
Mean (SD)	12.13 (11.98)
CI 95%	(10.48,13.79)
Median	8.00
Range (Min, Max)	(1.00,68.00)
(Q1, Q3)	(4.00,16.50)
Total number of nights	2475
Palliative Care Unit	
Number	8
Missing	0
Mean (SD)	10.63 (8.33)
CI 95%	(3.66,17.59)
Median	9.00
Range (Min, Max)	(2.00,26.00)
(Q1, Q3)	(4.50,15.00)
Total number of nights	85
Other	
Number	29
Missing	0
Mean (SD)	9.10 (8.94)
CI 95%	(5.70,12.50)
Median	6.00
Range (Min, Max)	(1.00,34.00)
(Q1, Q3)	(3.00,9.00)
Total number of nights	264

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11 DISCUSSION

11.1 KEY RESULTS

The OZONE study included 766 treated patients from 11 countries in Europe and North America. Up to 84.3% of the treated patients were included in Europe and 15.7% were included in North America (United States and Puerto Rico).

A total of 601 (78.5%) patients did not complete the 24 months follow-up. The main reason for not completing the 24 months follow-up was death reported in 558 (92.9%) patients. Only 34 (5.66%) patients were lost to follow-up.

The treated patients included patients from both genders: male (59.5%) and female (40.5%). Median age of patients was 64 years ranging from 26 to 88 years. Of the treated patients, 48.3% were ≥65 years old, 9.2% were non-Caucasian, 35.0% had renal impairment, and 19.6% had hepatic impairment, matching the protocol hypothesis. ECOG PS was 0 or 1 for the vast majority of the patients (94.8%). Colon was the primary site for 73.5% of the patients and rectum for 25.6%. All patients had metastatic disease at baseline, 55.48% had more than 1 metastatic site; the most frequent metastatic sites were liver (67.5%) and lung (51.4%). Half of the patients (51.5%) had a KRAS mutated status. All treated patients were administered previous chemotherapy (97.8% including oxaliplatin), with 35% of them with more than one line for advanced disease. 58.6% of the patients had a prior exposure to bevacizumab.

In the overall population the median (Q1;Q3) duration of treatment was 16.4 (9.6-30.0) weeks. The median number of treatment cycles was 7 (4.0; 12.0) with median number of cycles with aflibercept, irinotecan and 5-FU of 6 (3.0; 11.0), 6 (4.0; 12.0) and 6 (4.0; 12.0), respectively and relative dose intensities of 79.0% (63.8; 92.8), 81.4% (67.6; 93.8) and 82.9% (70.4; 94.5), respectively.

Primary objective

The primary objective was to describe the safety of ZALTRAP® + FOLFIRI in patients treated in a daily practice.

During the study treatment period, almost every patient reported at least one TEAE (98.3%). Grade ≥3 TEAEs were reported in 523 patients (68.3%).TEAEs considered possibly related to the study medication were reported in 692 patients (90.3%). Serious TEAEs were reported in 334 patients (43.6%) and TEAEs leading to death, outside of a context of disease progression were reported in 14 patients (1.8%).

TEAEs most frequently reported were asthenic conditions (HLT) (58.4% of the patients) diarrhea (56.3%), stomatitis and ulceration (HLT) (39.3%), infections (SOC) (35.1%), nausea (33.4%), hemorrhage (grouped term) (29.5%), hypertension (grouped term) (29.1%), decreased appetite (22.7%), abdominal pain (21.7%) and vomiting (21.5%). Neutropenia was reported as a TEAE in 24.7% of patients, but there was no systemic collection of laboratory abnormalities in this study.

Corresponding Grade ≥3 TEAEs were reported in more than 5% of the patients for neutropenia as a TEAE (15.1%), asthenic conditions (HLT) (12.7%), hypertension (HLT) (10.3%), diarrhea (9.5%), infections (SOC) (9.0%) and stomatitis and ulceration (5.4%).

Other anti-VEGF class events were infrequent, with GI perforation reported in 0.9% of the patients (grouped term), GI fistula in 1.2%, fistula from other origin in 0.8%, osteonecrosis of the jaw in 0.4%, posterior reversible encephalopathy syndrome in 0.4%. Nephrotic syndrome was reported in one patient and no case of thrombotic microangiopathy was reported.

Overall serious TEAEs were reported in 334 patients (43.6%). The most frequently reported serious TEAEs were diarrhea (4.6%), general physical health deterioration (3.3%) and abdominal pain (2.9%). Possibly related serious TEAEs were reported in 185 patients (24.2%).

A total of 563 patients (73.5%) died at any time during the study. Of them, 530 patients (69.2%) died due to disease progression and 14 patients (1.8%) due to a TEAE not in the context of disease progression. Of these 14 patients, 13 patients (1.7%) died within 30 days from the last dose of study treatment in relation with a TEAE and another one post 30 days post last dose. The most frequent TEAEs leading to death were infections (5 patients) and GI perforation (3 patients).

- Safety in the elderly population:

  Among the 766 patients, 370 (48.3%) were aged 65 or more. All grades TEAEs were reported in 98.4% of the patients aged 65 or more and in 98.2% of the patients aged less than 65; with severe events (Grade ≥3) reported in 69.5% and 67.1% of the patients, respectively.

  Only few TEAEs were more frequent (by ≥5%, all grade) in the elderly population. Asthenia and decreased appetite were more frequent: asthenia (all grade: 43.5% vs 35.9%; Grades ≥3: 11.9% vs 6.6%), decreased appetite (all grade: 25.4% vs 20.2%; Grades ≥3: 3.0% vs 2.5%).

  Of importance for the elderly population, no increases by at least 5% in incidence were noted for diarrhea, dehydration, hemorrhages (grouped term), hypertension (grouped term) and renal failure events (grouped term).

- Safety in patients with impaired renal function at baseline

  Among the 738 patients with renal status documented at baseline, 258 (34.9%) were reported with creatinine clearance ≤80 mL/min.

  No TEAEs were more frequently (by ≥5%, all grade) reported in the patients with impaired renal function by comparison to these with normal renal function.

- Safety in patients with impaired liver function at baseline

  Among the 657 patients with liver function documented at baseline, 129 (19.6%) had an impaired liver function (defined as, total bilirubin >UNL or AST or ALT >1.5 UNL).

  At the SOC level, there was an excess in incidence (by ≥5%, all grade) for “any TEAE” in the patients with an impaired liver function for the Hepatobiliary disorders SOC, by comparison to the patients with normal liver function (11.6% vs 6.1%). This difference was not driven by any particular type of events.

At the PT level, all grades constipation was more frequent in patients with impaired liver function (23.3% vs 14.2%).

Hemorrhages, as a grouped term, were reported in more patients with impaired liver function population (all grades: 37.2% vs 30.1%; Grades ≥3: 5.5% vs 2.1%). The most frequent events were epistaxis (23.3% vs 19.3%) and hemorrhage of gastrointestinal origin (16.3% vs 12.1%).

- Safety in the non-Caucasian population

  Among the 762 patients with race documented at baseline, only 70 (9.2%) were non-Caucasian.

  By decreasing order of incidences, the following events were reported more frequently (by ≥5%, all grade) in the non-Caucasian population by comparison to the Caucasian population: nausea (41.4%vs 32.7%), vomiting (31.4% vs 20.7%), fatigue (31.4% vs 20.1%), abdominal pain (27.1% vs 21.2%), palmar-plantar erythrodysaesthesia syndrome (15.7% vs 6.1%), dehydration (14.3% vs 4.5%), cough (14.3% vs 5.8%), dizziness (11.4% vs 4.2%) and edema peripheral (11.4% vs 3.2%).

  Hemorrhages (grouped term) and (hypertension, as grouped term) were reported less frequently in the non-Caucasian population than in the Caucasian population (20.0% vs 30.2% and 15.7% vs 30.5%, respectively).

  Renal failure (grouped term) and proteinuria (grouped term) were reported at similar incidences in the non-Caucasian and Caucasian populations.

- Safety in patients with prior exposure to bevacizumab

  Among the 766 patients treated in the study, 449 (58.6%) had a prior treatment with bevacizumab.

  There were no flares in incidences of anti-VEGF class events. The only TEAE that was more frequently reported in patients who had a prior exposure to bevacizumab was fatigue (23.8% vs 17.0%, all grade).

Secondary objectives

Overall survival

At the study cut-off date, 563/766 (73.5%) patients had died at any time during the study.

Median (95% CI) OS in the overall population was 12.45 (11.56; 13.63) months.

Multivariate analyses were performed for subgroups of interest, including age (<65 vs ≥65), renal function status (impaired function, yes vs no), hepatic function status (impaired function, yes vs no), race (Caucasian vs non Caucasian), and prior anticancer treatments (number of lines: 1 vs ≥2 and prior bevacizumab: yes vs no).

- OS by Age:

  Median (95% CI) overall survival was 12.91 (11.56; 14.88) months in patients aged ≥65 years old and 11.96 (10.97; 13.63) months in patients aged less than 65 years old.

After adjustment on prognostic factors the estimated hazard ratio (95% CI) by multivariate analysis was 0.951(0.794; 1.139).

- OS by renal function status at baseline:

  Median (95% CI) overall survival was 12.52 (11.56; 15.08) months in patient with impaired renal function at baseline and 12.09 (11.17; 13.63) months in patients with normal renal function at baseline.

  After adjustment on prognostic factors the estimated hazard ratio (95% CI) by multivariate analysis was 0.908 (0.749; 1.000).

- OS by hepatic function status at baseline:

  Median (95% CI) overall survival was 8.739 (6.834; 10.64) in patients with hepatic impairment and 13.67 (12.12; 15.05) months in patients without hepatic impairment.

  After adjustment on prognostic factors, the estimated hazard ratio by multivariate analysis (95% CI) was 1.561 (1.255, 1.941), favoring the subgroup of patients with no hepatic impairment.

  There was a higher proportion of patients with liver metastasis in the subgroup of patients with impaired hepatic function by comparison to patients without impaired hepatic function (79.8% vs 64.8%) and more patients with impaired hepatic function were metastatic at diagnosis (81.4% vs 66.7%).

- OS by Race:

  Median (95% CI) overall survival was 12.12 (8.805; 14.39) months in non-Caucasian patients and 12.45 (11.47; 13.73) months in Caucasian patients.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.070 (0.789; 1.450).

- OS by number of prior lines of chemotherapy:

  Median (95% CI) overall survival was 12.58 (11.37; 14.59) months in patients with >1 line of anti-cancer therapy and 12.16 (11.01; 13.67) in patients with 0-1 line of prior anti-cancer therapy.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.916 (0.764; 1.097).

- OS by prior bevacizumab:

  Median (95% CI) overall survival was 10.61 (9.495; 11.73) months in patients with prior bevacizumab and 16.62 (14.09; 18.17) months in patients without prior bevacizumab.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.666 (1.379; 2.013), favoring the subgroup of patients without prior use of bevacizumab.

Progression free survival:

A total of 669/766 (87.3%) patients had a PFS event at the study cut-off date. Median (95% CI) PFS was 6.078 (5.552; 6.669) months.

As for the OS, multivariate analyses were performed on the subgroups of interest which results are expressed below:

- PFS by Age:

  Median (95% CI) progression free survival was 6.472 (5.684; 7.228) months in patients aged ≥65 years old and 5.552 (4.895; 6.275) months in patients aged less than 65 years old.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.871 (0.737; 1.028).

- PFS by renal function status at baseline:

  Median (95% CI) progression free survival was 6.275 (5.618; 7.228) months in patients with renal impairment at baseline and 5.881 (5.158; 6.669) months in patients normal renal function at baseline.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 0.960 (0.806; 1.144).

- PFS by hepatic function status at baseline:

  Median (95% CI) progression free survival was 4.402 (3.088; 5.585) months in patients with hepatic impairment and 6.275 (5.717; 6.998) months in patients without hepatic impairment.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.424 (1.160; 1.748), favoring the subgroup of patients with no hepatic impairment.

- PFS by Race:

  Median (95% CI) progression free survival was 4.402 (3.483; 6.834) months in non-Caucasian patients and 6.209 (5.618; 6.735) months in Caucasian patients.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.220 (0.924; 1.611).

- PFS by number of prior lines of chemotherapy:

  Median (95% CI) progression free survival was 5.782 (5.224; 6.669) months in patients with >1 line of anti-cancer therapy and 6.275 (5.388; 7.129) in patients with 0-1 line of prior anti-cancer therapy.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.096 (0.927; 1.296).

- PFS by prior bevacizumab:

  Median (95% CI) progression free survival was 5.224 (4.435; 5.782) months in patients with prior bevacizumab and 7.458 (6.275; 8.411) months in patients without prior bevacizumab.

  After adjustment on prognostic factors, the estimated hazard ratio (95% CI) by multivariate analysis was 1.585 (1.333; 1.883), favoring the subgroup of patients without prior use of bevacizumab.

Overall response rate

Of the 766 patients included, 125 patients reported objective response (CR or PR) to treatment. Overall response rate (95% CI) was 16.3% (13.77%, 19.13%). Ten (1.3%) patients reported a complete response and 115 (15.0%) patients reported a partial response.

Stable disease was reported as the best response in 264 (34.5%) patients.

Progressive disease was reported as the best response in 260 (33.9%) patients.

As for OS and PFS endpoints, analyses of objective response were performed for each subgroup of interest. ORR was analyzed using a multivariate logistic model:

- Response rate by age: responders' rate (95% CI) was 11.51% (8.52%; 15.10%) in patients <65 years and 19.18% (15.27%; 23.60%) in patients ≥65 years, showing an odds ratio (95% CI) 1.842 (1.208; 2.810) after adjustment on pre-selected prognostic factors.
- Response rate by renal function status: responders' rate (95% CI) was 13.47% (10.53%; 16.88%) in patients without renal impairment and 19.37% (14.69%; 24.78%) responders in patients with renal impairment, showing an odds ratio (95% CI) 1.517 (0.989; 2.328) after adjustment on pre-selected prognostic factors.
- Response rate by hepatic function status: responders' rate (95% CI) was 16.96% (13.83%; 20.47%) in patients without hepatic impairment and 10.85% (6.06%; 17.54%) responders in patients with hepatic impairment, showing an odds ratio (95% CI) 0.625 (0.333; 1.173) after adjustment on pre-selected prognostic factors.
- Response rate by race: responders' rate (95% CI) was 15.4% (12.77%; 18.33%) in Caucasian patients and 14.29% (7.07%; 24.71%) responders in non-Caucasian patients, showing an odds ratio (95% CI) 0.307 (0.007; 2.114) after adjustment on pre-selected prognostic factors.
- Response rate by number of prior lines of chemotherapy: responders' rate (95% CI) was 16.22% (12.46%; 20.59%) in patients with 0-1 line of anti-cancer therapy and 14.39% (11.16%; 18.13%) responders in patients with >1 line of anti-cancer therapy, showing an odds ratio (95% CI) 0.998 (0.656; 1.520) after adjustment on pre-selected prognostic factors.
- Response rate by prior bevacizumab: responders' rate (95% CI) was 20.58% (16.22%; 25.50%) in patients without previous use of bevacizumab therapy and 11.46% (8.65%; 14.79%) responders in patients with previous use of bevacizumab therapy, showing an odds ratio (95% CI) 0.511 (0.338; 0.775) after adjustment on pre-selected prognostic factors.

11.2 LIMITATIONS

The OZONE study had some limitations which are common to this type of study:

- The centers were not selected at random. Target number of sites that could participate in the study was determined by the protocol and to the possibilities of each participating country. Sites that were offered participation in the study were finally randomly selected in order to ensure representativeness of the sample. Although centers were selected at random, there are limitations regarding representativeness in a sense that the number of sites was determined by protocol and possibilities of each participating country.
- No standardized method for evaluation of efficacy could be used in the study which led to limitations in the interpretation of the response rate and progression free survival, in particular when comparing the results to those of the VELOUR study in which imaging evaluation were performed every 6 weeks, more frequently than in real life practice.
- Results of the laboratory tests that are systematically performed prior to administration of chemotherapy were not collected into the eCRFs of the OZONE study precluding comparison with the VELOUR study.

11.3 INTERPRETATION

The results of this OZONE study are in line with previous efficacy results of the Phase III VELOUR study (4). In VELOUR study 611 patients were treated with ZALTRAP® + FOLFIRI and in OZONE study 766 patients had been treated with ZALTRAP® + FOLFIRI.

The patients in the OZONE study were older than in the VELOUR study (median 64 years, 48.3% aged 65 or more, vs median 61 years, 33.5% aged 65 or more). Of the treated patients, 48.3% were ≥65 years old, 9.2% were non-Caucasian, 35.0% had renal impairment, and 19.6% had hepatic impairment.

Disease characteristics were not fundamentally different from the VELOUR study; however, as it could be expected (VELOUR was initiated in 2007), the 2 patient populations differed with regards to prior anti-cancer treatment. The proportion of patients who had neo/adjuvant chemotherapy and who had a prior exposure to bevacizumab were higher in OZONE (45.6% vs 26.5% and 58.6% vs 27.6%, respectively). The proportion of patients who had more than one line of chemotherapy was higher as well. Of note, KRAS status was not mandated in the VELOUR study, precluding any type of comparison between the 2 studies.

On the safety standpoint, for all grade events, and by comparison to the VELOUR study, hemorrhage, decreased appetite, dysphonia, hypertension, headache, diarrhea, stomatitis and ulceration and weight decrease were reported less frequently in the OZONE study, in a range spanning from 8 to 19% less. A similar trend was observed for the severe events (grade ≥3).

Anti-VEGF class effects, such as gastrointestinal perforation, gastrointestinal fistula, non-gastrointestinal fistula, osteonecrosis, wound healing disorders, nephrotic syndrome and reversible posterior leukoencephalopathy was uncommon and remained in the range of what was reported during the VELOUR study.

With all the usual limitation when comparing studies, several hypotheses can be formulated to explain this apparent more favorable safety profile reported in the OZONE study, including a shorter exposure (median of 7 treatment cycles vs 9 treatment cycles), a better knowledge of aflibercept in combination with irinotecan and 5-FU, and a greater experience in managing/preventing side effects. Overall, the safety profile of aflibercept in combination with aflibercept and 5-FU, as reported in the OZONE study, was consistent with that reported in the VELOUR study.

Importantly, no new safety signal emerged from the OZONE study.

Safety analyses by subgroup did not reveal major differences in the safety profile across age groups, renal status groups; and hepatic status groups. Prior treatment with bevacizumab did not negatively influence the safety profile of aflibercept.

Some differences were noted for the non-Caucasian population with some events (all grades) more frequently reported in the non-Caucasian population and others reported less frequently than in the Caucasian population. However, only70 non-Caucasian patients were evaluated and no firm conclusion can be made.

For the overall population the median overall survival was 12.45 months, the median PFS was 6.078 months and the overall response rate 16.3%. These results are consistent with these reported in the VELOUR pivotal study (median OS: 13.5 months, median PFS: 6.90 months and RR: 19.8%).

Of note, the proportion of patients in the OZONE study reported with stable disease as best response, was nearly half of that in the VELOUR study (34.5% vs 65.9%). A possible explanation to this notable difference might be in relation with the frequency of imaging in the VELOUR study (every 6 weeks), allowing more patients to have stable disease as best response than when performing imaging, as in real life practice, every 8 to 12 weeks.

After adjustment on prognostic factors, multivariate analysis of overall survival by subgroups showed no clinically meaningful differences between age groups, race groups, baseline renal function groups, and number of prior lines of chemotherapy group.

Median OS was shorter in patients with hepatic impairment than in patients without hepatic impairment (8.74 vs 13.67 months). The estimated HR by multivariate analysis (95% CI) was 1.424 (1.160; 1.748). In patients with hepatic impairment, the higher proportion of patients with liver metastasis (79.8% vs 64.8%), and the higher proportion of patients diagnosed with upfront metastatic disease (81.4% vs 66.7%) may have contributed to the observed numerical differences in median OS.

Median OS was longer in patients who had no prior treatment with bevacizumab (16.62 vs 10.61 months). The estimated HR by multivariate analysis (95% CI) was 1.666 (1.379; 2.013). In the VELOUR study the median OS in the subgroup of patients who had no prior exposure to bevacizumab was 13.9 months and 12.5 months in patients with prior exposure to bevacizumab, The same pattern for a numerical difference in the control group of the VELOUR study (FOLFIRI) was noted with median OS in the subgroup of patients who had no prior exposure to

bevacizumab of 12.4 months and 11.7 months in patients with prior exposure to bevacizumab. In the absence of control in the OZONE study the results are difficult to interpret. A restriction of the use of anti-EGFR treatment to the wild KRAS population was implemented after the last patient completed treatment in the VELOUR study. This landmark change in the treatment of patients with mCRC may have contributed to this favorable 16.62 month median OS in the group of patients with no prior exposure to bevacizumab by selecting wild KRAS population for this subgroup.

11.4 VALIDITY AND GENERALIZABILITY

The OZONE study has compiled a large experience on the management of metastatic colorectal cancer patients treated with aflibercept in combination with irinotecan and 5-FU in current clinical practice from 11 participating countries, complementing the pivotal phase 3 VELOUR study. On the safety standpoint results were consistent with those reported in the Phase 3 study, even in a less selected population. In many instances crude incidences of frequently reported TEAES (such as hemorrhage, decreased appetite, dysphonia, hypertension, headache, diarrhea, stomatitis and ulceration and weight decrease) were lower than those reported in the VELOUR study, possibly reflecting a lower exposure by comparison to VELOUR and an increasing knowledge of the management of the drug by the prescribing physicians. The less-frequent anti-VEGF class adverse drug reaction, such as GI perforation, fistula, severe hemorrhage, posterior reversible encephalopathy syndrome, nephrotic syndrome or thrombotic microangiopathy, were not reported at significantly higher incidences than in the VELOUR study. Importantly, no new safety signal was noted. With respect to generalizability, limitations persist for characterizing of the safety profile for certain subgroups of patients, such as non-Caucasian patients (70 patients) and patients with severely impaired organ functions.

12 OTHER INFORMATION

None.

13 CONCLUSION

In conclusion, the results of the OZONE study, conducted in real life conditions, and in a less selected population, do not contradict the results of the VELOUR pivotal study, and no new safety signal was identified.

14 REFERENCES

1. Cancer facts and figures. American Cancer Society, 2005.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkim DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.

3. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin. 1999;49(1):8-31.

4. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, et al. Additiona of ZALTRAP 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;30:3499-506.

ANNEXES

Annex 1 List of stand-alone documents

None.

Annex 2 Supportive Documents

Protocol

Clinical trial protocol (01 July 2013)

Protocol amendment 1 (12 December 2013)

Protocol amendment 2 (01 February 2016)

Case report form (CRF) / Patient questionnaire

Sample case report form

Informed consent form

Informed consent form (10 February 2016)

Lists of investigators

List of investigators who enrolled

List of investigators who never enrolled

Other documents relevant to the study

List of steering committee members

Steering committee charter (31 July 2018)

List of service providers

Statistical analysis plan (SAP)

Statistical analysis plan

Other study information

Tables and Listings

Patient narratives

Regulatory authorities' submissions by country

List of IEC/IRB

Study report approval

Principal or coordinating investigator's signature form - Chau

The company's approval

Sponsor approval form - Castan

Annex 3 Administrative and Legal Considerations

Ethical Considerations

Ethical principles

This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

Laws and regulations

This study was conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the study was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

Regulatory authorities' submissions by country are presented

Data Protection

The patient's personal data and Investigator's personal data which were to be included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Record Retention

The Investigator was responsible for the retention of the study documentation until the end of the study. In addition, the Investigator had to comply with specific local regulations and recommendations regarding patient record retention.

The Company Audits and Inspections by Competent Authorities (CA)

The Investigator agreed to allow the Company's auditors and Competent Authorities' inspectors to have direct access to records of the study for review, it being understood that all personnel with access to patients' records are bound by professional secrecy and as such, could not disclose any personal identity or personal medical information.

The Investigator had to make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as notification from the authorities for an inspection was received by the Investigator, he/she had to inform the

Company and authorize the Company to participate in this inspection. The confidentiality of the data to verify and the protection of the patients must be respected during these inspections. Any results or information arising from the inspections by the Competent Authorities were to be immediately communicated by the Investigator to the Company. The Investigator had to take appropriate measures required by the Company to ensure corrective actions for all problems found during audits and inspections.

Ownership of Data and Use of Study Results

Unless otherwise specified by local laws and regulations, the Company retains ownership of data, results, reports, findings, and discoveries related to the study. Therefore, the Company reserves the right to use the data from the present study for any purpose, including to submit them to the Competent Authorities of any country.

The Study Committee, if any involved in the study, has full access to the final data base allowing for appropriate academic analysis and reporting of the study results.

Annex 4 Additional information

None.